Titankatalysierte Hydroaminierung von Alkenen und Alkinen in der Wirkstoffsynthese

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Angenommene Dissertation

von

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Zusammenfassung

Im Rahmen dieser Arbeit wurden neue Titankomplexe bezüglich ihrer Aktivität zur Hydroaminierung von Alkenen untersucht und verglichen. Als Testreaktion diente die intramolekulare Hydroaminierung von 2,2-disubstituierten Aminopent-4-enen. Dabei stellte sich heraus, dass alle untersuchten Komplexe katalytische Aktivität bei der Umsetzung von Amino-2,2-diphenylpent-4-en zeigen. Durch Variation des eingesetzten Amins konnte festgestellt werden, dass der neue homoleptische Komplex $TiBn_4$ ähnliche Aktivität wie der bereits bekante $Ti(NMe_2)_4$ Komplex besitzt. Der untersuchte Benzofulvenkomplex (mit Indenylliganden) zeigte zum Ind_2TiMe_2 analoge Ergebnisse. Auch wenn die Pentafulvenkomplexe (mit Cp-Liganden) nur Thorpe-Ingold aktivierte Aminoalkene cyclisieren konnten, besitzen diese ebenfalls wie der Benzofulvenkomplex ein sehr hohes Potential für mechanistische Studien.

Der Hauptteil der vorliegenden Arbeit befasst sich mit der Synthese von 1-Benzylisochinolin-Derivaten. Dieses Strukturmotiv findet sich in einer Reihe von pharmakologisch aktiven Naturstoffen wieder. Aus diesem Grund standen bereits einige 1-Benzylisochinolin-Derivate im Mittelpunkt von Untersuchungen zur Wirkstoffoptimierung. Allerdings beschränken sich die untersuchten Derivate nur auf elektronenreiche Isochinoline. Mit der hier verwendeten Syntheseroute wurden 1-Benzylisochinoline mit eletronenarmem sowie elektronisch neutralem A-Ring erhalten. Des Weiteren konnte die elektronische Situation am C-Ring variiert werden. Der Aufbau des A- und C-Rings erfolgte durch eine Sonogashira-Reaktion. Der B-Ring wurde durch eine intramolekulare Hydroaminierung etabliert. Die so gewonnenen 1-Benzyl-3,4-dihydroisochinolin-Derivate wurden direkt zu den 1-Benzyl-1,2,3,4-tetrahydroisochinolin-Derivaten reduziert oder zu den 1-Benzoyl-3,4-tetrahydroisochinolin-Derivaten oxidiert.

Abschließend konnte die Synthese durch die Entwicklung eines Ein-Topf-Verfahrens wesentlich vereinfacht werden. Dieses umschließt zwei Sonogashira-Kupplungen und eine Desilylierungsreaktion. So wurden mit dieser Methode in einem Schritt unterschiedlich substituierte Arylhalogenide mit Trimethylsilylacetylen zu den entsprechenden Bisarylalkinen umgesetzt. Die enthaltenen Sonogashira-Kupplungen können mit einer einzigen, sehr geringen Katalysatorladung realisiert werden. Die *in situ* Entschützung erfolgte durch Zugabe von wässrigem Methanol und Kaliumhydroxid.

Summary

Titanium complexes were examined and compared concerning their ability to catalyse intramolecular hydroamination reaction of 2,2-disubstited aminopent-4-enes. It turned out that all investigated complexes complexes show high catalytic activity for the conversion of 2,2-diphenylaminopent-4-ene. Although the bis(pentafulvene) complexes (Cp-ligand) could cyclise only Thorpe-Ingold activated aminoalkenes, these complexes as well as closely related bis(benzofulvene) complexes possess a very high potential for mechanistical studies.

The main part of this work describes the synthesis of 1-benzylisoquinoline derivatives. This structural motive appears in a many pharmacological natural products. For this reason some 1-benzylisoquinoline derivatives already stood in the center of active substance optimizations. However the derivatives examined were limited to electron rich isoquinolines. With the synthetic route used here, 1-benzylisoquinolines with electron poor as well as electronically neutral A-ring were synthesized. Furthermore, the electronic situation of the C-ring was varied. The A and C-ring were introduced via a Sonogashira reaction. The B-ring was generated by an intramolecular alkyne hydroamination reaction. The obtained 1-benzyl-3,4-dihydroisoquinolines were reduced directly to 1-benzyl-1,2,3,4-tetrahydroisoquinoline derivatives or oxidized to 1-benzoyl-3,4-tetrahydroisoquinoline derivatives.

Finally, the synthesis could be simplified by the development of a one-pot procedure. Two Sonogashira reactions and a desilylation could be achieved in one step. With this method diaryl alkynes were synthesized out of two differently substituted aryl halides and trimethylsilylacetylene. The entire sequence could be realized with only one, small (2 mol-%) catalyst loading. The *in situ* desilylation took place by addition of aqueous methanol and potassium hydroxide.

Aus dieser Arbeit sind folgende Veröffentlichungen hervorgegangen:

Publikationen

1. *Synthesis of Benzylisoquinoline Derivatives Possessing Electron-Withdrawing Substituents on the Benzene Ring of the Isoquinoline Skeleton*.
   R. Severin, D. Mujahidin, J. Reimer, S. Doye, *Heterocycles* **2007**, *74*, 683-700.

2. *One-Pot Synthesis of Fluorinated 1-Benzoyl-3,4-dihydroisoquinolines from ortho-Alkynylphenylethylamines by a Hydroamination/Oxidation Sequence.*
   R. Severin, J. Reimer, S. Doye, *Eur. J. Org. Chem.* **2010**, 51-54.

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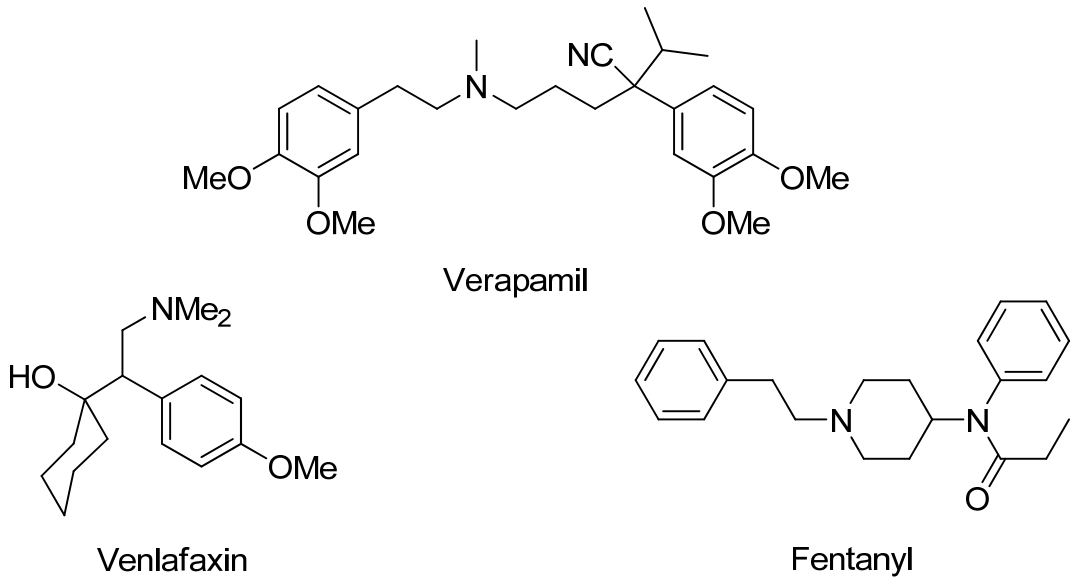
1. Einleitung

Stickstoffhaltige Verbindungen in Form von Aminen, Enaminen oder Iminen haben als Teil von Naturstoffen und durch ihr Vorkommen in biologischen Systemen einen hohen Stellenwert. Daher ist eine intensive Forschung zur Synthese solcher Verbindungen unausweichlich. Die hohe Bedeutung von Aminen zeigt sich ebenfalls in der Menge an industriell hergestellten Basis- und Feinchemikalien, die sich auf mehrere Millionen Tonnen beläuft.[1] Die pharmazeutische Industrie synthetisiert aminhaltige Verbindungen aufgrund ihrer biologischen Aktivität für nahezu alle medizinischen Bereiche. Hierbei sei als Beispiel auf neurologisch aktive Verbindungen wie Phenylethylamine hingewiesen, die das zentrale Nervensystem stimulieren (Schema **1**).[2]

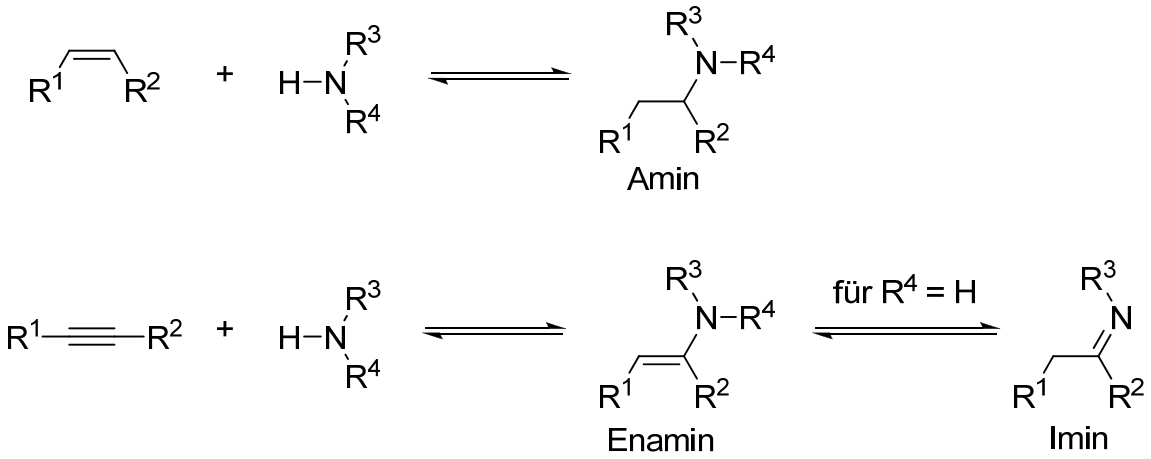


Schema 1 Ausgewählte phamakologisch aktive β-Phenylethylamine.

Die klassischen Synthesen zur Herstellung von Aminen sind vielfältig. Bekannt sind reduktive Aminierungsreaktionen von entsprechenden Ketonen oder Reaktionen von Benzaldehyden mit Nitroalkanen mit anschließender Reduktion. Ebenfalls möglich sind einfache nukleophile Substitutionen von Ammoniak sowie, primären und sekundären Aminen oder die Reduktion stickstoffhaltiger Verbindungen wie z.B. Nitrilen, Iminen, Aziden, Oximen und Nitroverbindungen.[3] Obwohl all diese Methoden im letzten Jahrhundert entwickelt wurden, rückte in den letzten zwei

Jahrzehnten die Hydroaminierung als weitere Methode zur Herstellung von Aminen in den Fokus zahlreicher Untersuchungen.

Die einfache Addition von Ammoniak, primären oder sekundären Aminen an eine Kohlenstoff-Kohlenstoff (C-C) Mehrfachbindung bezeichnet man als Hydroaminierung (Schema **2**). Die Synthese von Aminderivaten und *N*-heterocyclischen Verbindungen mit Hilfe der Hydroaminierung zeichnet sich durch die Atomökonomie[4,5,6] (100 %) sowie durch die leicht zugänglichen Edukte aus.

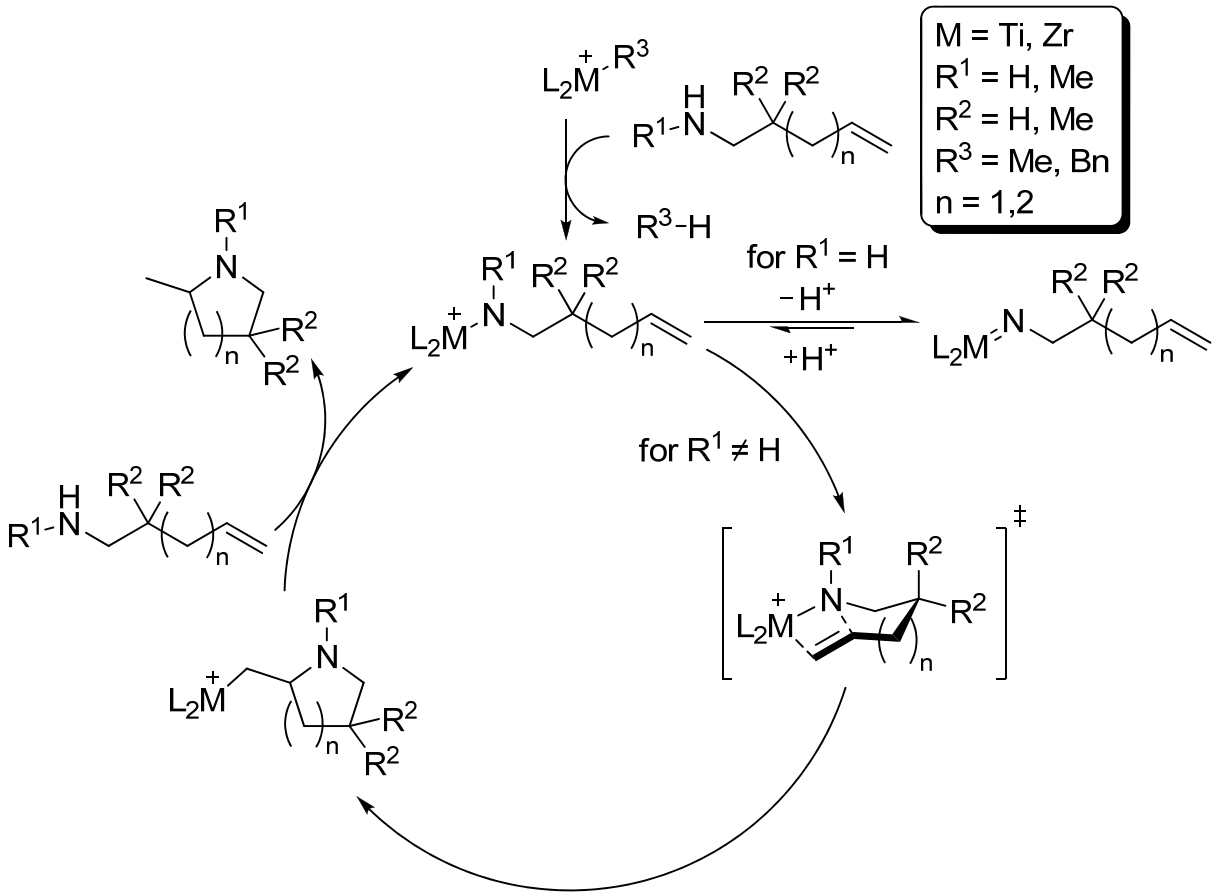


Schema 2 Hydroaminierung von Alkenen und Alkinen.

Aufgrund der hohen Aktivierungsenergie für diese Reaktion (resultierend aus der elektronischen Abstoßung der Edukte) ist die Verwendung eines Katalysatorsystems aus ökonomischer und ökologischer Sicht unausweichlich.[7] Dies führt noch heute zu intensiver Forschungstätigkeit und zeigt sich deutlich in der stark zunehmenden Anzahl an Publikationen auf diesem Gebiet allein in den letzten Jahren. Obwohl die ersten Hydroaminierungen von Alkenen[8] und Alkinen[9] seit mehreren Jahrzehnten bekannt waren, begannen detailliertere Untersuchungen dieser Reaktionen erst Ende der 1980er Jahre durch Marks[10] bzw. Anfang der 1990er Jahre durch die Arbeiten von Bergman[11,12] und Livinghouse.[13] Die seither entwickelten Katalysatorsysteme erstrecken sich über Vertreter aus Alkalimetallen, frühen und späten Übergangsmetallen, Lanthanoiden und Aktiniden bis hin zu Brønsted-Säuren und -Basen. Da im Folgenden nur auf Gruppe IV Metallkomplexe als Hydroaminierungskatalysatoren näher eingegangen wird, sei hier auf die letzten ausführlichen Übersichtsartikel hingewiesen.[14,15]

1.1 Mechanistische Untersuchungen zur Hydroaminierung von Alkenen

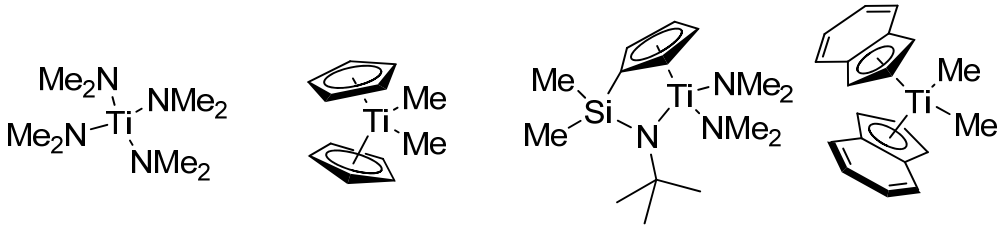
Die Untersuchungen auf dem Gebiet der Hydroaminierung von Alkenen sind nicht soweit fortgeschritten wie bei Alkinen. Obwohl die Wiederaufnahme der Forschung zu beiden Gebieten fast gleichzeitig in den 1990er Jahren begann, wirft die Hydroaminierung von Alkenen noch immer viele Fragen auf. Besonders bei der Verwendung von Gruppe IV Metallkomplexen gibt es noch immer keinen allgemein anerkannten Mechanismus. Hier muss zwischen geladenen und neutralen Katalysatoren unterschieden werden. Anfang 2004 konnte Scott über erste Cyclisierungen von Aminoalkenen unter Verwendung von kationischen Zirkonium- und Titankomplexen berichten.[16] Für kationische Komplexe wird der in Schema **3** gezeigte Mechanismus vorgeschlagen. Dieser ist angelehnt an den Mechanismus für Seltenerdmetalle.[17]



Schema 3 Postulierter Mechanismus für die intramolekulare Hydroaminierung von Alkenen unter Verwendung von kationischen Gruppe IV Metallkomplexen.

Der Einsatz von kationischen Gruppe IV Katalysatoren zur Hydroaminierung von Alkenen ist allerdings auf sekundäre Amine beschränkt. Bei der Umsetzung eines primären Amins kommt es zu einer Deprotonierungsreaktion und die resultierende Imido-Spezies wird katalytisch inaktiv.[16,18,19]

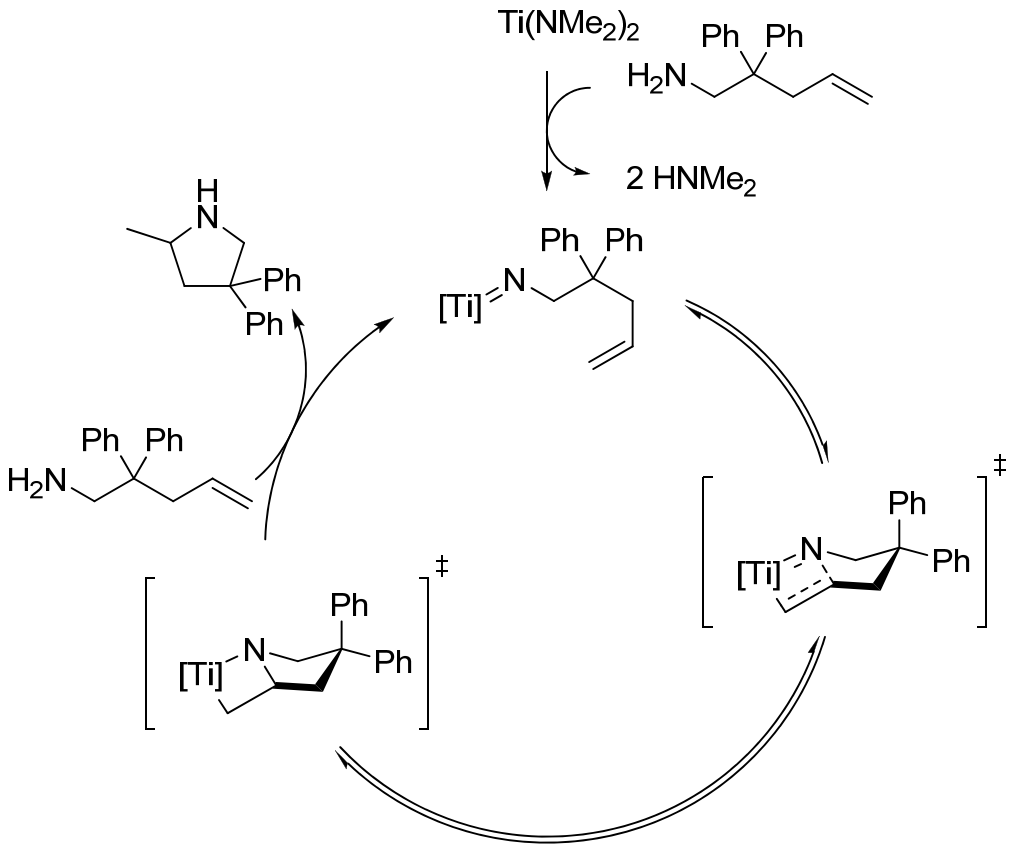
Über den ersten neutralen Titankomplex (**I**) zur Hydroaminierung von Alkenen wurde 2005 von Schafer berichtet.[20] In den folgenden zwei Jahren wurden weitere neutrale Titankomplexe identifiziert (Abbildung **1**).[21,22,23,24,25,26,27,28]



I II III IV

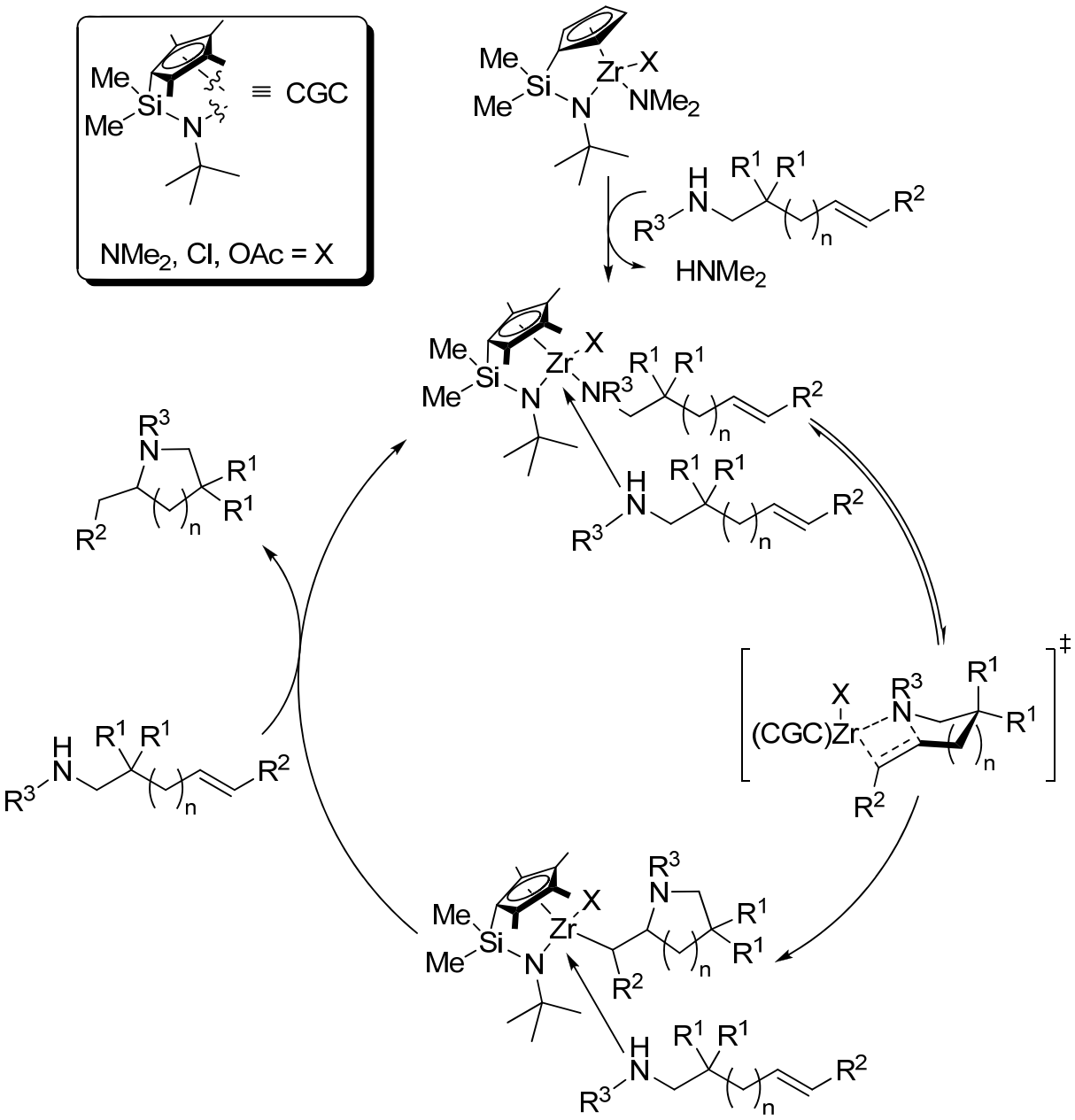
Abbildung 1 Auswahl bekannter Titan-Katalysatoren für die Hydroaminierung von primären Aminoalkenen.

Im Gegensatz zu kationischen Metallkomplexen können neutrale Titankomplexe primäre Aminoalkene umsetzen. Umso verständlicher erscheint die Schlussfolgerung, die Reaktion würde über eine [2 + 2]-Cycloaddition des Alkens an eine Metall-Imido-Spezies mit anschließender Protonierung des gebildeten Azametallacyclobutankomplexes verlaufen (Schema **4**).



Schema 4 Postulierter Mechanismus für die Hydroaminierung von Alkenen unter Verwendung von neutralen Gruppe IV Metallkomplexen.

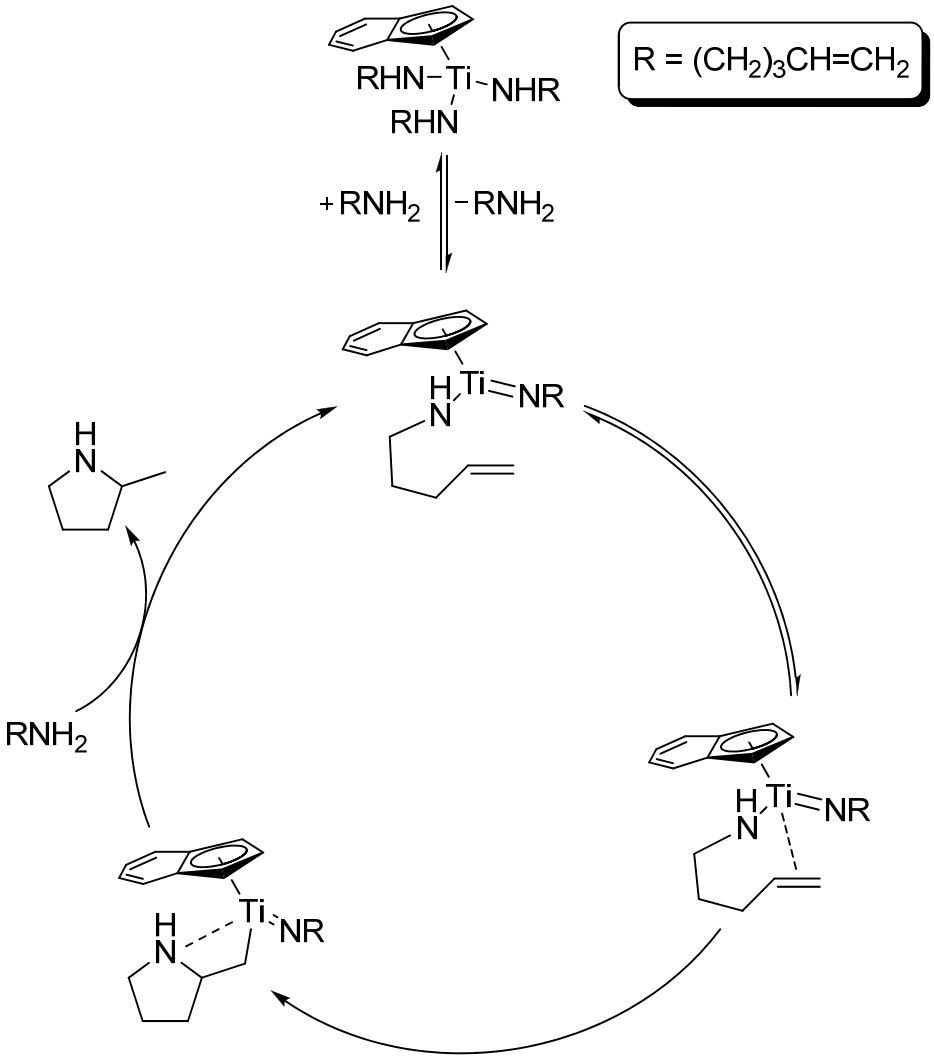
Der postulierte Mechanismus (Schema **4**) war angelehnt an den 1993 von Bergman vorgeschlagenen Mechanismus für die katalytische Hydroaminierung von Alkinen.[29] Für diesen Mechanismus sprachen die von Bergman beobachteten Zirkonocen-Azametallacyclobutankomplexe.[30] Allerdings muss beachtet werden, dass die Cycloaddition reversibel und das Cycloadditionsprodukt nur in Anwesenheit von überschüssigem Alken stabil ist.[31,32] Des Weiteren gilt, in Analogie zum Mechanismus von Alkinen, dass der Katalysator bei Ausbildung eines Imido-Komplexes im Gleichgewicht mit dem entsprechenden Dimer sowie dem bis-Amido-Komplex vorliegen sollte. Das Dimer sowie der bis-Amido-Komplex sind für die Hydroaminierung inaktiv. Bei der Entwicklung von allgemein anwendbaren Titankatalysatoren zur Hydroaminierung von Alkinen wurde durch Verwendung von sterisch anspruchsvollen Ligandensystemen die Dimerisierung bzw. die bis-Amid-Bildung unterdrückt.[33] Aufgrund der fehlenden sterischen Hinderung bei aktiven Titankomplexen zur Hydroaminierung von Alkenen zieht man daher einen weiteren Mechanismus in Betracht (Schema **5**).[34]



Schema 5 Von Marks postulierter Mechanismus für die Zr-katalysierte Hydroaminierung von Alkenen.

Der in Schema **5** dargestellte Mechanismus beschreibt eine 1,2-Insertion, gefolgt von einer Protonierung der erhaltenen Metall-Alkyl Verbindung. Er steht wie der Mechanismus für kationische Gruppe IV Metallkomplexe in Analogie zu dem Mechanismus für Seltenerdmetallkomplexe. Start- und Ausgangspunkt ist ein Metall-Amido-Komplex. Dadurch könnten auch die kürzlich gefunden Ergebnisse erklärt werden, in denen Gruppe IV Metallkomplexe ebenfalls die intramolekulare Hydroaminierung von sekundären Aminen katalysieren.[35]

Computerunterstützte Rechnungen, basierend auf der Dichtefunktional-Theorie (DFT) zur intramolekularen Hydroaminierung von Alkenen mit dem neutralen Katalysator Ind_2TiMe_2, weisen als katalytisch aktive Spezies auf einen Titan-Imido-Amido-Komplex hin.[36] Einerseits kann dieser Komplex wie in Schema **4** gezeigt eine energetisch begünstigte [2 + 2]-Cycloaddition durchlaufen. Andererseits ist auch eine energetisch höher liegende Insertion der C-C Doppelbindung in eine Ti-N-Einfachbindung möglich (Schema **6**).



Schema 6 Von Doye postulierter Mechanismus für die Hydroaminierung von Alkenen unter Verwendung von neutralen Gruppe IV Metallkomplexen.

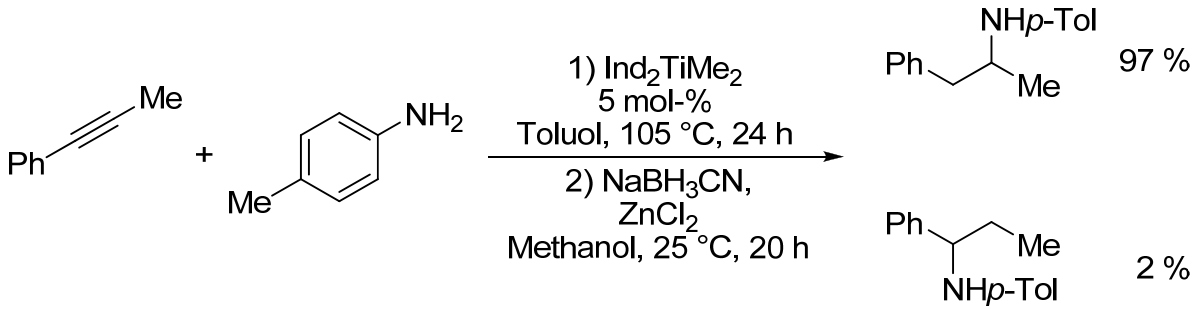
Aufgrund der geringen Energiedifferenz zwischen dem in Schema **4** und in Schema **6** gezeigten Mechanismus bleibt die Frage nach dem genauen Ablauf der Reaktion offen. Der in Schema **5** dargestellte Mechanismus, in dem keine Metall-

Imido Spezies gebildet wird, scheint jedoch aus energetischer Sicht für die titankatalysierte Hydroaminierung von Alkenen sehr unwahrscheinlich.

Die Grenze zwischen den verschiedenen Mechanismen scheint jedoch bei der Verwendung von Gruppe IV Metallkatalysatoren zu verwischen. Dies zeigen die kürzlich gefundenen Ergebnisse zur intramolekularen Hydroaminierung von sekundären Aminen. Die Reaktionen verliefen unter Verwendung von Ind_2TiMe_2 mit geringen Ausbeuten (13 %)[35], oder es mussten drastische Reaktionsbedingungen (150 °C, 5 Tage) unter Verwendung des $Zr(NMe_2)_4$ Katalysators eingesetzt werden.[37] Dennoch sind diese Ergebnisse ein klares Zeichen über einen alternativ ablaufenden Reaktionsmechanismus, falls der in Schema **6** gezeigte Mechanismus nicht durchlaufen werden kann.

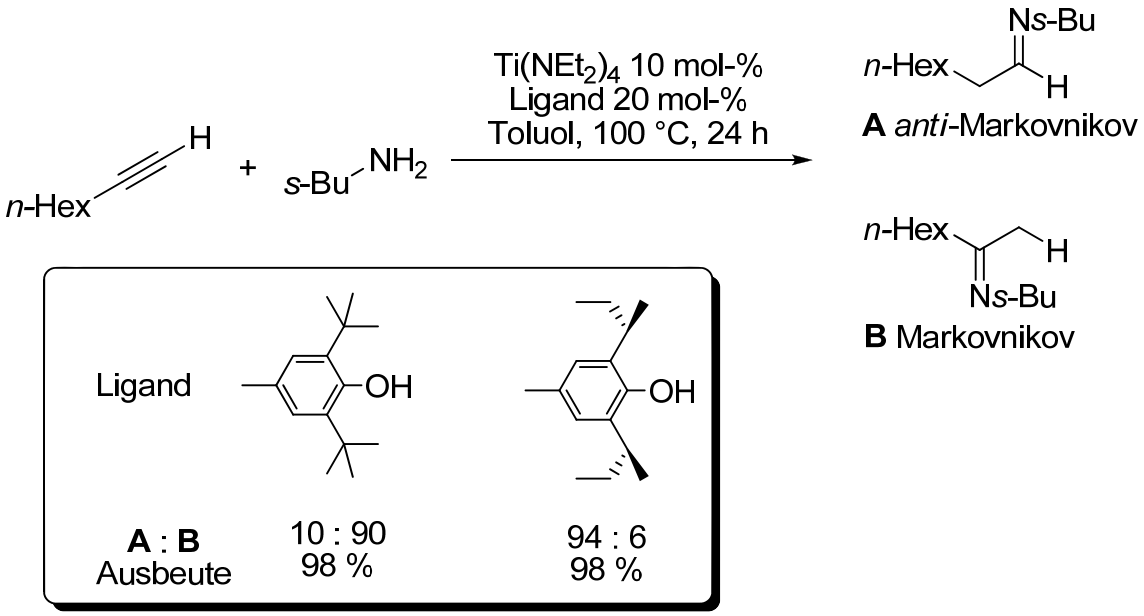
1.2 Die Hydroaminierung von Alkinen und deren Anwendung

Der Mechanismus der Hydroaminierung von Alkinen von Gruppe IV Metallkomplexen wurde intensiv untersucht und aufgeklärt.[11,31,32,29,30,38,39,40,41] Für die katalytische Addition von 4-Methylanilin an 1-Phenylpropin unter Verwendung von Cp_2TiMe_2 ließ sich 2001 ein [2 + 2]-Cycloadditionsmechanismus nachweisen.[42] Einen weiteren Fortschritt stellte die Identifizierung des generell anwendbaren Katalysators Ind_2TiMe_2 dar.[33] Die mit diesem Katalysator durchgeführten Hydroaminierungen von primären Aryl-, tertiären Alkyl-, sekundären Alkyl- sowie *n*-Alkylaminen mit internen und terminalen Alkinen liefern hohe Ausbeuten. Im Falle von 1-Phenyl-2-alkylalkinen wird in moderater bis exzellenter Regioselektivität das anti-Markovnikov Produkt gebildet (Schema **7**).



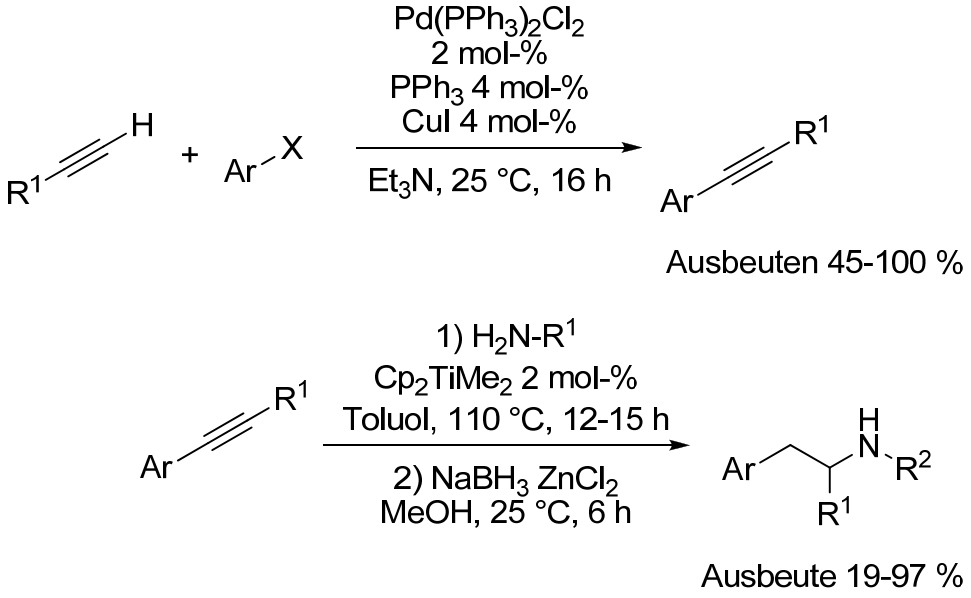
Schema 7 Ausgewähltes Beispiel für die hohe Regioselektivität der Hydroaminierung unter Verwendung von Ind_2TiMe_2.

Die Regioselektivität der Hydroaminierung mit Gruppe IV Metallkomplexen war jedoch nicht nur auf das anti-Markovnikov Produkt begrenzt. Neue Katalysatorsysteme mit Phenolatliganden bildeten selektiv das gewünschte Regioisomer bei der Hydroaminierung von terminalen Alkinen (Schema **8**).[43]



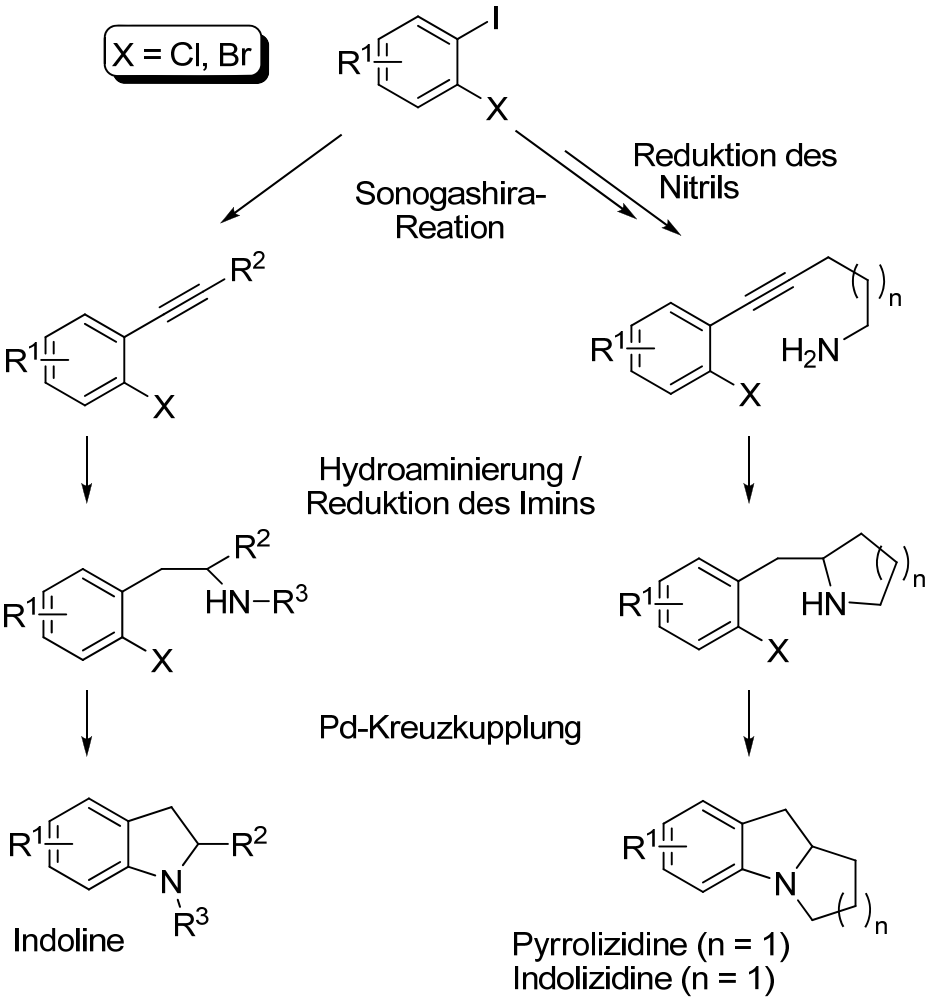
Schema 8 Ausgewähltes Beispiel für die Kontrolle der Regioselektivität bei der Titan-katalysierten Hydroaminierung von terminalen Alkinen.

Aufgrund des guten Verständnisses des Mechanismus und der hohen Substratbreite titankatalysierter Hydroaminierungen von Alkinen fand diese Methode breite Anwendung in der organischen Synthese. Diverse Phenylethylamine konnten mit Hilfe einer Kombination aus einer Sonogashira-Kreuzkupplung und einem Hydroaminerungs/Reduktions-Ein-Topf-Verfahren erhalten werden (Schema **9**).[44,45]



Schema 9 Syntheseroute zu Phenylethylaminen durch eine Sequenz aus Sonogashira-Kreuzkupplung, Hydroaminierung und Reduktion.

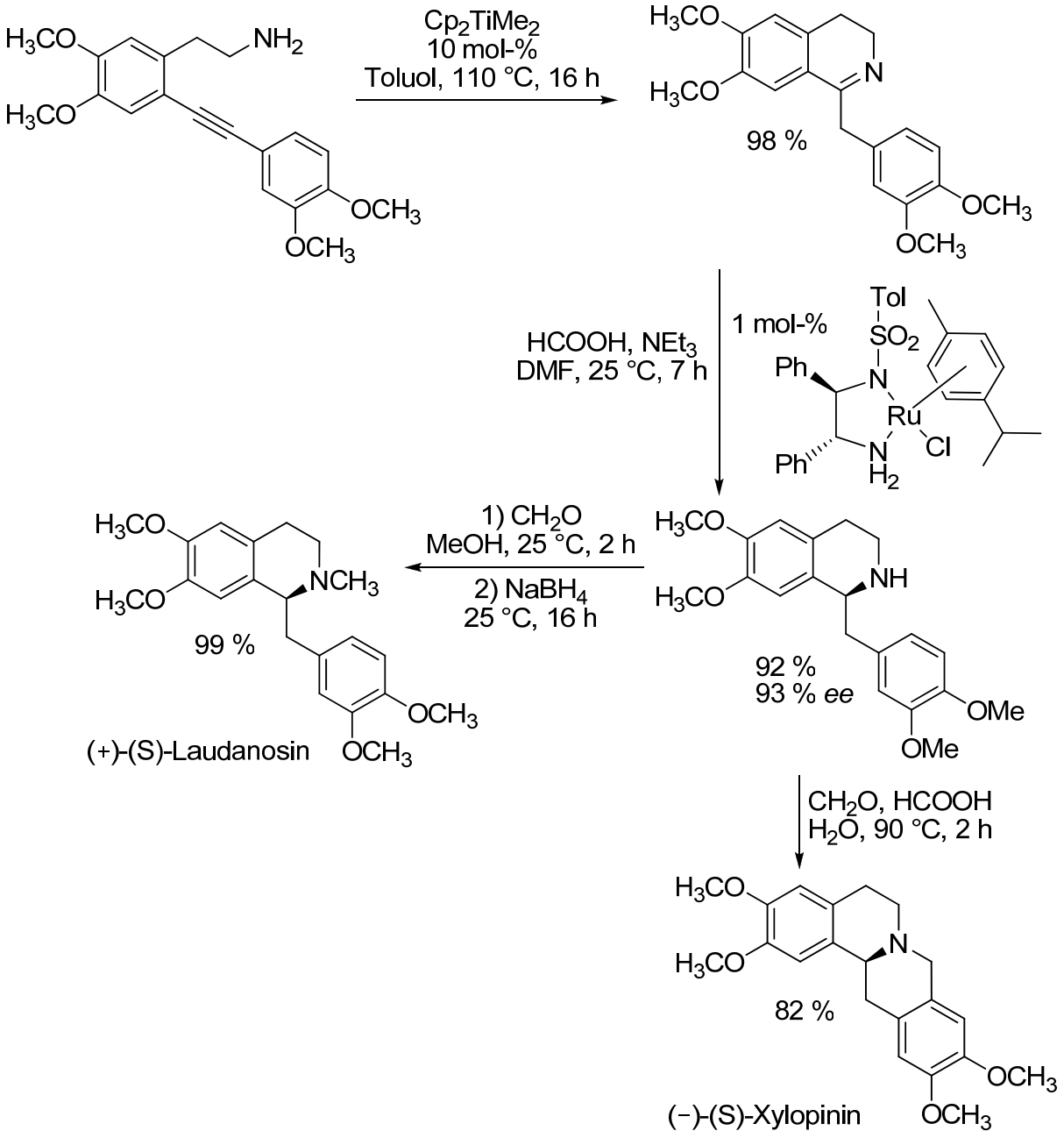
Da Arylchloride nicht in die Hydroaminierungsreaktionen eingreifen, erhielt man durch eine anschließende Kreuzkupplungsreaktion eine weitere Synthesemöglichkeit für Indolizidine, Pyrrolizidine und Indoline (Schema **10**).[46] Auch die Synthese von Indolen, Pyrrolen und Pyrrolidinen konnte durch die Hydroaminierung realisiert werden.[47,48,49]



Schema 10 Syntheseroute für Pyrrolizidine, Indolizidine und Indoline durch eine Hydroaminierungs/Kreuzkupplungs Sequenz.

Eine weitere und für die vorliegende Arbeit sehr wichtige Errungenschaft stellt die Synthese von Isochinolin-Derivaten mit Hilfe der Hydroaminierung dar. Der Aufbau des B-Rings wurde in den Arbeiten von Schafer noch durch eine Pictet-Spengler Reaktion erhalten.[50] Allerdings stellte Doye bereits 2002 eine völlig neue Synthesemöglichkeit von Isochinolinen vor,[51] die 2005 zur Synthese der Opium-Alkaloide (+)-(*S*)-Laudanosin und (−)-(*S*)-Xylopinin verwendet wurde (Schema **11**).[52]

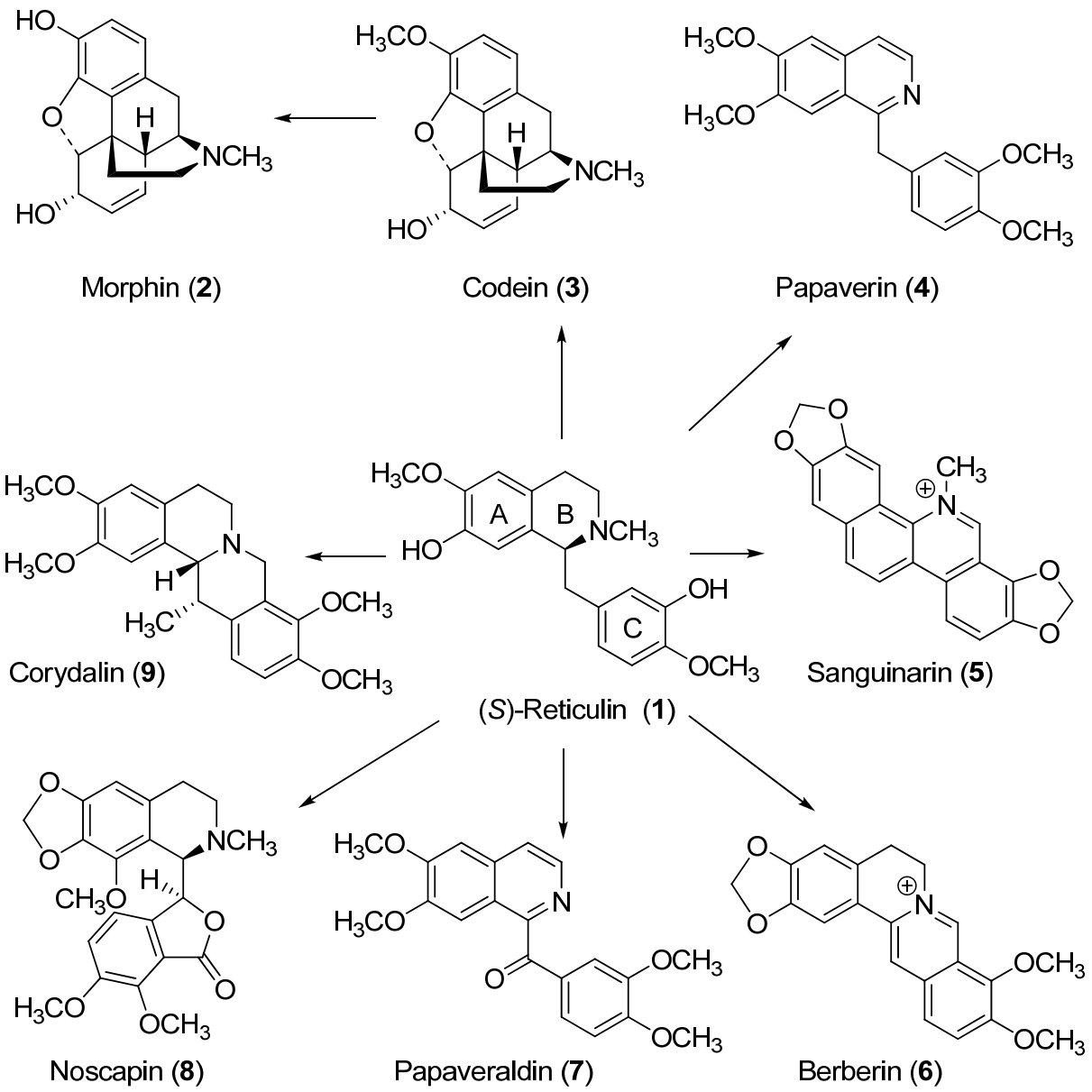
Die Synthese kombinierte eine Sonogashira-Reaktion mit anschließender intramolekularen Hydroaminierung und enantioselektiver Reduktion.



Schema 11 Synthese von (+)-(*S*)-Laudanosin und (−)-(*S*)-Xylopinin nach Doye.

1.3 1-Benzylisochinoline und 1-Benzyl-1,2,3,4-tetrahydroisochinoline in der Natur- und Wirkstoffchemie

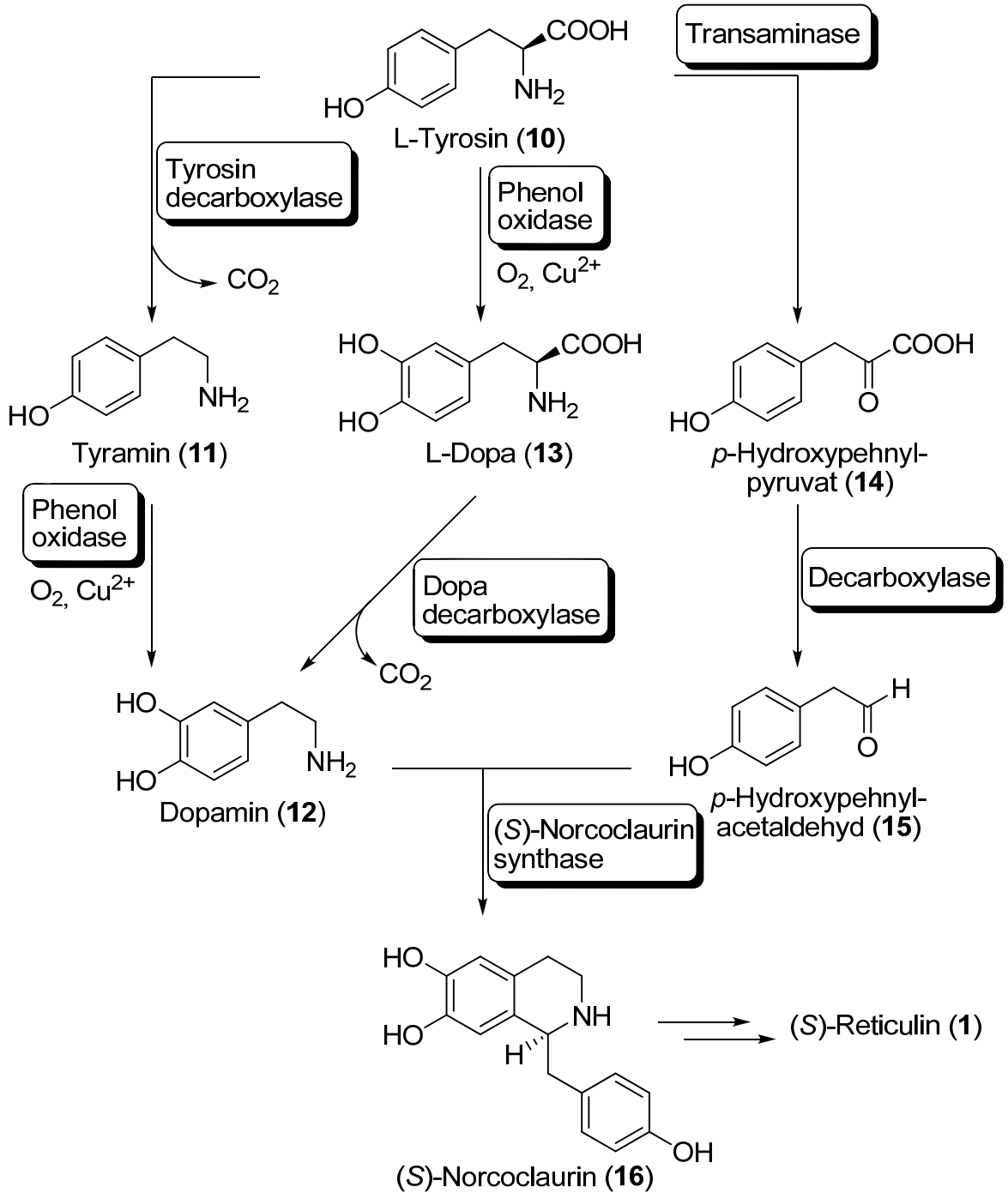
1-Benzylisochinolin (bzw. 1-Benzyl-1,2,3,4-tetrahydroisochinolin) stellt das Grundgerüst einer Untergruppe von Isochinolin-Alkaloiden dar. Alkaloide allgemein sind stickstoffhaltige, organische Verbindungen natürlicher Herkunft. Bisher sind mehr als 20.000 Naturstoffe überwiegend pflanzlicher, selten tierischer Herkunft bekannt.[2] Terpen- und Steroid-Alkaloide zeichnen sich durch ihr isoprenoides Kohlenstoffgrundgerüst aus. Zusätzlich besitzen sie einen eingebauten Heterocyclus oder eine Seitenkette mit Amino- oder Amido-Funktion. Acyclische Amine wie β-Phenylethylamine, Polyamin-Amide und spezielle Cyclopeptide werden als nicht heterocyclische Alkaloide bezeichnet. Eine weitere Gruppe enthält Heterocyclen und wird entsprechend in z.B. Pyridin-, Indol- und Isochinolin-Alkaloide eingeteilt. Die enthalten Ringe werden analog zu den Stereoiden mit A, B und C (bzw. D usw.) gekennzeichnet (siehe Schema **12**, Verbindung **1**). Die Wirkung, bereits geringer Mengen, auf den menschlichen Organismus kann vielfältig sein.[2] Das Spektrum reicht von beruhigender, gefäßerweiternder, krampflösender und schmerzbetäubender über anregende, gefäßverengende, euphorisierende bis hin zu halluzinogener Wirkung. Das wohl bekannteste der über 3000 verschiedenen Isochinolin-Alkaloide ist das analgetisch wirkende Morphin (**2**). Aufgrund der pharmakologischen Eigenschaften finden auch Codein (**3**) (Antitussivum), Papaverin (**4**) (Muskelrelaxanz) sowie Sanguinarin (**5**) und Berberin (**6**) (antimikrobielle Substanzen) Anwendung in der Medizin.[53] Hauptsächlich kommen Isochinolin-Alkaloide in Mohn- (Papaveraceae), Mondsamen- (Menispermaceae), Hahnenfuß- (Ranunculaceae,) und Berberitzengewächsen (Berberidaceae) vor. [54]



Schema 12 Ausgewählte pharmazeutisch interessante 1-Benzylisochinoline die in der Natur aus (*S*)-Reticulin erhalten werden.

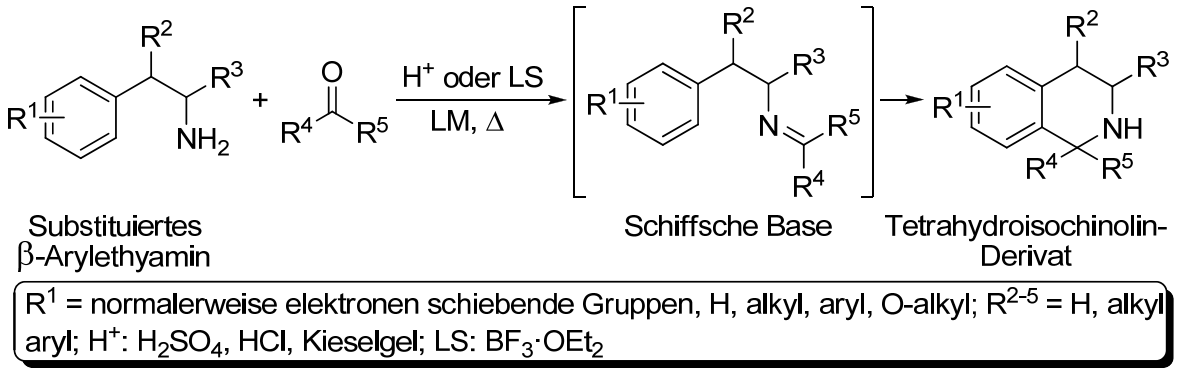
Ausgehend vom (*S*)-Reticulin (**1**) werden in der Natur verschiedene Isochinolin-Alkaloide mit bemerkenswerten Strukturunterschieden erhalten (Schema **12**). Die Synthese von 1-Benzylisochinolin-Alkaloiden in der Natur beginnt mit zwei Molekülen L-Tyrosin (**10**) (Schema **13**).[55] Eines wird entweder erst zum Tyramin (**11**) decarboxyliert und anschließend durch eine Phenoloxidase zu Dopamin (**12**) transformiert oder erst durch eine Phenoloxidase zu L-Dopa (**13**) und dann durch Decarboxylierung zu Dopamin (**12**) umgewandelt. Das zweite Molekül L-Tyrosin (**10**) wird durch eine Transaminase zu *p*-Hydroxyphenylpyruvat (**14**) oxidiert und anschließend durch Decarboxylierung in *p*-Hydroxyphenylacetaldehyd (**15**) umgewandelt. Als nächstes erfolgt die stereoselektive Kondensation zu (*S*)-

Norcoclaurin (**16**). Dieses wird durch weitere enzymkatalysierte Transformationen in (*S*)-Reticulin (**1**) umgewandelt.



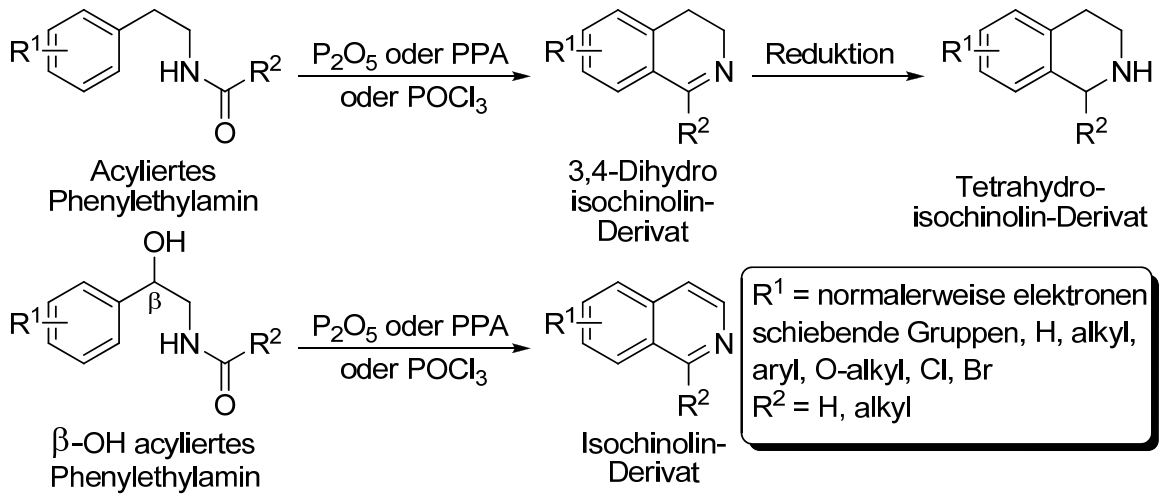
Schema 13 Biosynthese von (*S*)-Norcoclaurin (**16**).

Über den in Schema **13** gezeigten Kondensationsschritt zur Synthese von 1,2,3,4-Tetrahydroisochinolinen berichteten bereits 1911 Pictet und Spengler.[56] Die Umsetzung eines β-Arylethylamins mit einer Carbonylverbindung unter sauren Bedingungen wird daher als Pictet-Spengler-Reaktion bezeichnet (Schema **14**).[57]



Schema 14 Pictet-Spengler-Reaktion.

Nach Bildung der Schiffschen Base erfolgt eine Protonierung des Imins mit anschließender 6-endo-trig Cyclisierung. Durch spätere Deprotonierung wird das 1,2,3,4-Tetrahydroisochinolin Derivat erhalten. Neben einer Protonen- oder Lewis-Säure benötigt die Reaktion thermische Energie. Zu beachten ist, dass nur elektronenreiche β-Arylethylamine gute Ausbeuten liefern. Dies gilt auch für die Bischler-Napieralski-Reaktion, die klassische Synthese für 3,4-Dihydroisochinoline (Schema **15**).[58]

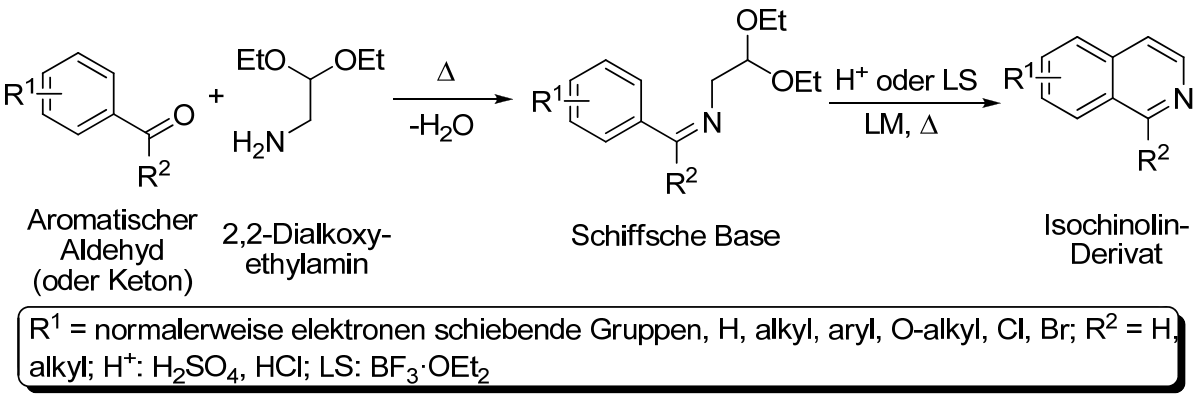


Schema 15 Bischler-Napieralski-Reaktion.

Wird ein acyliertes Phenylethylaminderivat mit dehydratisierenden Verbindungen wie $POCl_3$, P_2O_5, PPA (Polyphosphorsäure), TFAA (Trifluoressigsäureanhydrid) oder Tf_2O (Trifluormethansulfonsäureanhydrid) umgesetzt, so erfolgt eine Cyclisierungsreaktion. Das erhaltene 3,4-Dihydoisochinolin kann durch Reduktion der Imin-Funktion in die entsprechenden Tetrahydroisochinolin-Derivate überführt werden (Schema **15**, oben). Enthält die Startverbindung eine Hydroxygruppe in der β-Position zum N-Atom, so kommt es zu

einer weiteren Dehydratisierung und man erhält das entsprechende Isochinolin (Schema **15**, unten).[57]

Zur Synthese von Isochinolin-Derivaten ist noch eine weitere klassische Methode bekannt. Unabhängig voneinander berichteten Pomeranz und Fritsch 1893 von der Umsetzung eines Benzaldehyd-Derivates mit einem 2,2-Dialkoxyethylamin (Schema **16**).[59,60]



Schema 16 Pommeranz-Fritsch-Reaktion.

Unter Erwärmung erfolgt eine Dehydratisierung und die entstandene Schiffsche Base kann unter Protonen- oder Lewis-sauren Bedingungen in der Wärme cyclisieren. Anschließend erfolgt durch eine Eliminierungsreaktion die Aromatisierung zum gewünschten Isochinolin-Derivat. Allerdings wird auch hier ein elektronenreicher Aromat benötigt.[57]

Diese vorgestellten traditionellen Methoden wurden im letzten Jahrhundert optimiert so dass z.B. die Pictet-Spengler-Reaktion nun auch asymmetrisch durchgeführt werden kann.[61] Dennoch ist die Substratbreite aufgrund der benötigten elektronenschiebenden Gruppen am A-Ring eingeschränkt.

Wie bereits oben erwähnt, sind die Anwendungen von Naturstoffen mit 1-Benzylisochinolinmotiv in der Medizin sehr vielfältig. Diese lassen sich in vielen Fällen durch Wechselwirkungen mit Dopamin-Rezeptoren im menschlichen Körper erklären. Ursprünglich teilte man Dopamin-Rezeptoren in zwei Gruppen (D_1 und D_2) ein. Diese unterschieden sich durch ihre Pharmakologie sowie ihr Bindungsverhalten an Adenylylcyclasen (an die Zellmembran gebundene Enzyme) und den daraus resultierenden unterschiedlichen Signalweg.[62,63] Durch Fortschritte in der molekularen Biologie (Klonen der Rezeptoren) konnten die Dopamin-Rezeptoren besser klassifiziert werden. Aufgrund der entsprechenden Aminosäurensequenzen

und pharmakologischer Eigenschaften unterscheidet man gegenwärtig fünf Dopamin-Rezeptoren (D_1 bis D_5). Diese werden in zwei Hauptklassen eingeteilt, D_1-ähnlich (D_1 und D_5) sowie D_2-ähnlich (D_2, D_3 und D_4). Dopamin stellt einen wichtigen Neurotransmitter im Nervensystem von Säugetieren dar. Nervenzellen, in denen Dopamin vorkommt, bezeichnet man als dopaminerge Neuronen. Im Zentralnervensystem ist Dopamin an der Kontrolle des extrapyramidalmotorischen Systems (Steuerung der Bewegung), dem emotionalen Empfinden, wesentlichen kognitiven Funktionen, neuroendokrinen Ausschüttungen (Hormonhaushalt) sowie dem Abhängigkeitsverhalten maßgeblich beteiligt.[64] Im vegetativen Nervensystem werden lebenswichtige Funktionen wie Blutdruck und Verdauung (u.a. Vitalfunktionen) durch Dopamin beeinflusst.[65,66]

Rezeptoren und Rezeptor-Agonisten funktionieren nach dem Schlüssel-Schloss-Prinzip. Daher ist die Form des agonistischen Systems ausschlaggebend für die Selektivität. Aufgrund der hohen Flexibilität bezüglich seiner räumlichen Anordnung, kann Dopamin viele Konformationen einnehmen (Abbildung **2**).[64]

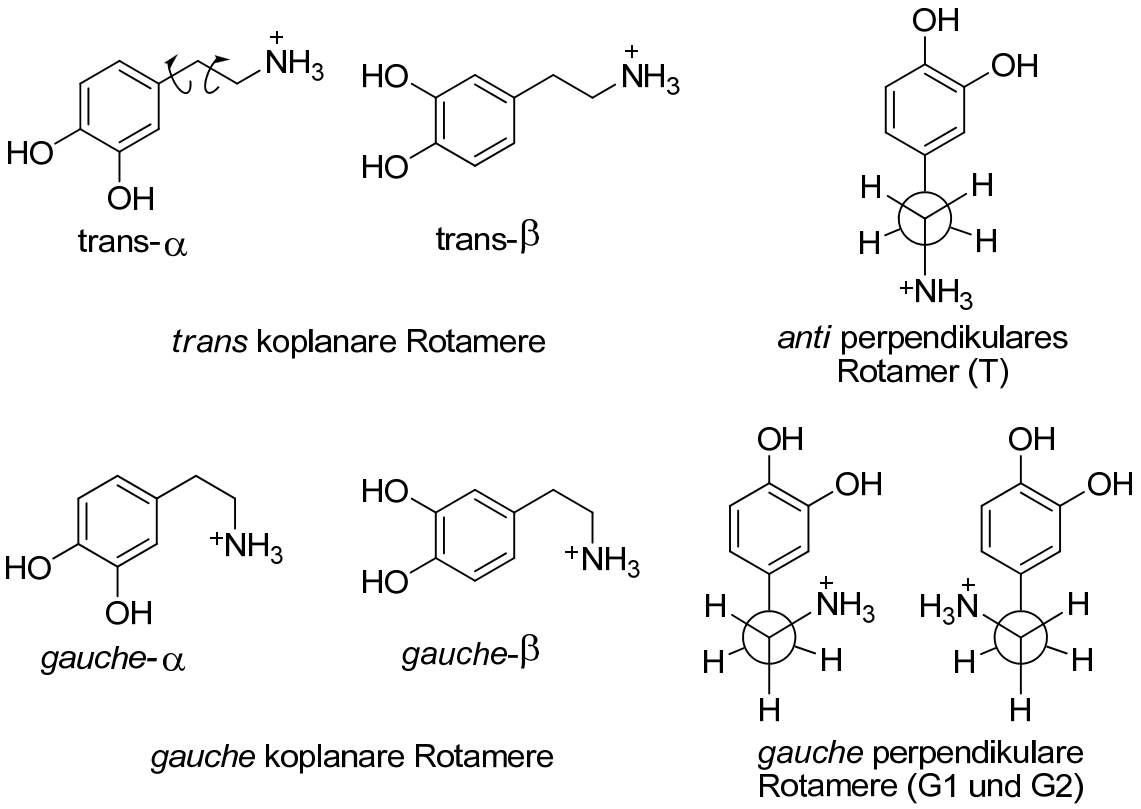
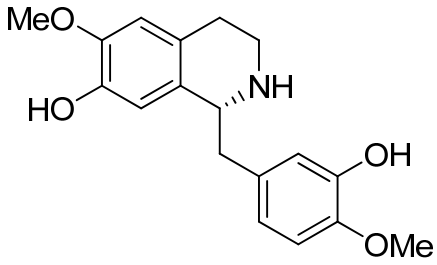


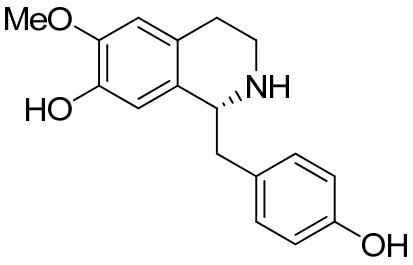
Abbildung 2 Mögliche Konformatinen des *N*-protonierten Dopamins.

Mit Hilfe theoretischer Untersuchungen ließen sich für physiologische Bedingungen (pH = 7.4, wässriges Milieu) drei Konformationen identifizieren, die im Gleichgewicht miteinander stehen. Diese sind eine *anti*- (**T**) und zwei *gauche*- (**G1** und **G2**) Konformationen. Einige Berechnungen durch *ab initio* Methoden weisen auf eine höhere Konzentration des *gauche*-Konformeren hin. NMR Experimente in D_2O zeigten jedoch eine Verschiebung des Gleichgewichts zugunsten des *anti*-Isomers (**T)** bei Erhöhung des pH-Werts. Aufgrund dieser hohen Flexibilität ist eine einfache Ableitung des Pharmakophors, also der Eigenschaften des pharmakologisch wirkenden Molekülabschnitts, nicht möglich. Daher erfolgt die Identifizierung von Pharmakophoren hauptsächlich durch computerunterstützte quantitative Struktur-Wirkungs-Beziehungen (Quantitative Structure-Activity Relationship: QSAR). Die Ergebnisse der QSAR werden z.B. durch vergleichende molekulare Feldanalysen (Comparative Molecular Field Analysis: CoMFA) ausgewertet. Die daraus resultierenden Leitstrukturen bilden die Grundlage für die Entwicklung eines Arzneistoffkandidaten.[64]

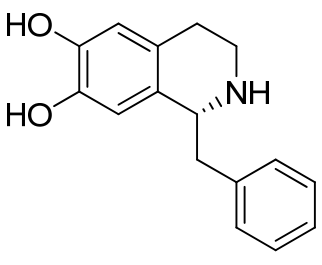
Eine Vielzahl von neurologischen Erkrankungen (z.B. Parkinson, Chorea Huntington sowie das Tourette-Syndrom), Störungen des Sucht- und Empfindungsverhaltens sowie psychische Störungen (z.B. Schizophrenie) stehen im direkten Zusammenhang mit Dopamin-Rezeptoren. Daher ist verständlich, dass dieses Gebiet in den letzten drei Jahrzehnten zu den am intensivsten untersuchten Forschungsgebieten der Pharmakologie zählt. So wurden verschiedene Isochinolin-Derivate identifiziert, die bereits im mikro- bis nanomolaren Bereich an Dopamin-Rezeptoren binden (Abbildung **3**).[64]



(*S*)-Reticuline (**1**)
$K_i(D_1)$ = 1.04 µM
$K_i(D_2)$ = 0.33 µM



(*R*)-Coclaurine (**17**)
$K_i(D_1)$ = 0.14 µM
$K_i(D_2)$ = 92.8 µM

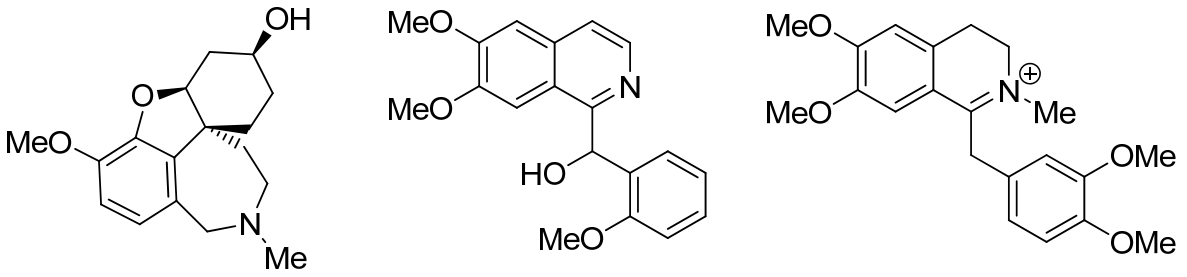


6,7-diOH-BTHIQ (**18**)
$K_i(D_1)$ = 9.27 µM
$K_i(D_2)$ = 0.64 µM

Abbildung 3 Ausgewählte Isochinolin-Derivate mit hohem Bindungspotential an Dopamin Rezeptoren.

Dabei deuten niedrige K_i-Werte auf eine großes inhibitorisches Potenzial hin.[65] Am Beispiel von (*R*)-Coclaurine (**17**) erkennt man die gewünschte Differenzierung der angesprochenen Rezeptoren (Vergleich $K_i(D_1)$ zu $K_i(D_2)$) am besten. Im Idealfall spricht der entsprechende Wirkstoff selektiv nur den Zielrezeptor an und vermeidet so das Auftreten von Nebenwirkungen.

Wie gering teilweise die Strukturunterschiede und die daraus resultierende pharmakologische Wirkung von Isochinolin-Derivaten sind, zeigen die beiden folgenden Beispiele: Das Alzheimer-Leiden ist ein schwerwiegendes gesundheitliches Problem besonders für ältere Menschen. Hierfür verantwortlich erscheint unter anderem ein cholinergisches Defizit (Acetylcholinmangel) im Gehirn. Um die Konzentration zu erhöhen werden Inhibitoren der Acetylcholinesterase (AChE) verwendet. AChE ist ein Enzym, das für den metabolischen Abbau von Acetylcholin verantwortlich ist. Ein bekannter Inhibitor ist Galanthamin (**19**), allerdings stellen auch verschiedene Isochinolin-Derivate potentielle Acetylcholinesterase Inhibitoren dar (Abbildung **4**).[67]



Galanthamin (**19**) IC_{50} = 0.59 µM

20 IC_{50} = 6.94 µM

21 IC_{50} = 5.50 µM

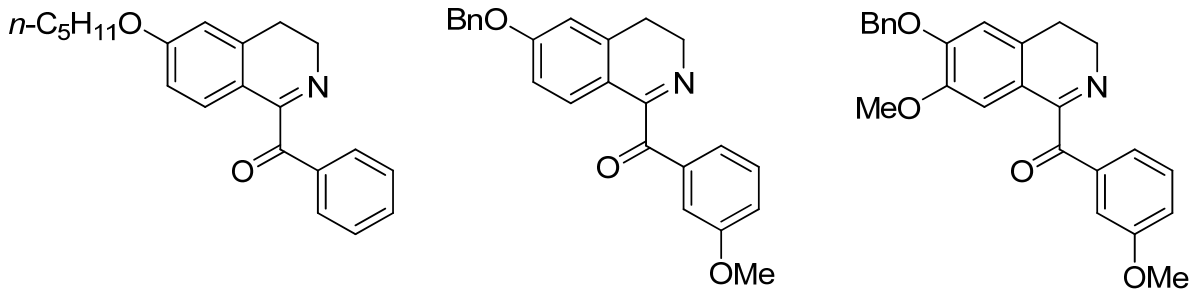
Abbildung 4 Ausgewählte AChE Inhibitoren.

Der IC_{50} Wert bezeichnet die Konzentration, bei der eine halbmaximale Inhibition des Rezeptors beobachtet wird und gibt somit Aufschluss über die Wirkaktivität des Antagonisten. Daher zeigen die Verbindungen **20** und **21** zwar Potential als AChE Inhibitoren, sind jedoch aufgrund der hohen IC_{50} Werte ungeeignet.

Andere 1-Benzylisochinolin-Derivate wurden aufgrund ihrer zelltoxischen Wirkung als Zytostatika untersucht. So zeigt Berberin (**6**) bereits bei einer Konzentration von 10 µg/mL eine vollständige Eliminierung von *Leishmania major*.

Dies ist eine Unterart der Leishmanien, einzelligen Lebewesen, die bei Mensch und Tier die Infektionskrankeit Leishmaniose auslösen.[68]

1-Benzoyldihydroisochinolin-Derivate hingegen zeigen eine hohe Aktivität bei *in vitro* Experimenten gegen Leukämie L 1210 Zelllinien. Eine eukaryotische Zelle durchläuft im Zellzyklus zwei Phasen. Zum einen die Interphase (Zwischenphase vor und nach der Kernteilung) und die Mitose (Kernteilung). Die Zwischenphase ist wiederum in G_1-, S- und G_2-Phase unterteilt. In der G_1-Phase agieren verschiedene komplexe Signale, die entscheidend für die Weiterentwicklung der Zelle sind. Eine Fehlfunktion in diesem Teilabschnitt des Zellzyklus ist ein kritischer Moment für Tumorigenese und Tumorentwicklung. Hier setzt nun die pharmakologische Wirkung von 1-Benzoyldihydroisochinolin-Derivaten ein. Die Zellen werden in der G_1-Phase eingeschlossen und es kommt somit zum Zelltot (Apoptose). Abbildung **5** zeigt anhand der geringen IC_{50} Werte das große Potential von 1-Benzoyldihydroisochinolin-Derivaten als neue Zytostatika in der Krebstherapie.[69]



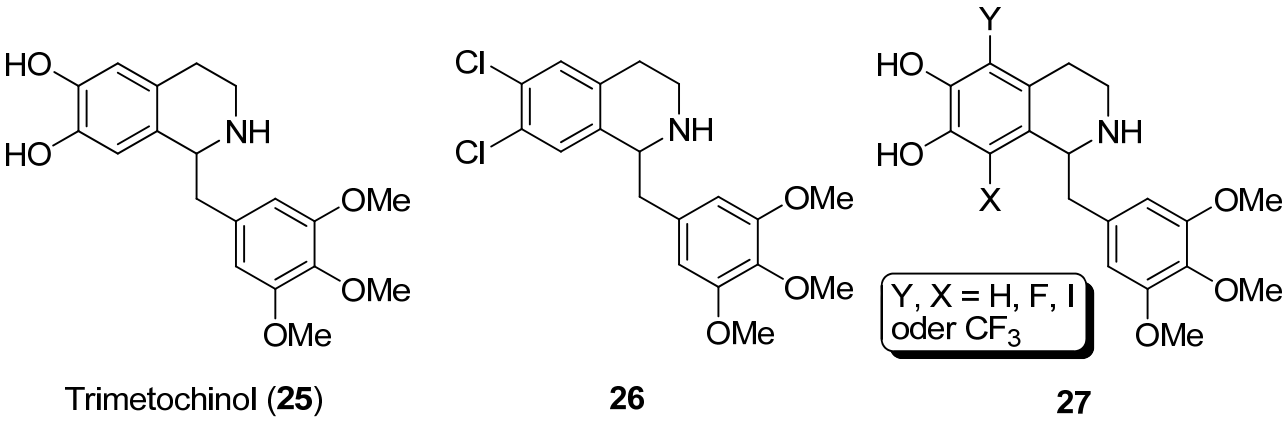
22 IC_{50} = 1.00 µM

23 IC_{50} = 1.40 µM

24 IC_{50} = 2.50 µM

Abbildung 5 Ausgewählte 1-Benzoyldihydroisochinolin-Derivate mit zytostatischer Wirkung.

Abschließend sollten auch die Modifikationsversuche an 6,7-Dihydroxy-1-(3,4,5-trimethoxybenzyl)-1,2,3,4-tetrahydroisochinolin (Trimetochinol **25**) erwähnt werden. Trimetochinol ist ein β-Adrenozeptor Agonist. Adrenerge Rezeptoren spielen eine Schlüsselrolle für die Vermittlung der Wirkung des vegetativen Nervensystems. Mitte der 1980er Jahre wurde versucht durch Austausch der Hydroxygruppen mit Chloratomen einen β-Adrenozeptor Antagonisten zu erhalten (Abbildung **6**). Allerdings war die Aktivität bzw. die blockierende Wirkung relativ gering.[70]



Trimetochinol (**25**) **26** **27**

Abbildung 6 Trimetochinol und seine Derivate.

Anfang der 1990er Jahre versuchte man durch Einführung von Fluor-, Iod- oder Trifluormethylsubstituenten (X und Y kann H, F, I, CF_3 sein) am A-Ring eine Steigerung der Aktivität gegenüber Trimetochinol (**25**) zu erhalten (Abbildung **6**). Jedoch zeigten die neu synthetisierten Verbindungen keine höhere Aktivität als der eigentliche Transmitter.[71]

2. Aufgabenstellung

2.1 Untersuchung neuer Titankatalysatoren zur intramolekularen Hydroaminierung von Alkenen

Im Gegensatz zur Hydroaminierung von Alkinen ist der genaue Mechanismus für die Hydroaminierung von Alkenen noch immer unbekannt. Bisher fehlen aktive Katalysatorsysteme, welche sich ohne weitere Modifikationen für mechanistische Untersuchungen eignen. Des Weiteren ist die Suche nach effizienten und generell einsetzbaren Gruppe IV Katalysatoren ein intensiv untersuchtes Forschungsgebiet. Im Rahmen der vorliegenden Arbeit sollten verschiedene Titankatalysatoren der Arbeitsgruppe Beckhaus auf ihr Potential zur intramolekularen Hydroaminierung getestet und mit bereits bekannten Systemen verglichen werden. Ein Schwerpunkt lag dabei auf einer Vergrößerung der Substratbreite bezüglich der eingesetzten Aminoalkene.

2.2 Synthese von 1-Benzylisochinolin-Derivaten mit elektronenarmem A-Ring

Ausgehend von der bereits erwähnten Synthese von (+)-(*S*)-Laudanosin unter Verwendung einer intramolekularen Hydroaminierung sollten in dieser Arbeit Derivate von (±)-Norlaudanosin mit neutralem oder elektronenarmem A-Ring synthetisiert werden. Aufgrund der angestrebten Testung auf biologische Aktivität sollte auch die elektronische Situation am C-Ring verändert werden. Die resultierenden 1-Benzyltetrahydroisochinoline würden sich durch einen neutralen oder elektronenarmen A-Ring und einen elektronenarmen bis elektronenreichen C-Ring auszeichnen. In diesem Zusammenhang sollten ebenfalls die entsprechenden 1-Benzoyl-dihydroisochinoline synthetisiert werden. Die erhaltenen Derivate könnten sich ebenfalls durch eine potenziell biologische Aktivität als Zytostatika auszeichnen. Ein weiteres Ziel stellte die Optimierung des Syntheseweges dar, um somit einen einfachen und schnellen Zugang zu den benötigten Diarylnitriloalkinen mit gleich bleibender Flexibilität bezüglich der Substituenten zu erhalten.

3. Ergebnisse und Diskussion

3.1 Anwendung von Titankatalysatoren zur intramolekularen Hydroaminierung von Alkenen

Von C. Müller wurden im Rahmen seiner Dissertation verschiedene Titankomplexe (Abbildung **7**) der Arbeitsgruppen Beckhaus und Doye sowie der kommerziell erhältliche homoleptische Tetrakis(dimethylamino)titan (**I**) getestet. Diese Arbeit zeigte bereits, dass sich die verwendeten Titankatalysatoren **I**, **IV** und **VI** für die intramolekulare Hydroaminierung von Alkenen eignen. Im Rahmen dieser Arbeit wurden weitere Titankomplexe der Arbeitsgruppe Beckhaus (**V**, **VII** und **VIII**) als Hydroaminierungskatalysatoren getestet und mit den bereits bekannten Verbindungen (**I**, **IV** und **VI**) verglichen (Abbildung **7**).

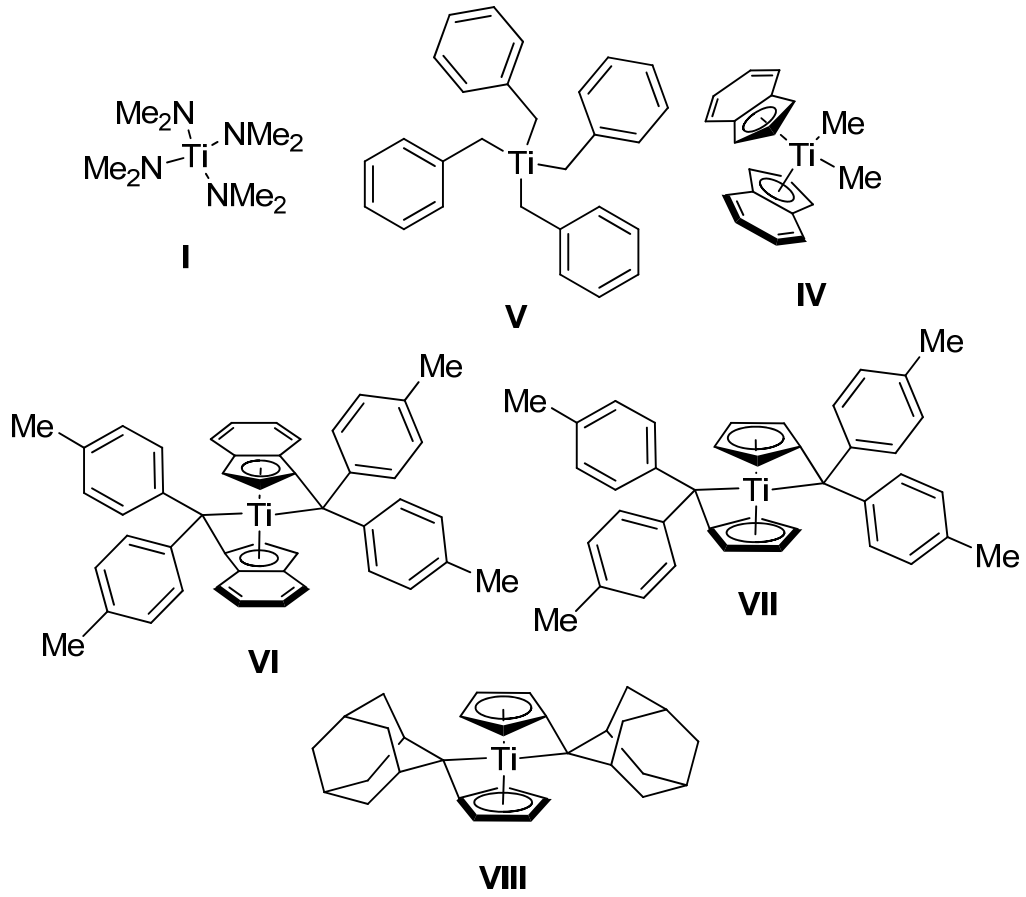
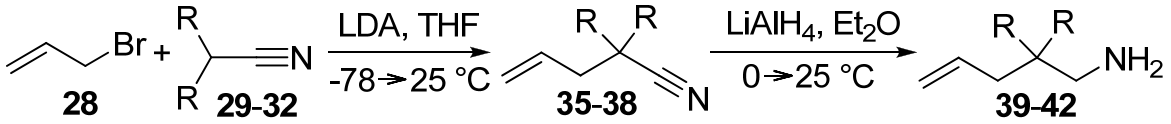


Abbildung 7 Strukturen der getesteten Titankatalysatoren.

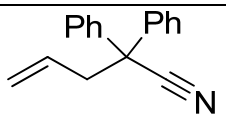
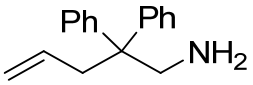
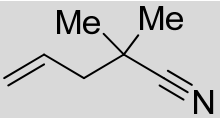
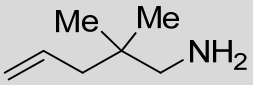
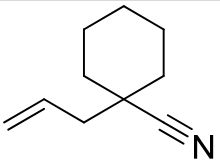
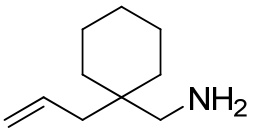
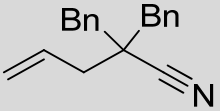
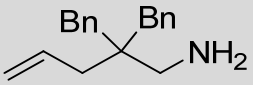
Um eine qualifiziertere Aussage über die Unterschiede der Titankatalysatoren **I** bis **VIII** treffen zu können, wurde die Substratbreite erweitert. Hierzu wurden diverse

1-Amino-4-pentene synthetisiert, die in der 2-Position unterschiedliche Substituenten tragen (Tabelle **1**).

Tabelle 1 Darstellung der Aminoalkene als Startmaterialien für die intramolekularen Hydroaminierungen zu 2-Metyhlpyrrolidin-Derivaten.



28 **29-32** **35-38** **39-42**

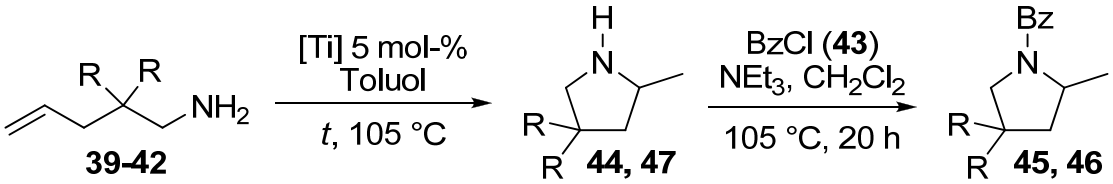
Nr.	Nitril	Ausbeute [%][a]	Aminoalken	Ausbeute [%][b]
1	 **35**	91	 **39**	86
2	 **36**	66	 **40**	90
3	 **37**	69	 **41**	52
4	 **38**[c]	80	 **42**	86

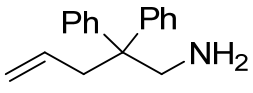
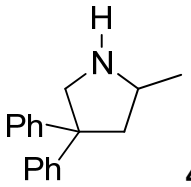
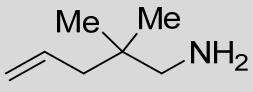
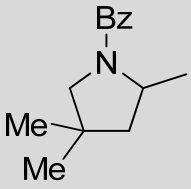
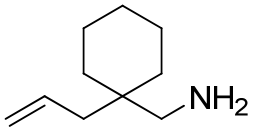
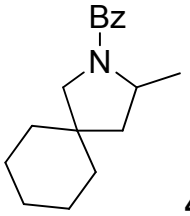
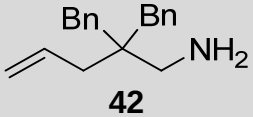
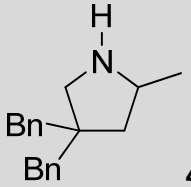
[a] Reaktionsbedingungen: Nitril (**29**-**32**, 1 eq), LDA (1.0 eq), Allylbromid (**28**) (2 eq), THF, −78 °C bis 25 °C, 16 h; Isolierte Ausbeuten (bei mehrmaliger Durchführung gemittelt); [b] Reaktionsbedingungen: Nitril (**35**-**38**, 1 eq), $LiAlH_4$ (1.5 eq), Et_2O, 0 °C bis 25 °C, 16 h; Isolierte Ausbeuten (bei mehrmaliger Durchführung gemittelt) [c] Startmaterial aus einer S_N-Reaktion von 3-Phenylpropannitril (**33**) und Benzylchlorid (**34**) synthetisiert.

Nach Deprotonierung des Nitrils in der α-Position mit Lithiumdiisopropylamid (LDA) erfolgt der nukleophile Angriff am Allylbromid (**28**). Die so erhaltenen Nitriloalkene (**35**-**38**) wurden in moderaten (66 %) bis sehr guten (91 %) Ausbeuten nach wässriger Aufarbeitung und Destillation erhalten. Die anschließenden Reduktionen mit Lithiumaluminiumhydrid ($LiAlH_4$) lieferten nach wässriger Aufarbeitung und Destillation (**40**, **41**) bzw. Säulenchromaographie (**39**, **42**) die gewünschten 2,2-disubstituierten Aminopent-4-ene (52-80 %).

Die Verbindungen **39** bis **41** sind bereits als Testsubstrate zur Bestimmung der katalytischen Aktivität von verschiedenen Metallkomplexen für intramolekulare Hydroaminierung von Alkenen etabliert.[21,20,72,37,73] Durch die räumlich anspruchsvollen Phenylliganden an der 2-Position ist Verbindung **39** stark Thorpe-Ingold aktiviert. Die daraus resultierende Vorordnung der Pentenylkette bringt die Amin- und Alkenfunktion in räumliche Nähe und erhöht dadurch die Reaktionsgeschwindigkeit.[74] Die Einwirkung der Titankatalysatoren auf Verbindung **39** gibt daher zunächst einmal Aufschluss über die generelle Fähigkeit zur intramolekularen Hydroaminierung (Tabelle **2**). Eine genauere Differenzierung der Aktivität lieferten die Umsetzungen mit den Aminen **40** und **41**. Diese sind geringer Thorpe-Ingold aktiviert, müssen jedoch nach der Hydroaminierung weiter transformiert werden, um Ausbeuteverluste im Laufe der Aufarbeitung zu vermeiden. Hierfür wurden die erhaltenen Amine mit Benzoylchlorid (**43**) geschützt. Einerseits wurde dadurch der Siedepunkt drastisch erhöht, andererseits konnten die erhaltenen benzoylgeschützten Hydroaminierungsprodukte säulenchromatographisch isoliert werden. Um die Einführung einer Schutzgruppe zu vermeiden wurde ein disubstituiertes Aminopent-4-ene mit geringer Thorpe-Ingold-Aktivität und hohem Siedepunkt gesucht. Dafür schien Verbindung **42** geeignet. Die räumlich anspruchsvollen Substituenten sind nicht direkt an die 2-Position gebunden, sodass man nur von einer geringen Aktivierung durch die Methylengruppen ausging. Diese Überlegung erwies sich jedoch als falsch, da alle getesteten Katalysatoren bei der Umsetzung der Verbindung **42** bereits nach 24 h gute Ausbeuten lieferten (58-94 %). Aus diesem Grund wurde die Auswirkung einer Verlängerung der Reaktionsdauer von 24 h auf 96 h nur bei der Hydroaminierung der Amine **40** und **41** untersucht.

Tabelle 2 Intramolekulare Hydroaminierungen zur Bildung von 2-Metyhlpyrrolidinderivaten.



Nr.	Edukt	Produkt	*t* [h]	[Ti]	Ausbeute[%][a]
1	 **39**	 **44**	24	**I**	92 (0)
2				**V**	91 (0)
3				**IV**	87 (0)
4				**VI**	88 (0)
5				**VII**	87 (0)
6				**VIII**	73 (0)
7	 **40**	 **45**	24	**I**	31 (21)
8				**V**	36 (34)
9				**IV**	34 (63)
10				**VI**	18 (38)
11				**VII**	0 (97)
12				**VIII**	0 (97)
13			96	**I**	59 (4)
14				**V**	49 (9)
15				**IV**	59 (9)
16				**VI**	31 (9)
17				**VII**	<5 (87)
18				**VIII**	0 (96)
19	 **41**	 **46**	24	**I**	88 (0)
20				**V**	73 (23)
21				**IV**	77 (13)
22				**VI**	70 (4)
23				**VII**	0 (97)
24				**VIII**	0 (98)
25			96	**I**	93 (0)
26				**V**	90 (8)
27				**IV**	98 (0)
28				**VI**	89 (0)
29				**VII**	0 (93)
30				**VIII**	0 (90)
31	 **42**	 **47**	24	**I**	86 (0)
32				**V**	92 (0)
33				**IV**	94 (0)
34				**VI**	93 (0)
35				**VII**	61 (30)
36				**VIII**	58 (32)

[a] Reaktionsbedingungen: Aminoalken (2.40 mmol), Katalysator (0.12 mmol, 5 mol-%), Toluol (2 mL), 105 °C, 24 bzw. 96 h; Isolierte Ausbeuten (bei mehrmaliger Durchführung gemittelt), in Klammern ist die Menge an isoliertem Edukt bzw. Bz-geschütztem Edukt angegeben.

Die erhaltenen Ausbeuten zeigen, dass alle Katalysatoren bei der Reaktion mit Amino-2,2-diphenylpent-4-en (Tabelle **2**, Nr. 1-6) eine deutliche Aktivität zur intramolekularen Hydroaminierung von Alkenen aufweisen. Bereits bei dieser Reaktion wurde jedoch ein Trend sichtbar, der sich bei der Untersuchung der Titankatalysatoren mit der Verbindung **42** deutlicher zeigt. So wird beim Einsatz der Titanpentafulvenkomplexe (**VII** und **VIII**) eine starke Abnahme in der Ausbeute des isolierten Produktes beobachtet. Die offensichtlich geringere Aktivität der Cp-tragenden Titanfulvenkomplexe (**VII** und **VIII**) zeigte sich deutlich beim Vergleich der Katalysatoren in der Reaktion mit den Aminoalkenen **40** und **41** (Tabelle **2**, Nr. 13-18 und 25-30). Hierbei konnte selbst nach 96 h kein nennenswerter Umsatz erziehlt werden. Der Vergleich zwischen den Titanverkatalysatoren **IV** und **VI** zeigt ebenfalls Unterschiede, obwohl beide ein Indenylligandensystem besitzen. Die isolierte Ausbeute war bei Verwendung des Katalysators Ind_2TiMe_2 (**IV**) höher. Beim Einsatz des Aminoalkens **40** lag nach 24 h die Ausbeute um 16 % und nach 96 h um 28 % höher (Tabelle **2**, Nr. 9,10 und 15,16). Der Vergleich des Titankatalysators **IV** mit den homoleptischen Titanverbindungen **I** und **V** zeigte, dass diese ähnlich effizient sind. Ein allgemeiner Trend kann jedoch nicht beobachtet werden.

Bei den Reaktionen mit dem Aminoalken **40** sind die teilweise hohen Verluste im Hinblick auf die Massenbilanz (geschütztes Produkt + geschütztes Edukt) überraschend (Diagramm **1**). Bei diesen Reaktionen ließen sich die Ergebnisse aus vorangegangen Versuchen in der Arbeitsgruppe Doye nicht reproduzieren.[21] Die Resultate im Hinblick auf die Umsetzung von **40** mit $Ti(NMe_2)_4$ (**I**) stimmen jedoch mit den Ergebnissen aus der Arbeitsgruppe Schafer überein.[20]

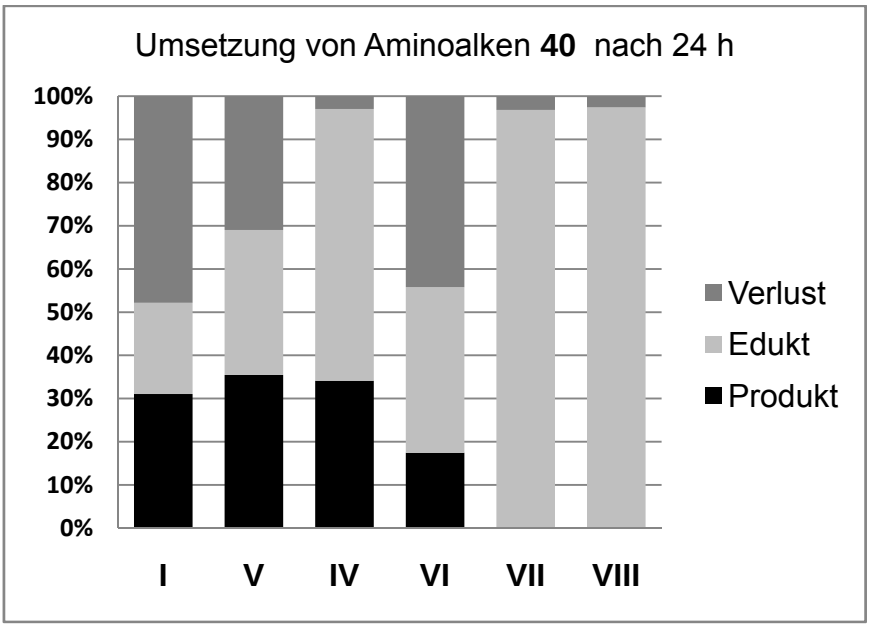
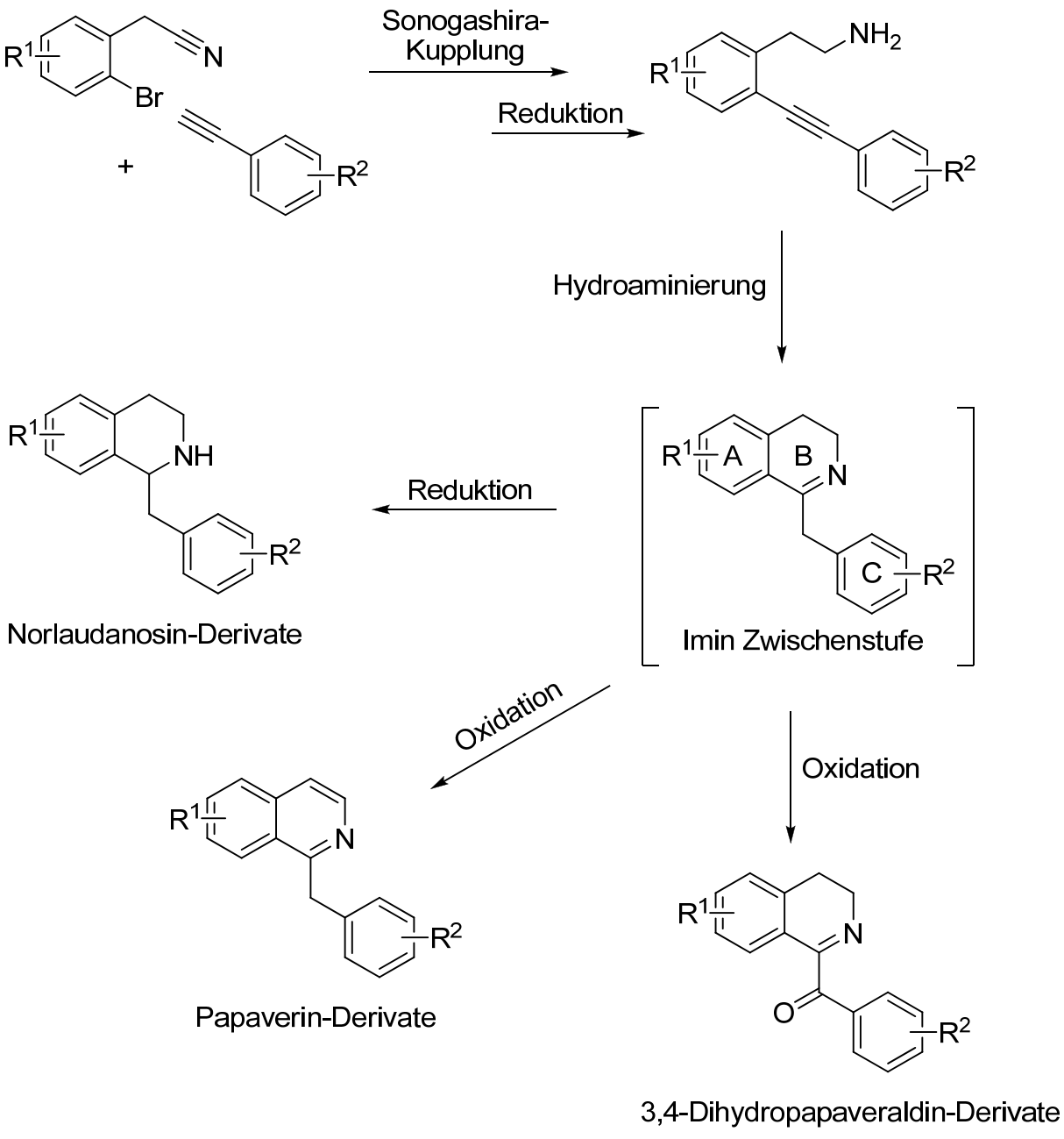


Diagramm 1 Umsetzung von Aminoalken **40** mit verschiedenen Katalysatoren nach 24 h.

Die geringen Ausbeuten könnten auf unerwünschte Nebenreaktionen wie z.B. Polymerisation zurückgeführt werden. Durch Blindversuche ohne Zugabe eines Katalysators mit anschließender Isolierung des Bz-geschützten Aminoalkens **40** (Ausbeuten > 95 %) kann ein präparativer Fehler ausgeschlossen werden. Hierfür sprechen ebenfalls die befriedigenden Massenbilanzen aus den Reaktionen unter Verwendung der Katalysatoren **VII** und **VIII** (Tabelle **2**, Nr. 11-12). In diesen Reaktionen wird ebenfalls das nicht umgesetzte Bz-geschützte Aminoalken **40** in sehr hohen Ausbeuten isoliert (Diagramm **1**).

3.2 Synthese von 1-Benzylisochinolin-Derivaten

Ein Zugang zu (−)-(*S*)-Xylopinin und (+)-(*S*)-Laudanosin sowie zwei weiteren Laudanosin-Derivaten, ausgehend von einem Benzylnitril und einem Arylalkin, wurde von D. Mujahidin vorgestellt (Schema **17**).[52,75] Die erhaltene Imin Zwischenstufe öffnet jedoch nicht nur einen Zugang zu Norlaudanosin-Derivaten.



Schema 17 Syntheseweg und mögliche Transformation der Imin Zwischenstufe.

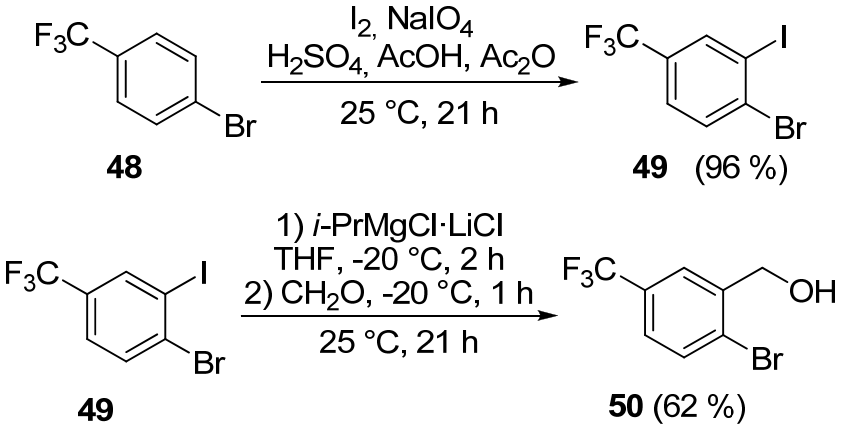
Neben der Reduktion sollte das aus der Hydroaminierung erhaltenen 1-Benzy-3,4-dihydroisochinolin (Imin-Zwischenstufe) durch Oxidation direkt in Papaverin- bzw. 3,4-Dihydropapaveraldin-Derivate überführt werden.

Das Substitutionsmuster am A-Ring (R^1) erstreckt sich dabei über neutrale bis elektronenziehende und am C-Ring (R^2) von elektronenschiebenden über neutrale bis zu elektronenziehenden Substituenten. Die benötigten Bisarylaminoalkine sollten durch eine Sonogashira-Kupplung eines Benzylnitrils mit einem Arylalkin und anschließender Reduktion erhalten werden können (Schema **17**).[75]

3.2.1 Synthese der benötigten Startmaterialien

3.2.1.1 Synthese der benötigten Benzylnitrile

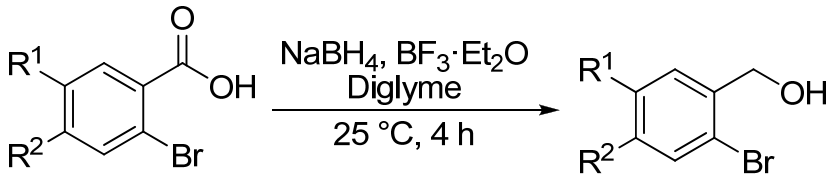
Die Synthese der 1-Benzylisochinoline startet bei den entsprechenden Aryl-Derivaten, die später den A-Ring verkörpern. Durch regioselektive Iodierung von kommerziell erhältlichem 4-Bromtrifluortoluol (**48**) konnte unter oxidativen Bedingungen die Verbindung **49** in sehr guter Ausbeute (96 %) erhalten werden (Schema **18**).[76] Es folgte ein selektiver I/Mg-Austausch unter Verwendung von Knochel's Reagenz (*i*-PrMgCl·LiCl in THF) und anschließende direkte Umsetzung mit monomerem Formaldehyd zum entsprechenden Benzylalkohol **50**.[77,78,79,80]



Schema 18 Synthese des Benzylalkohols **50**.

Die Startmaterialien für die mono- und difluorierten Derivate waren die kommerziell erhältlichen aromatischen Carbonsäuren **51** und **52** (Schema **19**). Durch Reduktion mit $NaBH_4$ in Gegenwart von $BF_3{\cdot}Et_2O$ wurden die entsprechenden Benzylalkohole **53** und **54** erhalten.[81] Diese Reaktion wurde anfangs unter

Verwendung von $LiAlH_4$ durchgeführt.[75] Durch die neu gewählten Bedingungen konnte die Ausbeute an **54** von 59 % (mit $LiAlH_4$) auf 77 % gesteigert werden.

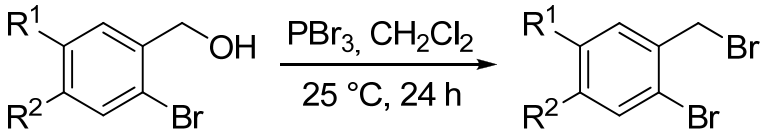


51: R^1 = F, R^2 = H
52: R^1 = F, R^2 = F

53: R^1 = F, R^2 = H (73 %)
54: R^1 = F, R^2 = F (77 %)

Schema 19 Synthese der elektronenarmen Bennzylalkohole **53** und **54**.

Die erhaltenen Benzylalkohole **50**, **53** und **54** wurden in die elektronenarmen Dibromide **55**, **56** und **57** überführt (Schema **20**). Die Reaktion verlief mit Hilfe von PBr_3 in CH_2Cl_2 in sehr guten Ausbeuten (79-94 %).

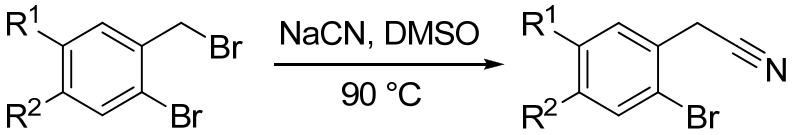


50: R^1 = CF_3, R^2 = H
53: R^1 = F, R^2 = H
54: R^1 = F, R^2 = F

55: R^1 = CF_3, R^2 = H (79 %)
56: R^1 = F, R^2 = H (87 %)
57: R^1 = F, R^2 = F (94 %)

Schema 20 Synthese der elektronenarmen Dibromide **55**, **56**, **57**.

Bei der anschließenden Umsetzung zu den elektronenarmen Benzylnitrilen **58**, **59** und **60** wurden unter Verwendung der ursprünglichen Methode, Natriumcyanid in heißem Dimethylsulfoxid, lediglich gute Ausbeuten erreicht (Schema **21**).



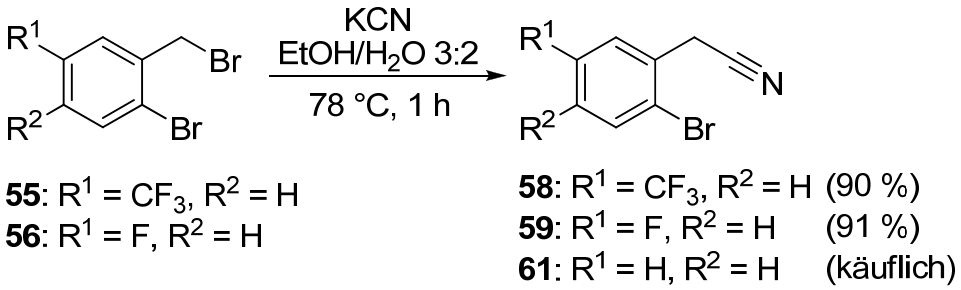
55: R^1 = CF_3, R^2 = H
56: R^1 = F, R^2 = H
57: R^1 = F, R^2 = F

58: R^1 = CF_3, R^2 = H (61 %)
59: R^1 = F, R^2 = H (60 %)
60: R^1 = F, R^2 = F (58 %)

Schema 21 Synthese der elektronenarmen Benzylnitrile durch Reaktion mit NaCN in DMSO.

Durch die Verwendung von Kaliumcyanid in einem Ethanol/Wasser Gemisch konnten die Ausbeuten an **58** und **59** um über 30 % gesteigert werden (Schema

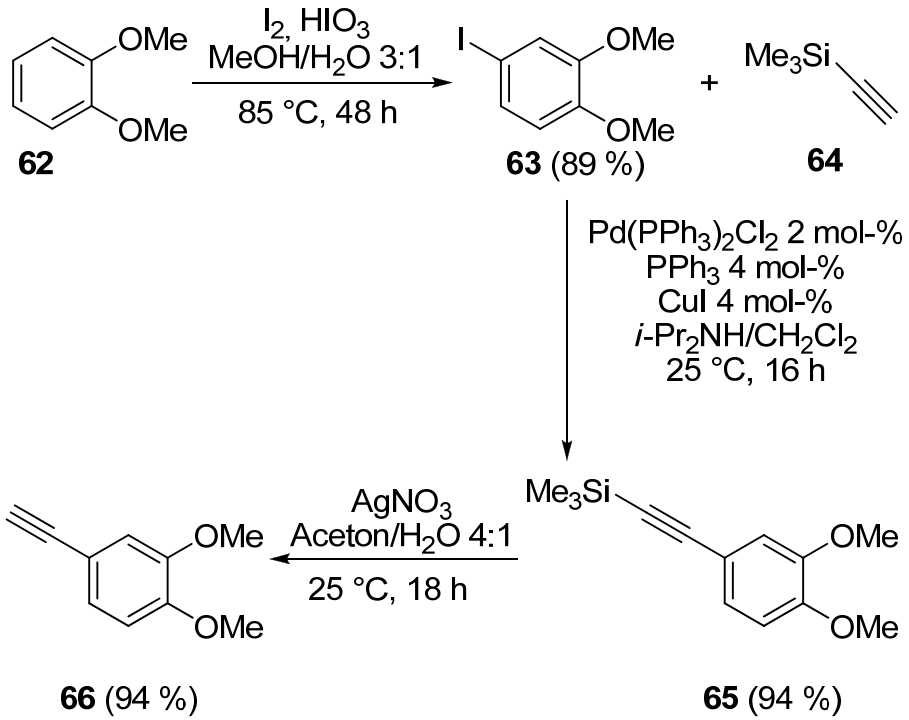
22).[82] Auf die Optimierung der Synthese von Verbindung **60** wurde verzichtet. Aufgrund der hohen Kosten der Diflurbenzoesäure und des ähnlichen chemischen Verhaltens zur Monofluorverbindung wurde nur ein Arylakin mit der Difluorverbindung umgesetzt (siehe Abschnitt 3.2.1.3). Anstelle der Verbindung **60** wurde die kommerziell erhältliche, unsubstituierte Verbindung **61** ($R^1 = R^2 = H$) in die Synthese aufgenommen. Dadurch standen ein neutrales (**61**) und zwei elektronenarme Benzylnitrile (**58** und **59**) zur Verfügung, die später die elektronische Situation am A-Ring des Isochinolin-Derivats bestimmten.



Schema 22 Synthese der elektronenarmen Benzylnitrile durch Kaliumcyanid in Ethanol/Wasser.

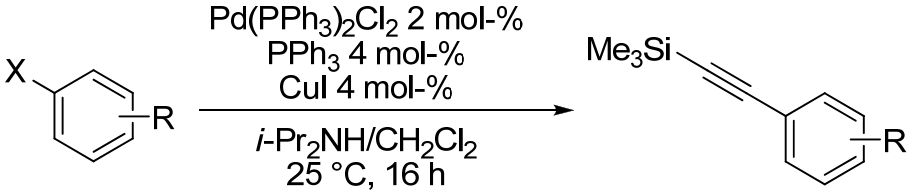
3.2.1.2 Synthese der benötigten Arylalkine

Vorrangig war die Synthese von elektronenarmen Norlaudanosin-Derivaten. Die Synthese des benötigten 4-Ethynyl-1,2-dimethoxybenzols (**66**) begann mit der Iodierung von Veratrol (**62**) (Schema **23**). Die modifizierte Königstein-Prozedur verläuft unter Verwendung von Iod und Iodsäure in einem Methanol/Wasser Gemisch in guten Ausbeuten.[83,84] Das erhaltene Iodveratrol (**63**) wurde anschließend in einer Sonogashira-Kupplung mit Trimethylsilylacetylen (**64**) umgesetzt.[75,52] Nach Entfernung der Acetylenschutzgruppe durch Silbernitrat in einem Aceton/Wasser Gemisch, wurde das gewünschte Arylalkin (**66**) erhalten.[85] Die Gesamtausbeute des Arylalkins **66** über alle drei Reaktionsschritte zusammen beträgt somit 79 %.



Schema 23 Synthese des Arylalkins **66**.

Die oben dargestellte Syntheseroute (Schema **23**) sollte auf weitere Arylhalogenide übertragen werden (Schema **24**).

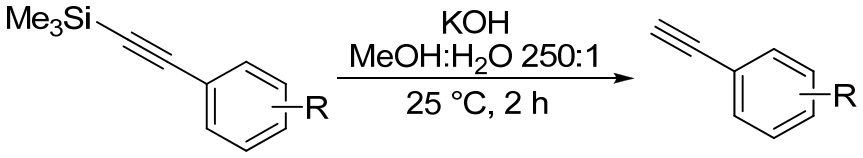


67 X = I, R = *p*-Me	**75** R = *p*-Me (98 %)
68 X = I, R = *p*-CF_3	**76** R = *p*-CF_3 (95 %)
69 X = Br, R = *p*-F	**77** R = *p*-F[a] (98 %)
70 X = I, R = *p*-Cl	**78** R = *p*-Cl (93 %)
71 X = I, R = *p*-OMe	**79** R = *p*-OMe (97 %)
72 X = I, R = *o*-Me	**80** R = *o*-Me (96 %)
73 X = I, R = *o*-CF_3	**81** R = *o*-CF_3 (97 %)
74 X = I, R = *o*-OMe	**82** R = *p*-OMe (97 %)

Schema 24 Synthese der einfach substituierten, geschützten Arylalkine. [a] Geänderte Reaktionsbedingungen: LM: *i*-Pr_2NH/Toluol, T = 80 °C.

Im Falle der *para*-fluorsubstituierten Verbindung **77** wurde für die Sonogashira-Kupplung Toluol anstelle von Dichlormethan als Lösungsmittel verwendet. Grund für diesen Wechsel waren die veränderten Reaktionsbedingungen der Sonogashira-Kupplung unter Verwendung von Arylbromiden. Anstelle der sonst

verwendeten Iodide wurde 1-Brom-4-fluorbenzol (**69**) eingesetzt. In diesem Fall musste die Reaktionslösung der Sonogashira-Kupplung auf 80 °C erwärmt werden. Die anschließende Freilegung der terminalen Acetylengruppe wurde unter Verwendung von KOH in MeOH/H_2O (250:1) erreicht (Schema **25**).[86] Diese Methode lieferte akzeptable (50 %) bis sehr gute (94 %) Ausbeuten. Aufgrund der kostengünstigen Base ist diese Methode der Entschützung durch Silbernitrat vorzuziehen.



75 R = *p*-Me
76 R = *p*-CF_3
77 R = *p*-F
78 R = *p*-Cl
79 R = *p*-OMe
80 R = *o*-Me
81 R = *o*-CF_3
82 R = *o*-OMe

83 R = *p*-Me (80 %)
84 R = *p*-CF_3 (65 %)
85 R = *p*-F (55 %)
86 R = *p*-Cl (54 %)
87 R = *p*-OMe (86 %)
88 R = *o*-Me (94 %)
89 R = *o*-CF_3 (74 %)
90 R = *p*-OMe (50 %)

Schema 25 Synthese der einfach substituierten Arylalkine.

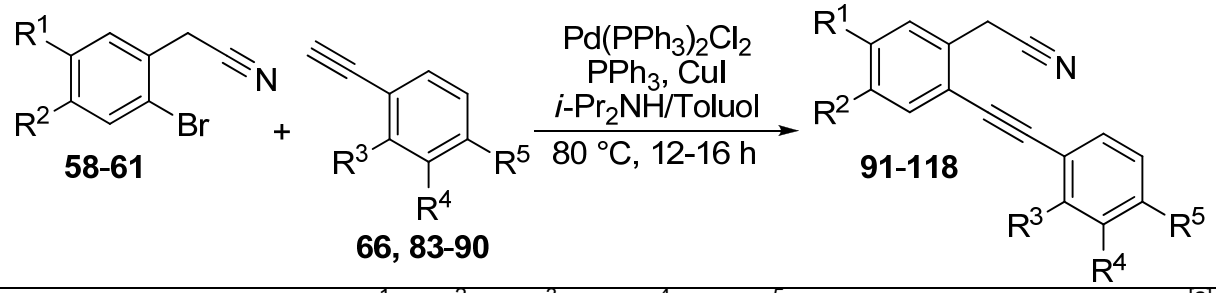
Der Grund für die teilweise niedrigen Ausbeuten war die hohe Flüchtigkeit einiger Verbindungen. Obwohl im GC eine vollständige Umsetzung zum gewünschten Arylalkin beobachtet wurde und die Siedepunkte relativ hoch sind (> 100 °C), konnten die entschützten Verbindungen teilweise nur mit akzeptabler Ausbeute (50 %) erhalten werden.

Eine mögliche und einfache Lösung dieses Problem lag im Verzicht der Isolierung des freien Arylalkins. Die Ergebnisse und die daraus resultierende Entwicklung einer Ein-Topf-Synthese der benötigten Hydroaminierungsvorstufen wird in Abschnitt 3.2.5 (s.u.) behandelt.

3.2.1.3 Synthese der benötigten Bisarylaminoalkine

Mit Hilfe einer zweiten Sonogashira-Reaktion konnten die zuvor hergestellten Benzylnitrile und Arylalkine miteinander gekuppelt werden. Die anschließenden Reduktionen lieferten die entsprechenden Hydroaminierungsvorstufen (Tabelle **3**).

Tabelle 3 Darstellung der Bisarylnitriloalkine.



Nr.	Edukt 1	Edukt 2	R^1	R^2	R^3	R^4	R^5	Produkt	Ausbeute [%][a]
1	**61**	**66**	H	H	H	OMe	OMe	**91**	88
2		**83**	H	H	H	H	Me	**92**	71
3		**84**	H	H	H	H	CF_3	**93**	82
4		**85**	H	H	H	H	F	**94**	88
5		**86**	H	H	H	H	Cl	**95**	93
6		**87**	H	H	H	H	OMe	**96**	86
7		**88**	H	H	Me	H	H	**97**	92
8		**89**	H	H	CF_3	H	H	**98**	96
9		**90**	H	H	OMe	H	H	**99**	96
10	**58**	**66**	CF_3	H	H	OMe	OMe	**100**	96[b]
11		**83**	CF_3	H	H	H	Me	**101**	79
12		**84**	CF_3	H	H	H	CF_3	**102**	86
13		**85**	CF_3	H	H	H	F	**103**	79
14		**86**	CF_3	H	H	H	Cl	**104**	92
15		**87**	CF_3	H	H	H	OMe	**105**	88
16		**88**	CF_3	H	Me	H	H	**106**	95
17		**89**	CF_3	H	CF_3	H	H	**107**	88
18		**90**	CF_3	H	OMe	H	H	**108**	94
19	**59**	**66**	F	H	H	OMe	OMe	**109**	87[b]
20		**83**	F	H	H	H	Me	**110**	86
21		**84**	F	H	H	H	CF_3	**111**	73
22		**85**	F	H	H	H	F	**112**	95
23		**86**	F	H	H	H	Cl	**113**	93
24		**87**	F	H	H	H	OMe	**114**	80
25		**88**	F	H	Me	H	H	**115**	95
26		**89**	F	H	CF_3	H	H	**116**	89
27		**90**	F	H	OMe	H	H	**117**	91
28	**60**	**66**	F	F	H	OMe	OMe	**118**	79[b]

[a] Reaktionsbedingungen: Benzylnitril (1 eq), Arylalkin (1.1 eq), $Pd(PPh_3)_2Cl_2$ (2 mol-%), PPh_3 (4 mol-%), CuI (1 mol-%), *i*-Pr_2NH, Toluol, 80 °C, 16 h. Isolierte Ausbeute; [b] Reaktionsbedingungen: Benzylnitril (1 eq), Arylalkin (1.1 eq) $Pd(PPh_3)_2Cl_2$ (4 mol-%), PPh_3 (8 mol-%), CuI (8 mol-%), *i*-Pr_2NH, DMF, 80 °C, 16 h. Isolierte Ausbeute.

Die Ausbeuten der Bisarylnitriloalkine lagen in einem guten bis exzellenten Bereich (71 bis 96 %). Auch hier wurden die Bedingungen im Laufe der Synthese verändert. Die Menge des verwendeten Katalysatorsystems ($Pd(PPh_3)_2Cl_2$ + 2 PPh_3) wurde auf die Hälfte verringert (2 mol-%). Des Weiteren wurde anstelle von

Dimethylformamid (DMF) als Lösungsmittel Toluol verwendet und die Menge von CuI auf 1 mol-% reduziert. Alle Bisarylnitriloalkine wurden nach Säulenchromatographie als Feststoffe isoliert. Für Verbindung **109** (Tabelle **3**, Nr. 19) konnten zusätzlich geeignete Kristalle für die Röntgenkristallstrukturanalyse erhalten werden (Abbildung **8**). Das Bisarylnitriloalkin **109** kristallisierte aus *d*-Chloroform ($CDCl_3$) monoklin in der Raumgruppe $P2_1/c$ aus.

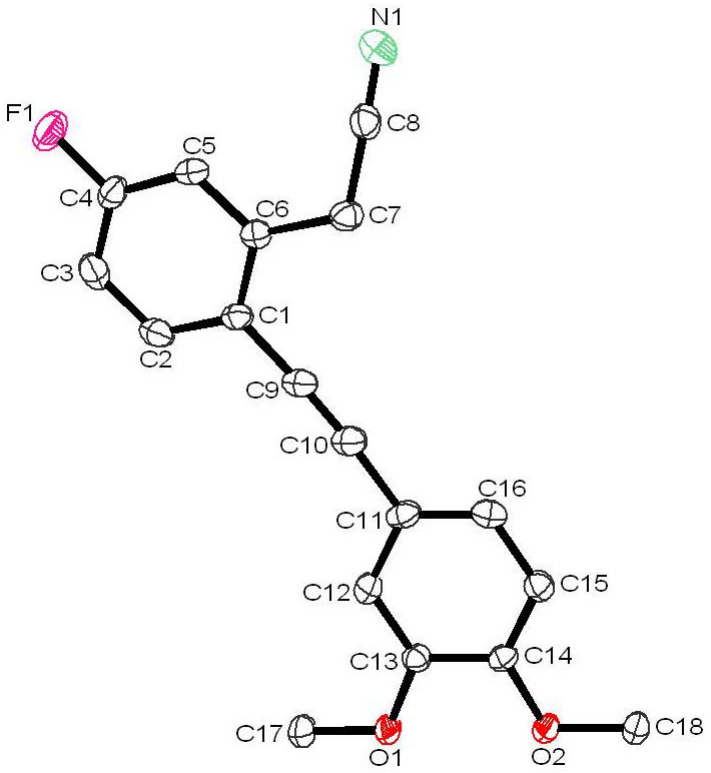
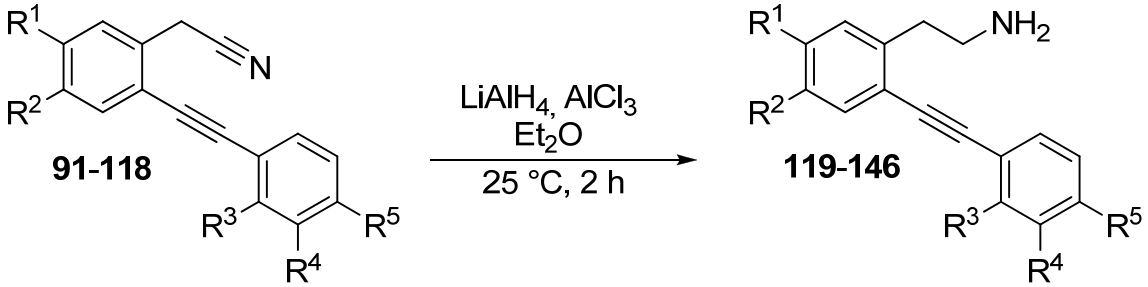


Abbildung 8 Molekülstruktur der Röntgenkristallstrukturanalyse des Bisarylnitriloalkins **109**.

Die anschließende Reduktion erfolgte durch eine Suspension aus Aluminiumtrichlorid ($AlCl_3$) und Lithiumaluminiumhydrid ($LiAlH_4$) in Diethylether. Die isolierten Bisarylaminoalkine wurden als Öle in guten bis exzellenten Ausbeuten (65 bis 96 %) erhalten (Tabelle **4**). Zur längeren Lagerung der Amine wurden diese in trockenem Diethylether gelöst und anschließend mit etherischer Salzsäure in die entsprechenden farblosen Hydrochloride überführt. Vor der nachfolgenden Hydroaminierung wurden die Ammoniumsalze durch Ausschütteln mit wässriger Kaliumhydroxidlösung und Dichlormethan in die entsprechenden Amine zurück überführt.

Tabelle 4 Darstellung der Hydroaminierungsvorstufen.

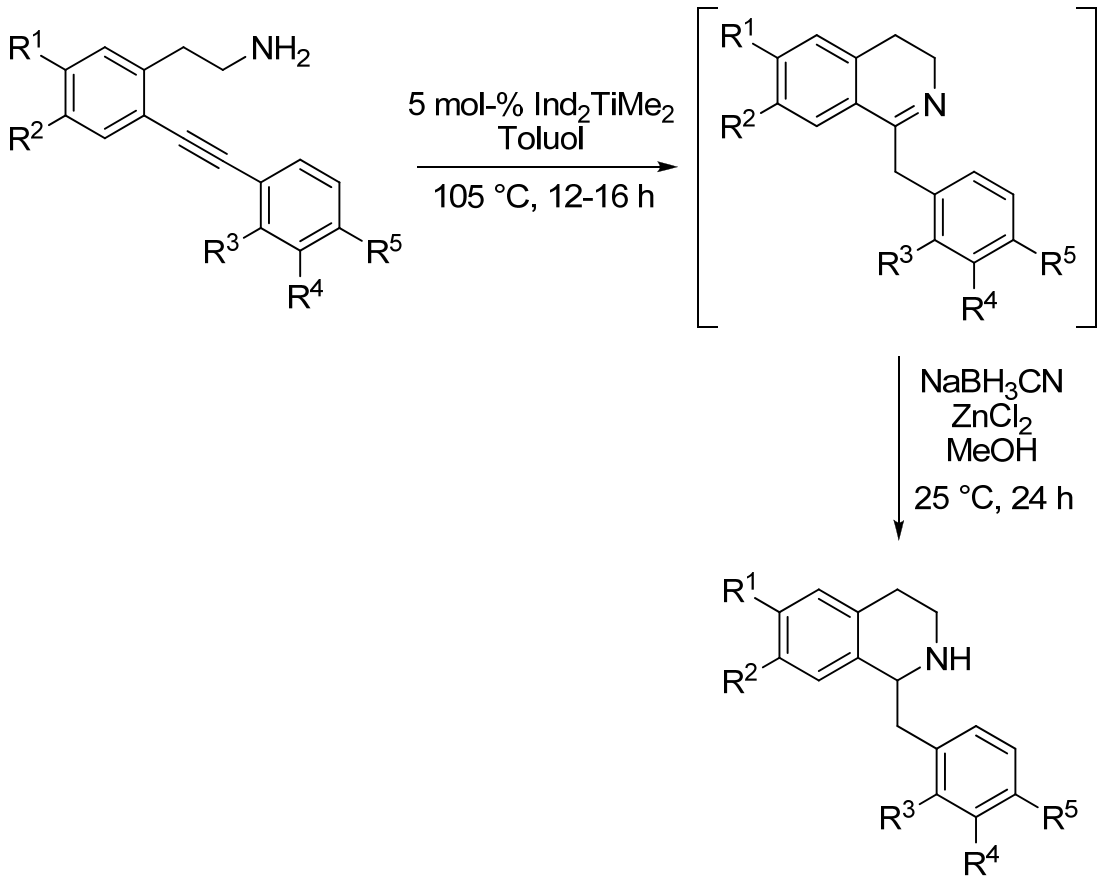


Nr.	Edukt	R^2	R^3	R^4	R^5	Produkt	Ausbeute [%][a]
1	**91**	H	H	OMe	OMe	**119**	95
2	**92**	H	H	H	Me	**120**	87
3	**93**	H	H	H	CF_3	**121**	80
4	**94**	H	H	H	F	**122**	82
5	**95**	H	H	H	Cl	**123**	96
6	**96**	H	H	H	OMe	**124**	78
7	**97**	H	Me	H	H	**125**	84
8	**98**	H	CF_3	H	H	**126**	76
9	**99**	H	OMe	H	H	**127**	89
10	**100**	H	H	OMe	OMe	**128**	93
11	**101**	H	H	H	Me	**129**	91
12	**102**	H	H	H	CF_3	**130**	96
13	**103**	H	H	H	F	**131**	86
14	**104**	H	H	H	Cl	**132**	86
15	**105**	H	H	H	OMe	**133**	85
16	**106**	H	Me	H	H	**134**	86
17	**107**	H	CF_3	H	H	**135**	93
18	**108**	H	OMe	H	H	**136**	81
19	**109**	H	H	OMe	OMe	**137**	90
20	**110**	H	H	H	Me	**138**	88
21	**111**	H	H	H	CF_3	**139**	83
22	**112**	H	H	H	F	**140**	78
23	**113**	H	H	H	Cl	**141**	65
24	**114**	H	H	H	OMe	**142**	71
25	**115**	H	Me	H	H	**143**	88
26	**116**	H	CF_3	H	H	**144**	82
27	**117**	H	OMe	H	H	**145**	91
28	**118**	F	H	OMe	OMe	**146**	91

[a] Reaktionsbedingungen: $AlCl_3$ (1 eq), $LiAlH_4$ (1 eq), Bisarylnitriloalkin (1 eq), Et_2O, 25 °C, 0.5-2 h. Isolierte Ausbeute.

3.2.2 Synthese von Norlaudanosin-Derivaten

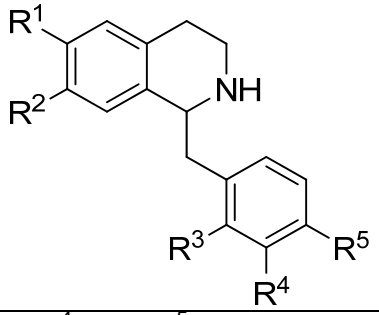
Mit Hilfe der intramolekularen Hydroaminierung und anschließender Reduktion der erhaltenen Imin Funktion konnten die synthetisierten Bisarylaminoalkine in einer Ein-Topf-Reaktion in die gewünschten Norlaudanosin-Derivate überführt werden. Als Katalysator wurde der bekannte Titankatalysator Ind_2TiMe_2 (**IV**) verwendet.[33] Die nachfolgende Reduktion erfolgte durch Zugabe eines Suspension aus Natriumcyanoborhydrid ($NaBH_3CN$) und Zinkchlorid ($ZnCl_2$) in Methanol, welches zur abgekühlten Reaktionslösung zugefügt wurde (Schema **26**).[87]



Schema 26 Synthese der Norlaudanosin-Derivate.

Die isolierten Ausbeuten der racemischen Norlaudanosin-Derivate sind in Tabelle **5** aufgeführt und lagen in einem guten bis exzellenten Bereich (67–96 %).

Tabelle 5 Ausbeuten der racemischen Norlaudanosin-Derivate.



Nr.	Edukt	R^1	R^2	R^3	R^4	R^5	Produkt	Ausbeute [%][a]
1	**119**	H	H	H	OMe	OMe	***rac*-147**	67
2	**120**	H	H	H	H	Me	***rac*-148**	80
3	**121**	H	H	H	H	CF_3	***rac*-149**	70
4	**122**	H	H	H	H	F	***rac*-150**	75
5	**123**	H	H	H	H	Cl	***rac*-151**	84
6	**124**	H	H	H	H	OMe	***rac*-152**	90
7	**125**	H	H	Me	H	H	***rac*-153**	79
8	**126**	H	H	CF_3	H	H	***rac*-154**	85
9	**127**	H	H	OMe	H	H	***rac*-155**	76
10	**128**	CF_3	H	H	OMe	OMe	***rac*-156**[b]	96
11	**129**	CF_3	H	H	H	Me	***rac*-157**	78
12	**130**	CF_3	H	H	H	CF_3	***rac*-158**	87
13	**131**	CF_3	H	H	H	F	***rac*-159**	87
14	**132**	CF_3	H	H	H	Cl	***rac*-160**	83
15	**133**	CF_3	H	H	H	OMe	***rac*-161**	84
16	**134**	CF_3	H	Me	H	H	***rac*-162**	84
17	**135**	CF_3	H	CF_3	H	H	***rac*-163**	79
18	**136**	CF_3	H	OMe	H	H	***rac*-164**	86
19	**137**	F	H	H	OMe	OMe	***rac*-165**	94
20	**138**	F	H	H	H	Me	***rac*-166**	88
21	**139**	F	H	H	H	CF_3	***rac*-167**	83
22	**140**	F	H	H	H	F	***rac*-168**	77
23	**141**	F	H	H	H	Cl	***rac*-169**	76
24	**142**	F	H	H	H	OMe	***rac*-170**	85
25	**143**	F	H	Me	H	H	***rac*-171**	76
26	**144**	F	H	CF_3	H	H	***rac*-172**	80
27	**145**	F	H	OMe	H	H	***rac*-173**	68
28	**146**	F	F	H	OMe	OMe	***rac*-174**[b]	96

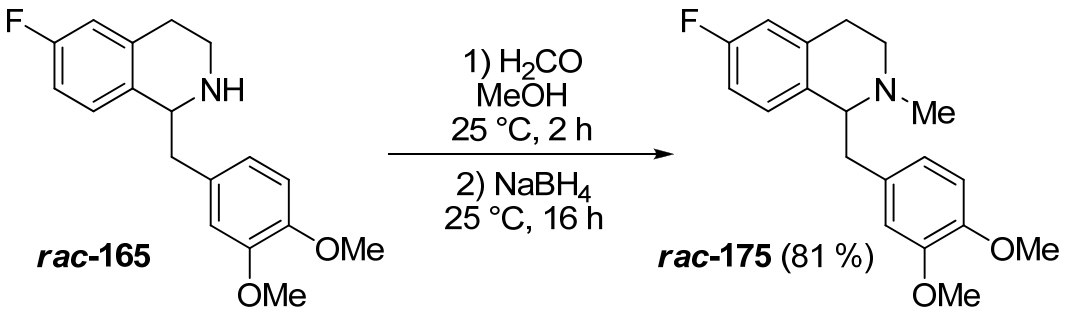
[a] Reaktionsbedingungen: 1) Bisarylaminoalkin (1 eq), Ind_2TiMe_2 (5 mol-%), Toluol, 105 °C, 12-16 h; 2) $NaBH_3CN$ (2 eq), $ZnCl_2$ (1 eq), Methanol; Isolierte Ausbeute; [b] Bereits durch D. Mujahidin synthetisierte Verbindung.

Bis auf Derivat ***rac*-147** (67 %) und ***rac*-173** (68 %) konnten die Verbindungen mit einem elektronenreichen C-Ring (***rac*-152**, ***rac*-155**, ***rac*-156**, ***rac*-161**, ***rac*-164**, ***rac*-165**, ***rac*-170**, ***rac*-174**) in sehr guten Ausbeuten (84-96 %) erhalten werden. Die Verbindungen mit neutralem C-Ring (Tabelle **5**, R^3 oder R^5 = Me) wurden in guten

Ausbeuten (76-88 %) erhalten. Ähnliche Ausbeuten (70-87 %) zeigten sich auch bei den Reaktionen der Verbindungen mit eletronenarmem C-Ring (Tabelle **5**, R^3 oder $R^5 = CF_3$ oder $R^5 = F$).

Die unterschiedliche elektronische Situation am A-Ring (neutrale bis elektronenarme Substituenten) wirkte sich nicht auf die Ausbeute aus. Vergleicht man z.B. die Reaktionen mit *para*-methoxysubstituiertem (***rac*-152**, ***rac*-161** und ***rac*-170**) oder *ortho*-trifluormethylsubstituiertem C-Ring (***rac*-154**, ***rac*-163** und ***rac*-172**) so unterscheiden sich die Ausbeuten gerade um ± 6 %.

Um zu beweisen, dass eine Transformation in die entsprechenden Laudanosin-Derivate möglich ist, wurde exemplarisch Verbindung ***rac*-165** am N-Atom methyliert. Die Umsetzung erfolgte analog der Vorschrift zur vorgestellten Totalsynthese von (*S*)-(+)-Laudanosin (Schema **11**).[52,75] Nach Umsetzung des Norlaudanosin-Derivates ***rac*-165** mit wässriger Formaldehyd-Lösung und anschließender Reduktion mit Natriumborhydrid ($NaBH_4$), wurde Verbindung ***rac*-175** in sehr guter Ausbeute (81 %) erhalten (Schema **27**).

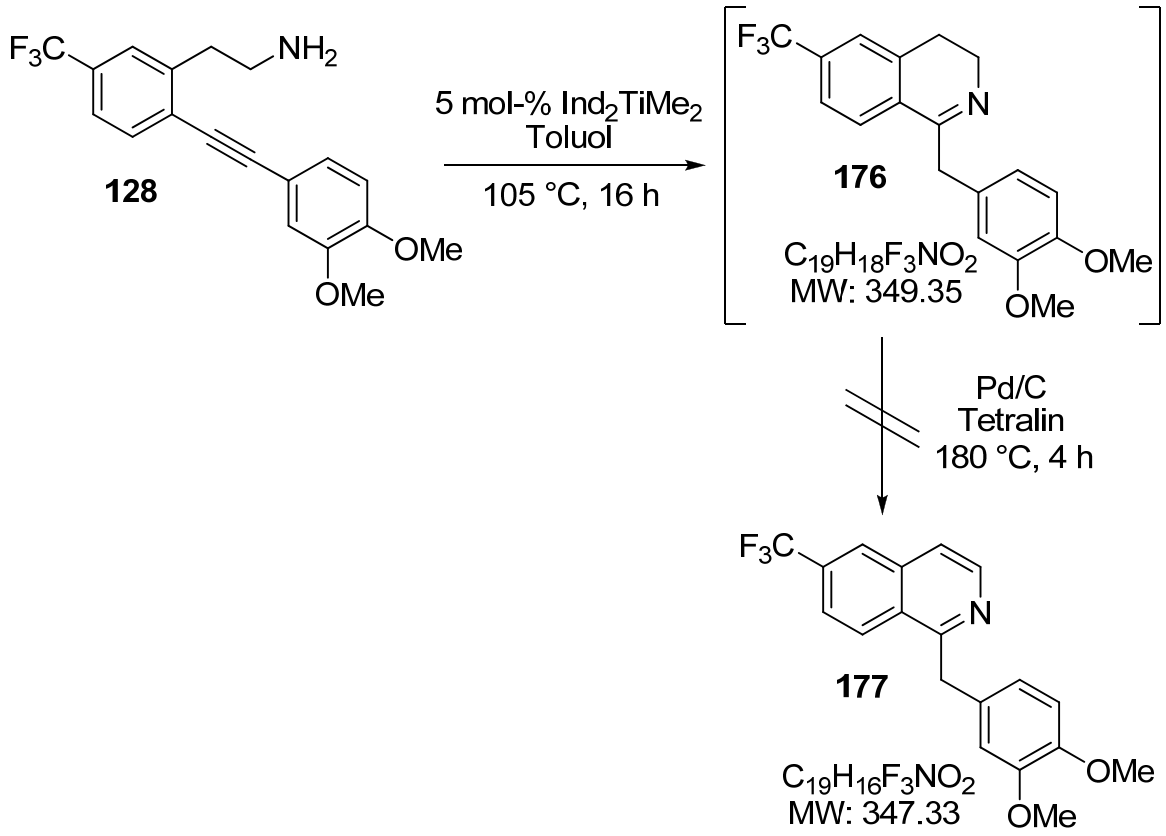


***rac*-165** ***rac*-175** (81 %)

Schema 27 Methylierung des racemischen Norlaudanosin-Derivates ***rac*-165**.

3.2.3 Synthese von Papaverin-Derivaten

Ausgehend von den Bisarylaminoalkinen (**119**-**146**) sollte nach der intramolekularen Hydroaminierung die Transformation in die entsprechenden aromatischen Papaverin-Derivate durch einfache Dehydrierung möglich sein. Erste Versuche den B-Ring mit Hilfe von Palladium auf Kohle in Tetrahydronaphthalin zu aromatisieren, führten jedoch zu überraschenden Ergebnissen.



Schema 28 Versuch zur Aromatisierung des B-Ringes der Verbindung **176** mit Pd/C.

Nach erfolgreicher Hydroaminierung der Verbindung **128** wurde zum Reaktionsgemisch Palladium auf Kohle sowie Tetrahydronaphthalin zugefügt und für 4 h bei 180 °C gerührt (Schema **28**). Aus dem anschließend gemessenen GC/MS-Chromatogramm ging hervor, dass sich unerwartet Nebenprodukte gebildet hatten (Abbildung **9**). Das Signal mit der Retentionszeit von 23.2 Min wurde dem Produkt (**177**) und das Signal mit 23.6 Min dem Zwischenprodukt (**176**) zugeordnet. Die Signale der Nebenprodukte nach 25.1 Min und 25.2 Min zeigten einen Massenverlust (ca. 19 m/z) gegenüber dem Produkt (**177**).

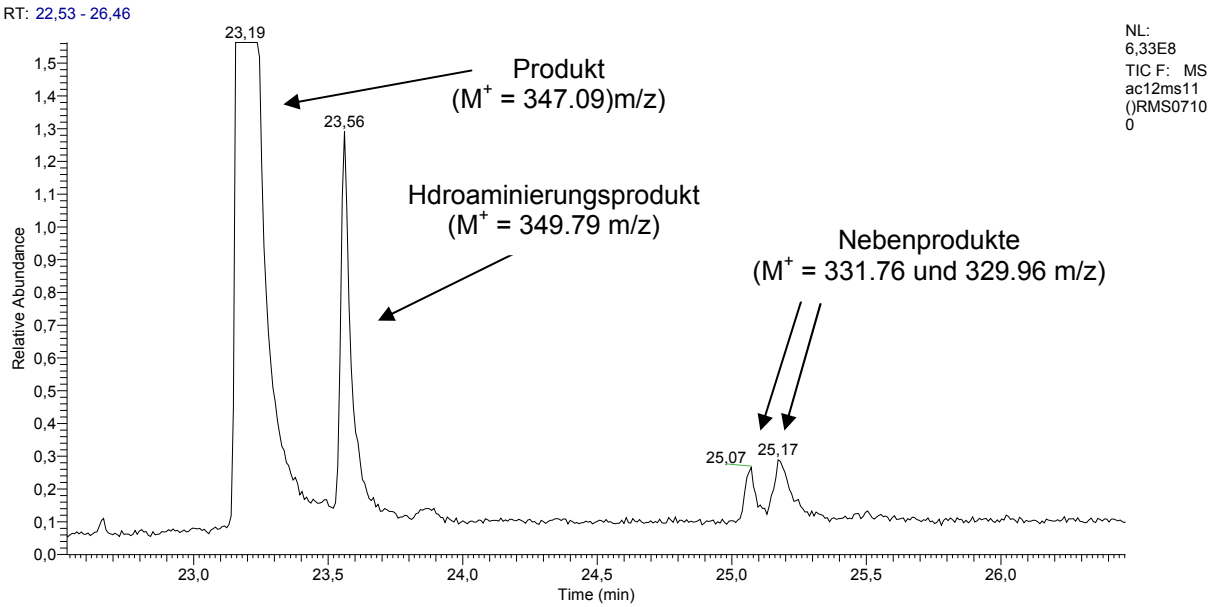
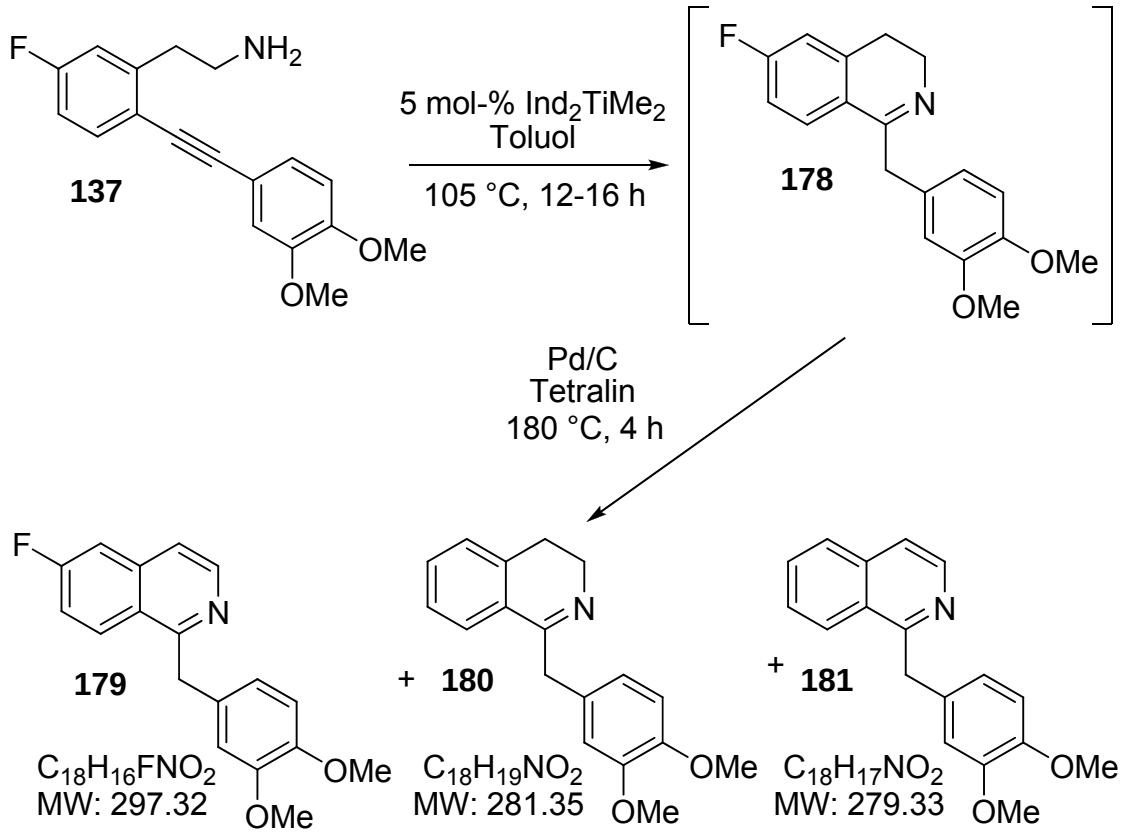


Abbildung 9 GC/MS-Chromatogramm nach Durchführung der in Schema **28** gezeigten Reaktion.

Die vorliegende Nebenreaktion zeigte sich bei der Umsetzung von Verbindung **137** zu dem gewünschten Produkt **179** noch deutlicher (Schema **29**).



Schema 29 Versuch zur Aromatisierung des B-Ringes der Verbindung **178** mit Pd/C.

Das gemessene GC/MS-Chromatogramm (Abbildung **10**) zeigte drei Signale die mittels der dazugehörigen Massenspektren den Verbindungen **179**, **180** und **181** zugeordnet wurden (Abbildung **11**).

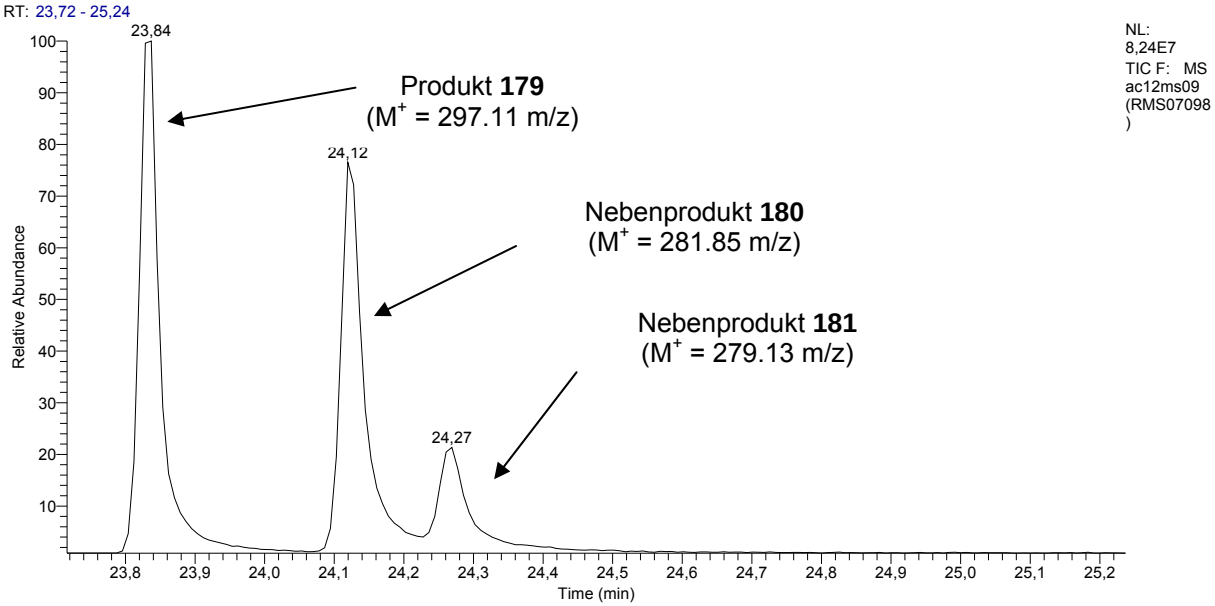


Abbildung 10 GC/MS-Chromatogramm nach Durchführung der in Schema **29** gezeigten Reaktion.

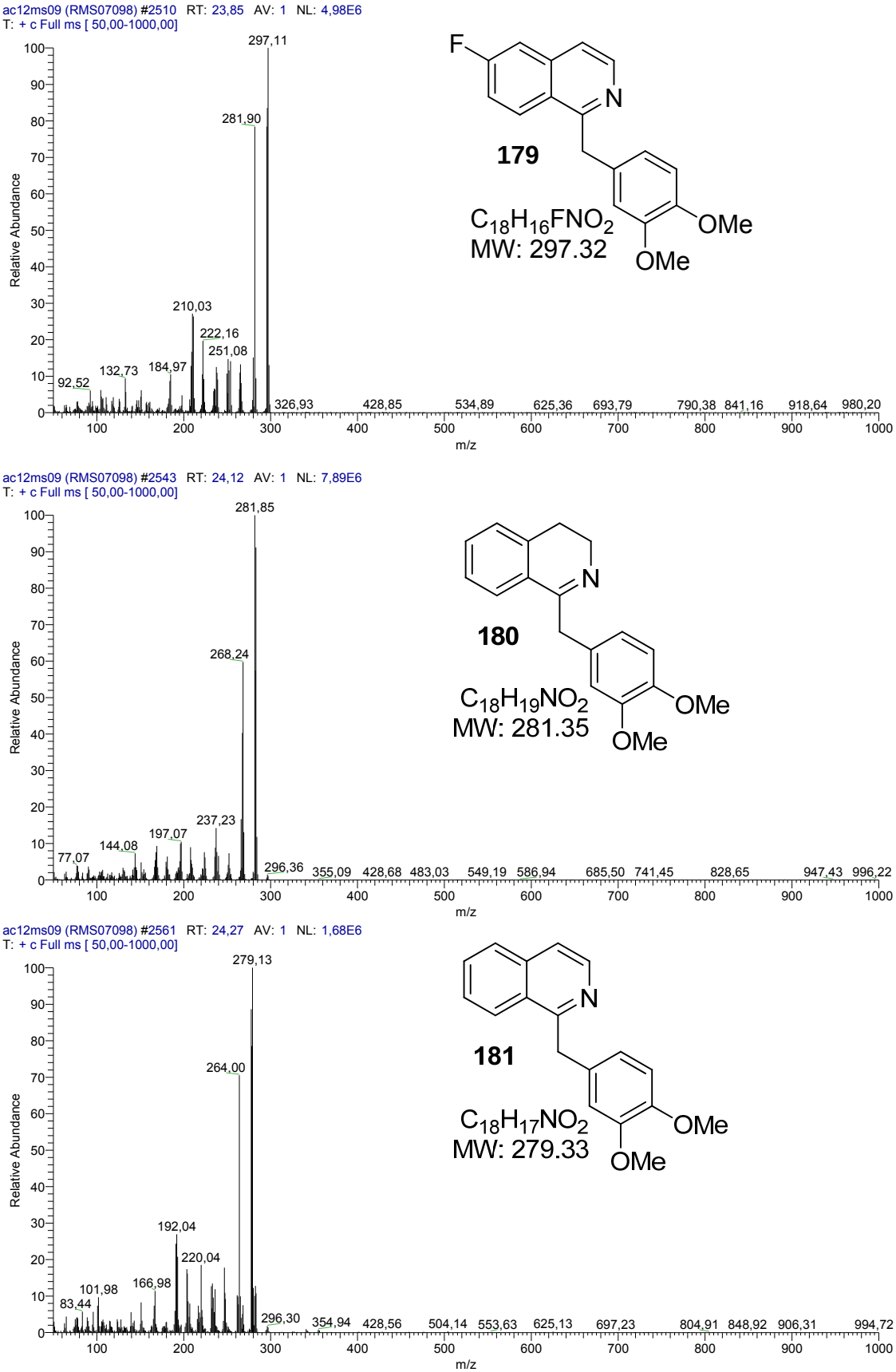
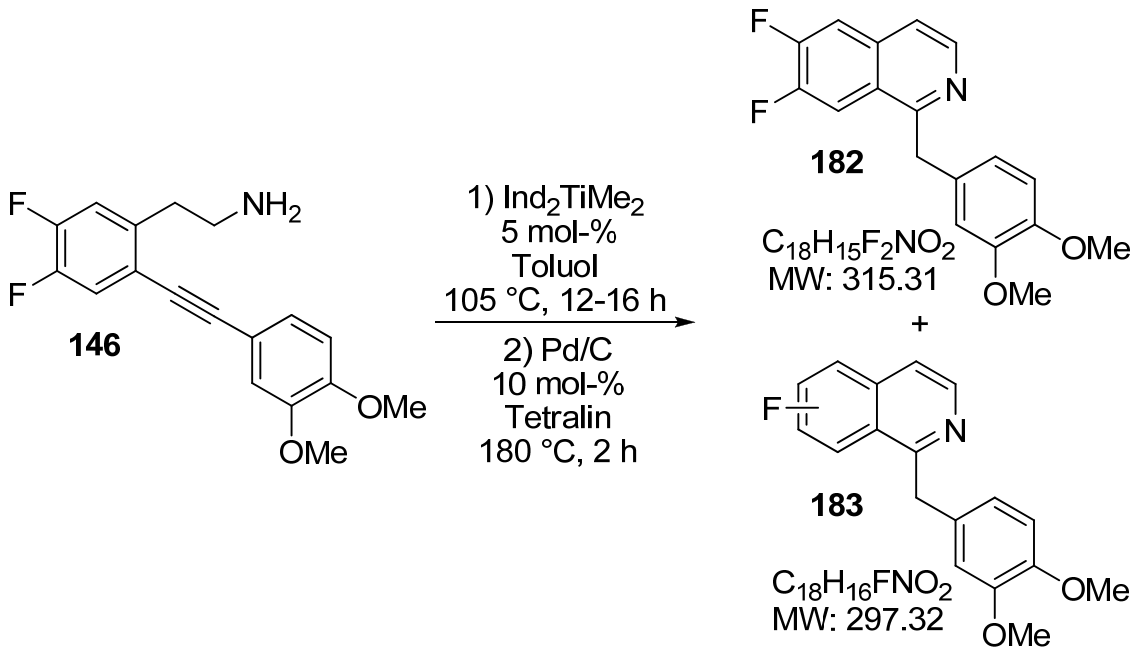


Abbildung 11 Massenspektren der GC/MS Analyse nach Durchführung der in Schema **29** gezeigten Reaktion.

Die gewünschte Dehydrierung verlief also parallel zu einer unerwünschten Dehalogenierung und führte zu einem Gemisch aus den Verbindungen **179**, **180** und **181**. Diese wurde auch bei der Umsetzung der Difluorverbindung **146** beobachtet (Schema **30**).



Schema 30 Hydroaminierung der Verbindung **146** mit anschließender Dehydrierung durch Pd/C.

Nach wässriger Aufarbeitung und einer Säulenfiltration wurden allerdings nur 24 % der erwarteten Produktmenge erhalten. Das aufgenommene Roh-NMR-Spektrum zeigte weitere Signale neben dem erwarteten Signalsatz für die Verbindung **182** (Abbildung **12**). Der Bereich zwischen 4.50 und 4.55 ppm zeigte zwei Signale. Diese resultierten von den Wasserstoffatomen der Methylengruppen der aromatisierten Verbindung (**182**) (integriertes Signal) und einer weiteren Verbindung. Auch im Aromatenbereich konnten sehr ähnliche Signale (z.B. δ = 7.80 ppm, dd, J = 8.9, 5.6 Hz, 1 H) neben den erwarteten (δ = 7.88 ppm, dd, J = 11.2, 7.9 Hz, 1 H) der Verbindung **182** beobachtet werden.

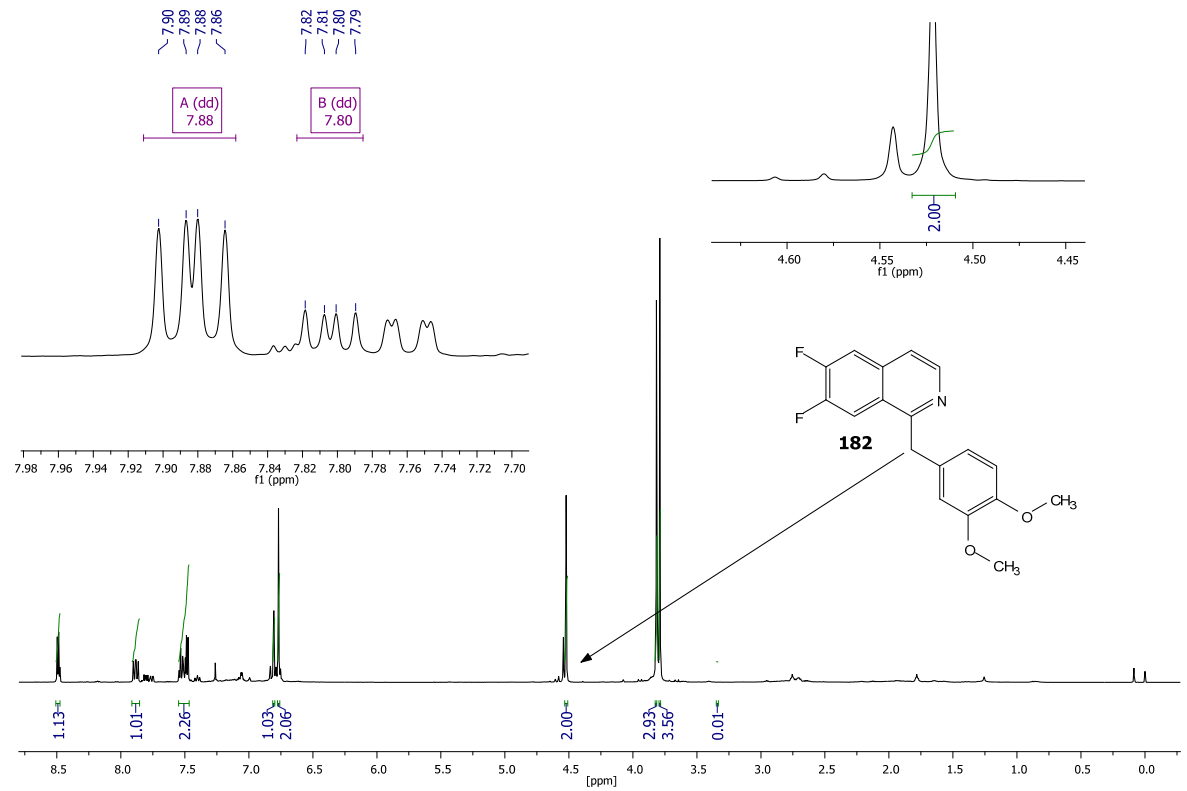


Abbildung 12 ^{1}H NMR-Spektrum der erhaltenen dehydrierten difluorsubstituierten Verbindung.

Zur weiteren Identifizierung der Verbindungen **182** und **183** wurde erneut die GC/MS-Analytik verwendet. Abbildung **13** zeigt, dass es sich um ein Gemisch aus zwei Substanzen handelte. Die Identifizierung der Substanzen (**182** und **183**) erfolgte durch Auswertung der zugehörigen Massenspektren.

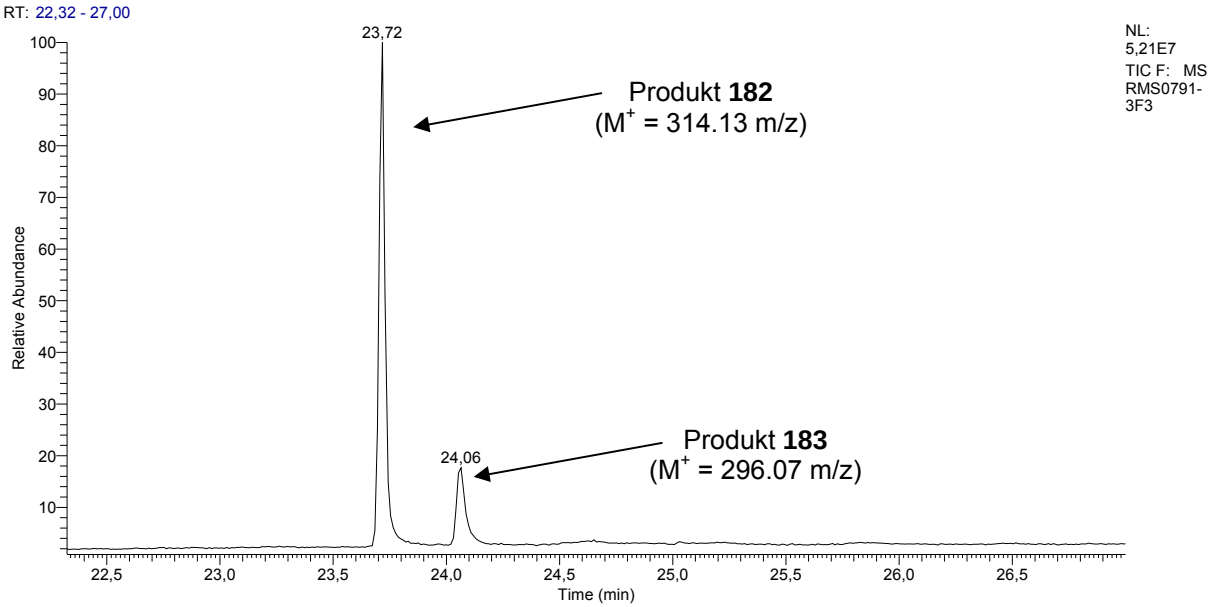


Abbildung 13 GC/MS-Chromatogramm nach Durchführung der in Schema **30** gezeigten Reaktion.

Wiederholte Versuche das Gemisch durch eine Säulenchromatographie zu trennen schlugen fehl. Allerdings kristallisierte Verbindung **182** (Ausbeute < 5 %) aus dem Produktgemisch in $CDCl_3$ in der triklinen Raumgruppe P-1 aus (Abbildung **14**). Die Lösung der Kristallstrukturanalyse bestätigte die Bildung des gewünschten Isochinolinringes. Die Bindungslänge C8-C9 kann mit einer Länge von 135.60 pm ebenso wie die von C1-N1 mit 132.70 pm einer C-C bzw. C-N Doppelbindung zugeordnet werden.

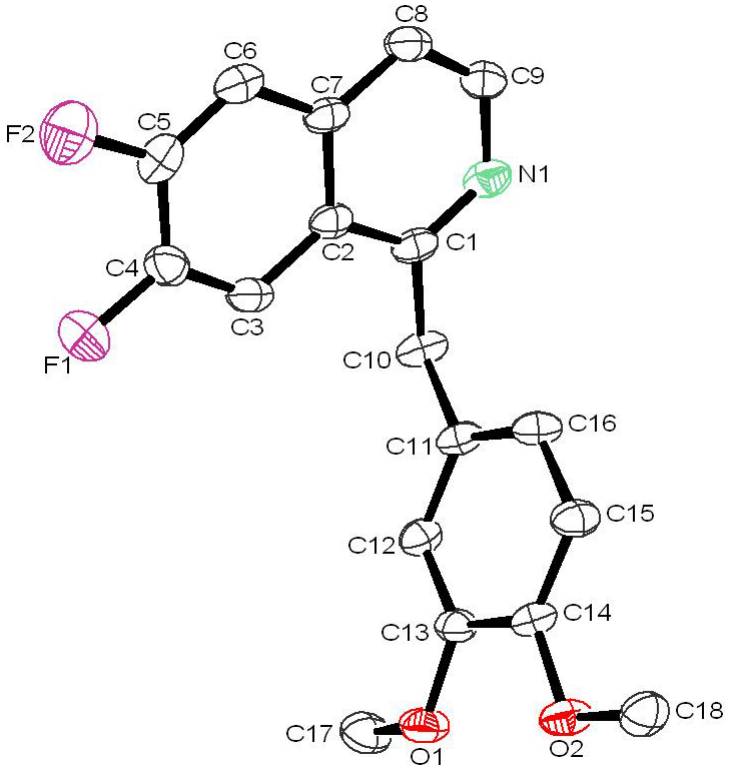
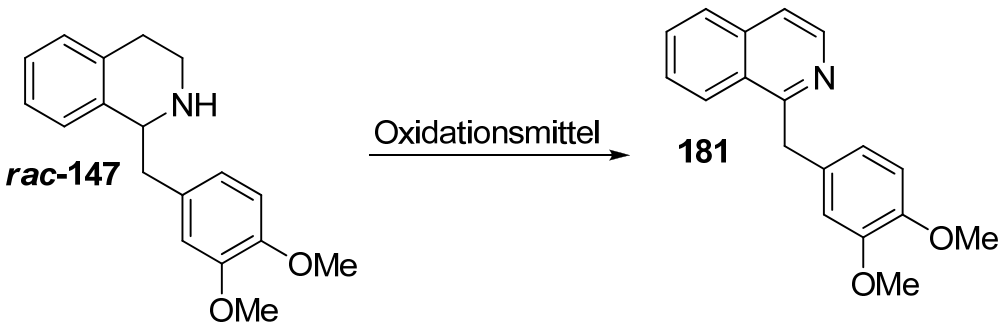


Abbildung 14 Molekülstruktur der Röntgenkristallstrukturanalyse des Papaverin-Derivates **182**.

Um die Defluorierung zu vermeiden, wurden anschließend die Reaktionsbedingungen variiert. Zuerst wurde versucht, die Dehydrierung mit Pd/C bei 110 °C in Toluol durchzuführen. Da selbst nach 8 h keine Reaktion eintrat, wurde Tetrahydronaphthalin zugegeben und die Temperatur in 20 °C Schritten für je 2 h erhöht. Eine Reaktion war allerdings erst ab 180 °C zu erkennen und führt ebenfalls wieder zu einem Gemisch aus **182** und **183**. Bei einem Katalysatorwechsel zu Pt/C konnte selbst bei 190 °C keine Dehydrierung beobachtet werden.

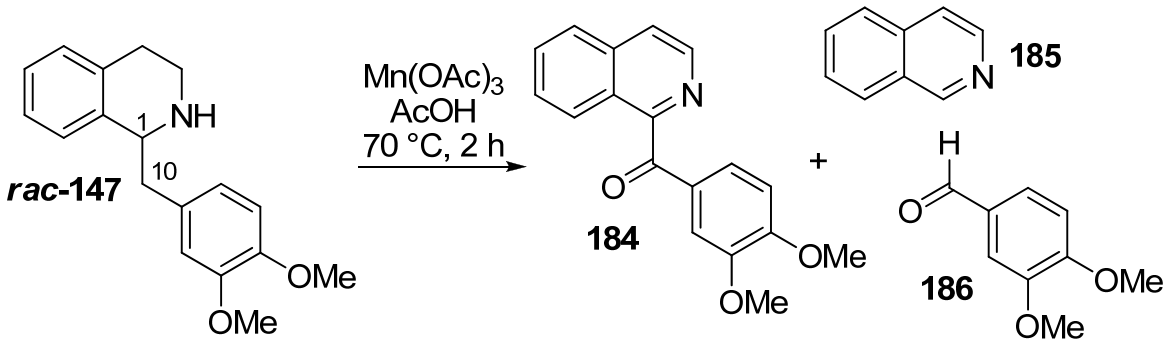
Da die unerwünschte Nebenreaktion nicht unterdrückt werden konnte, wurde ein anderer Syntheseweg eingeschlagen und verschiedene Oxidationsmittel für die

Aromatisierung des B-Rings getestet. Als Startmaterial wurde Verbindung ***rac*-147** verwendet, die mit den Oxidationsmitteln umgesetzt wurde (Schema **31**).



Schema 31 Versuch der Aromatisierung durch ein Oxidationsmittel.

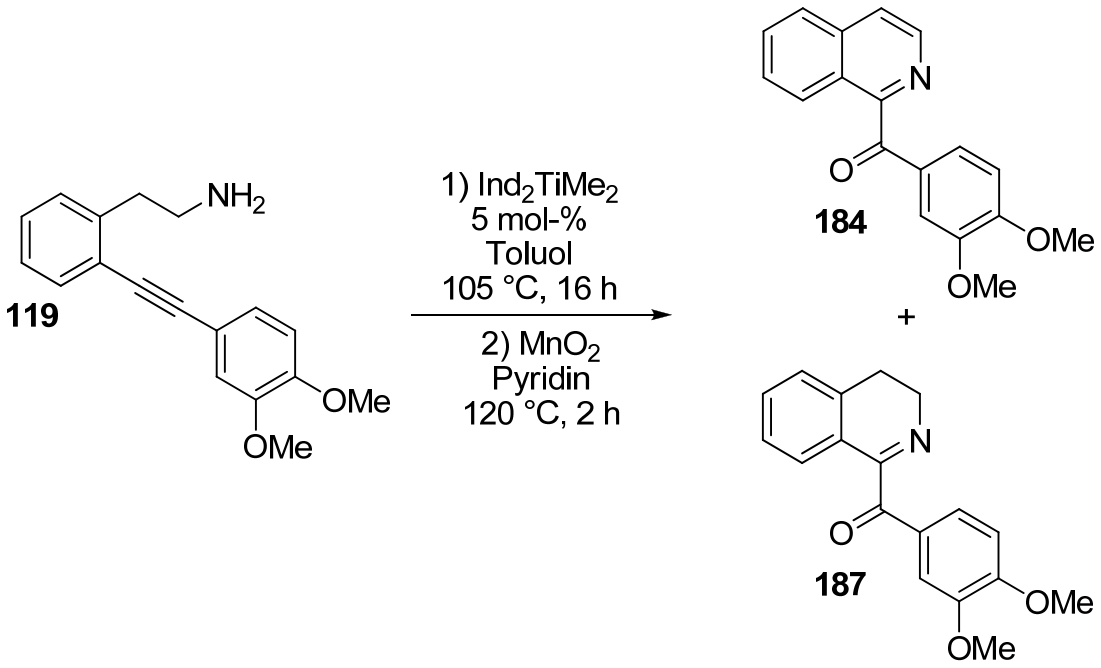
Eine Umsetzung von ***rac*-147** mit Dichlordicyanochinon (DDQ) bei Raumtemperatur lieferte jedoch keine verwendbaren Ergebnisse. Obwohl der Versuch mehrmals wiederholt wurde, konnte kein identifizierbares Produkt isoliert werden. Es wird angenommen, dass wie in der Literatur beschrieben der C-Ring zu 1,2-Benzochinon oxidiert wurde.[88] Die Umsetzungen mit Schwefel in Diphenylether bei 220 °C oder mit Natriumperiodat ($NaIO_4$) in DMSO lieferten ebenfalls nicht das gewünschte Produkt. In beiden Fällen wurde mit einer Ausbeute von ca. 50 % ein Gemisch aus dem Startmaterial (***rac*-147**) und einer zweiten Verbindung isoliert, die später als Verbindung **184** identifiziert wurde. Bei der Verwendung von Mangantriacetat ($Mn(OAc)_3$) wurde ebenfalls ein Produktgemisch (41 %) isoliert. Neben Verbindung **184** wurde Dimethoxybenzaldehyd (**186**) mit 17 % isoliert. Der erhalten Aldehyd resultiert aus einem oxidativen Bindungsbruch der C1-C10 Bindung (Schema **32**).



Schema 32 Versuch der Aromatisierung durch Mangantriacetat.

Um einen Bindungsbruch auszuschließen, wurde die Anwendung des milderen Oxidationsmittels MnO_2 untersucht. Die Umsetzung der Verbindung **119**

lieferte jedoch nach erfolgreicher Hydroaminierung und anschließender Zugabe von MnO_2 und Pyridin nicht das gewünschte Papaverin-Derivat **181** (Schema **33**).[89] Stattdessen wurden zwei Nebenprodukte isoliert (**184** und **187**).



Schema 33 Hydroaminierungs-Oxidationsversuch der Verbindung **119** mit MnO_2 in Pyridin.

Das erhaltene ^{1}H NMR-Spektrum (Abbildung **15**) der ersten Verbindung zeigte kein erwartetes Signal der Methylengruppe zwischen 4.0 ppm und 5.0 ppm (C10, siehe Abbildung **16**). Daher lag die Annahme nahe, dass während der Reaktion eine Oxidation zur Verbindung **187** stattgefunden hatte.

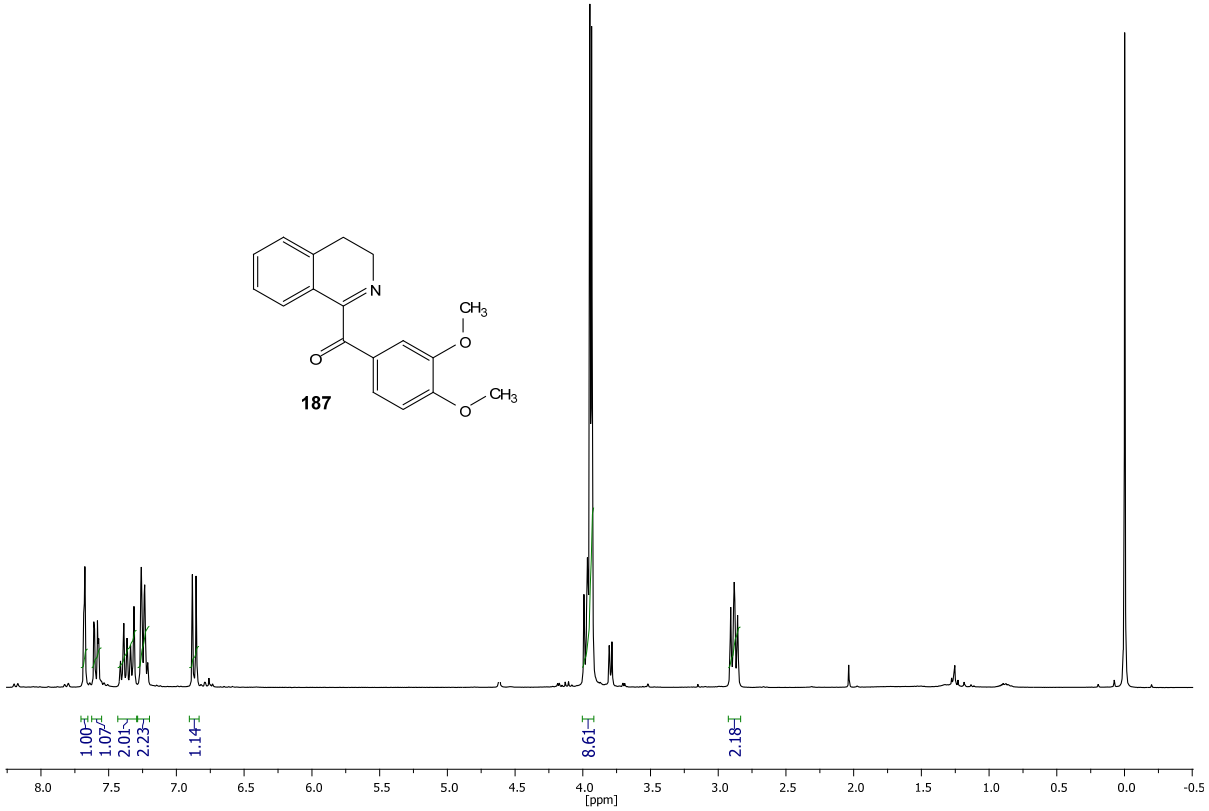


Abbildung 15 ^{1}H NMR-Spektrum des Nebenprodukts **187** aus dem Oxidationsversuchs mit MnO_2 in Pyridin (Schema **33**).

Als eindeutiger Strukturbeweis diente die röntgenkristallographische Untersuchung der aus $CDCl_3$ gewonnen Kristalle. Es zeigte sich, dass die Verbindung **187** orthorombisch in der Raumgruppe P_{bca} kristallisierte (Abbildung **16**). Die Bindungslänge C8-C9 beträgt 152.07 pm. Die Vergrößerung dieses Abstandes um 16.47 pm gegenüber Verbindung **182** beweist den Einzelbindungscharakter.

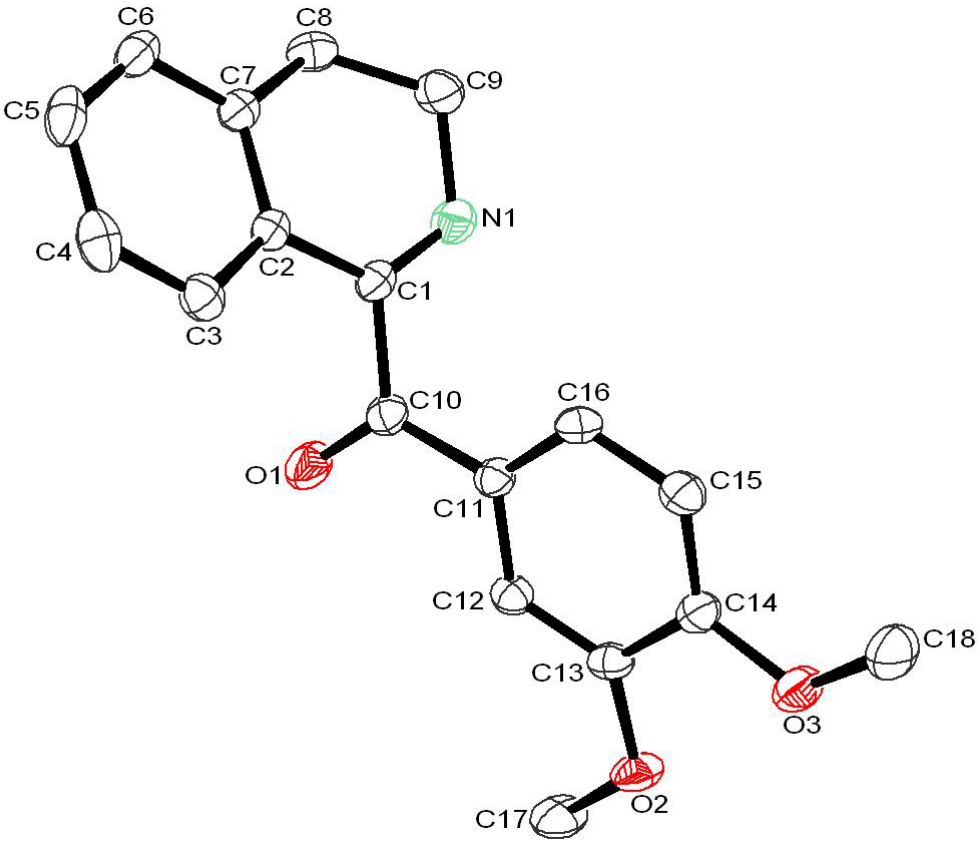


Abbildung 16 Molekülstruktur der Röntgenkristallstrukturanalyse des Papaveraldin-Derivates **187**.

In der zweiten erhaltenen Verbindung zeigte sich anhand des aufgenommenen ^{1}H NMR-Spektrums neben der Oxidation der Methylengruppe an C10 auch die gewünschte Oxidation des B-Rings (Abbildung **17**). Die Tripletts der beiden Wasserstoffatome an C8 und C9 der Verbindung **187** (siehe Abbildung **16**) waren im Spektrum nicht vorhanden. Stattdessen zeigten sich zwei weitere Dubletts im Aromatenbereich.

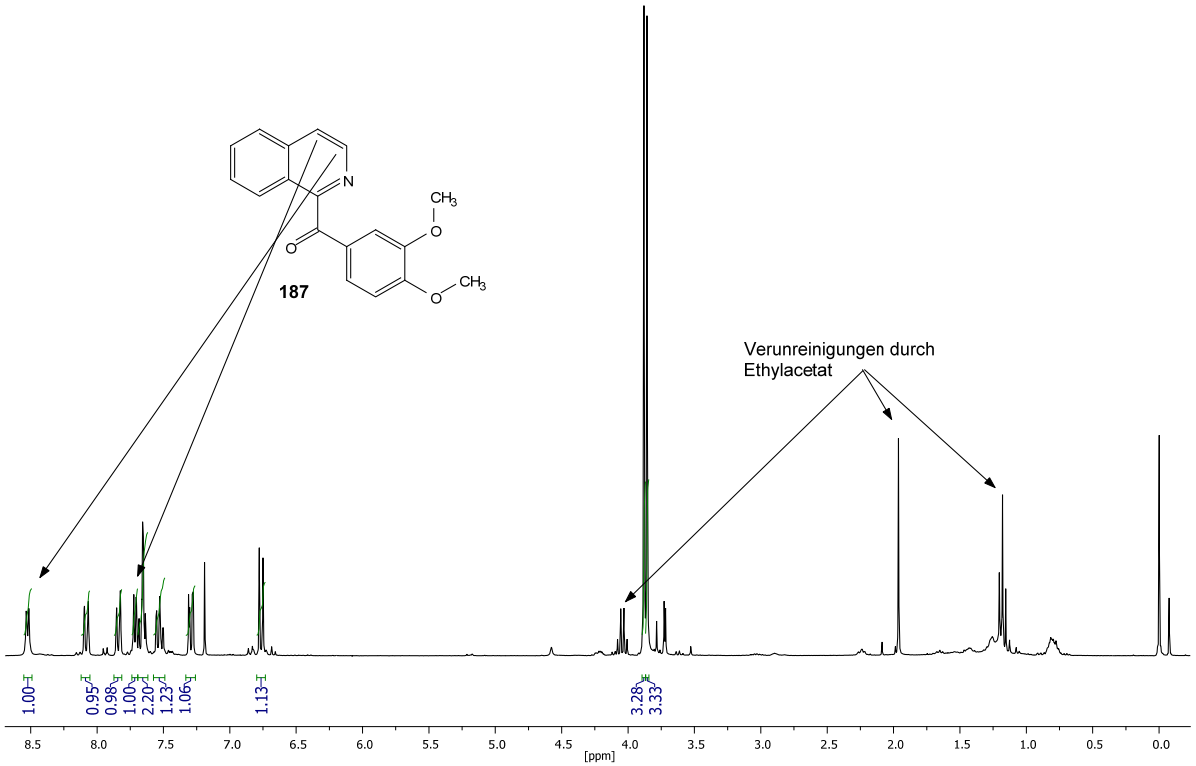
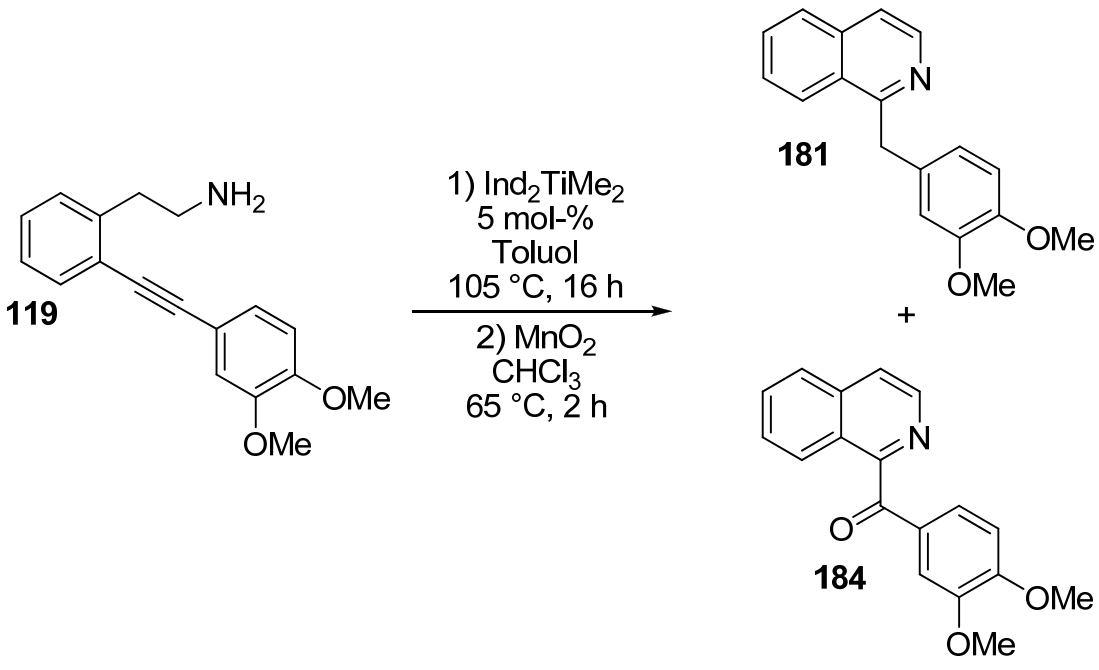


Abbildung 17 1H NMR-Spektrum des Nebenprodukts **184** aus dem Oxidationsversuchs mit MnO_2 mit Pyridin.

Ein Wechsel des Lösungsmittels beim Oxidationsschritt von Pyridin zu Chloroform ($CHCl_3$) führte zu einem anderen Produktgemisch (Schema **34**).[90]



Schema 34 Hydroaminierungs-Oxidationsversuch der Verbindung **119** mit MnO_2 in Chloroform.

Durch die Verwendung von $CHCl_3$ konnte auch das gewünschte Papaverin-Derivat **181** (Abbildung **18**) mit einer Ausbeute von 3 % isoliert werden. Hauptprodukt der Reaktion war Verbindung **184** mit 8 %. Im erhaltenen ^1H NMR-Spektrum des Papaverin-Derivates **181** war das Singulett der Methylengruppe zwischen 4.0 ppm und 5.0 ppm deutlich zu erkennen.

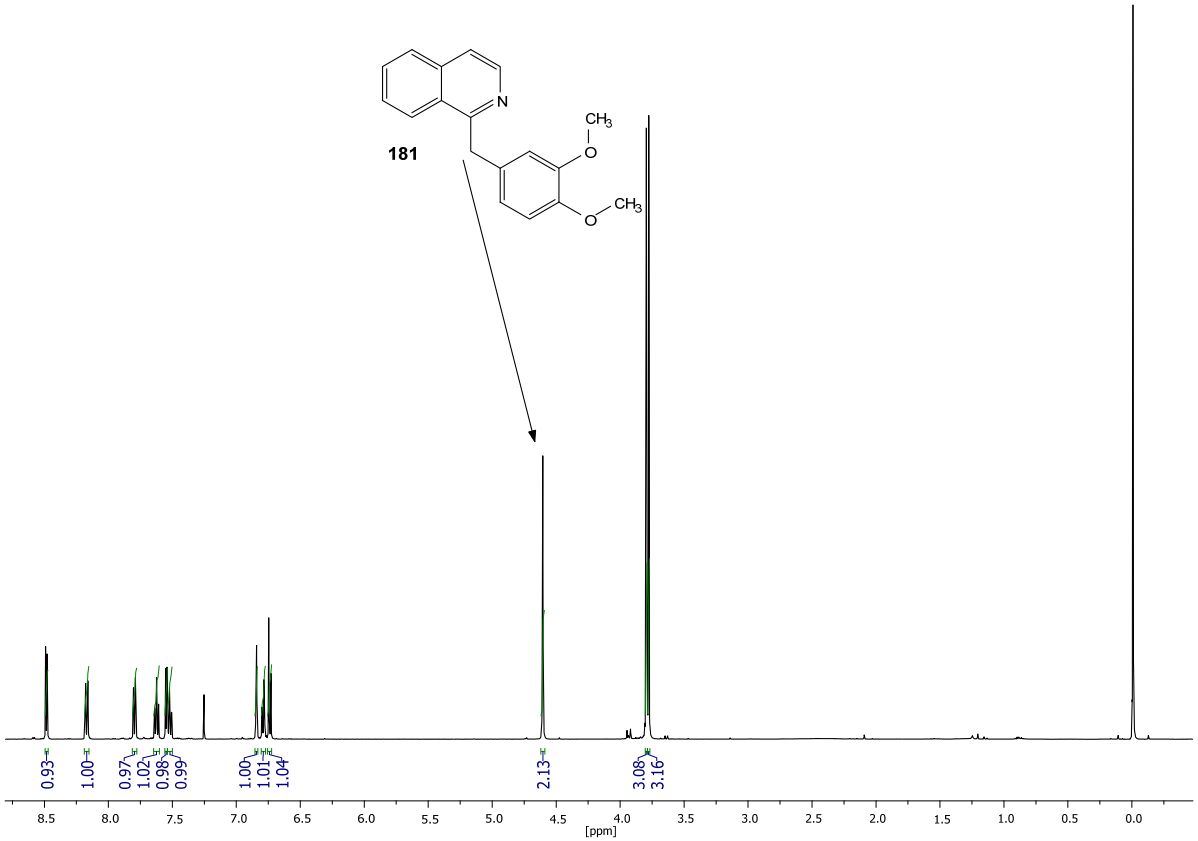


Abbildung 18 ^1H NMR-Spektrum des Papaverin-Derivates **181**.

Die Verbindungen **181** und **184** sind im ^{13}C NMR-Spektrum leicht zu unterschieden. Charakteristisch für Verbindung **184** ist die stark tieffeldverschobene Carbonyl-Funktion bei 193 ppm. Anstelle dieses Signals war im Spektrum der Verbindung **181** die Methylengruppe bei 42 ppm zu beobachten (Abbildung **19**).

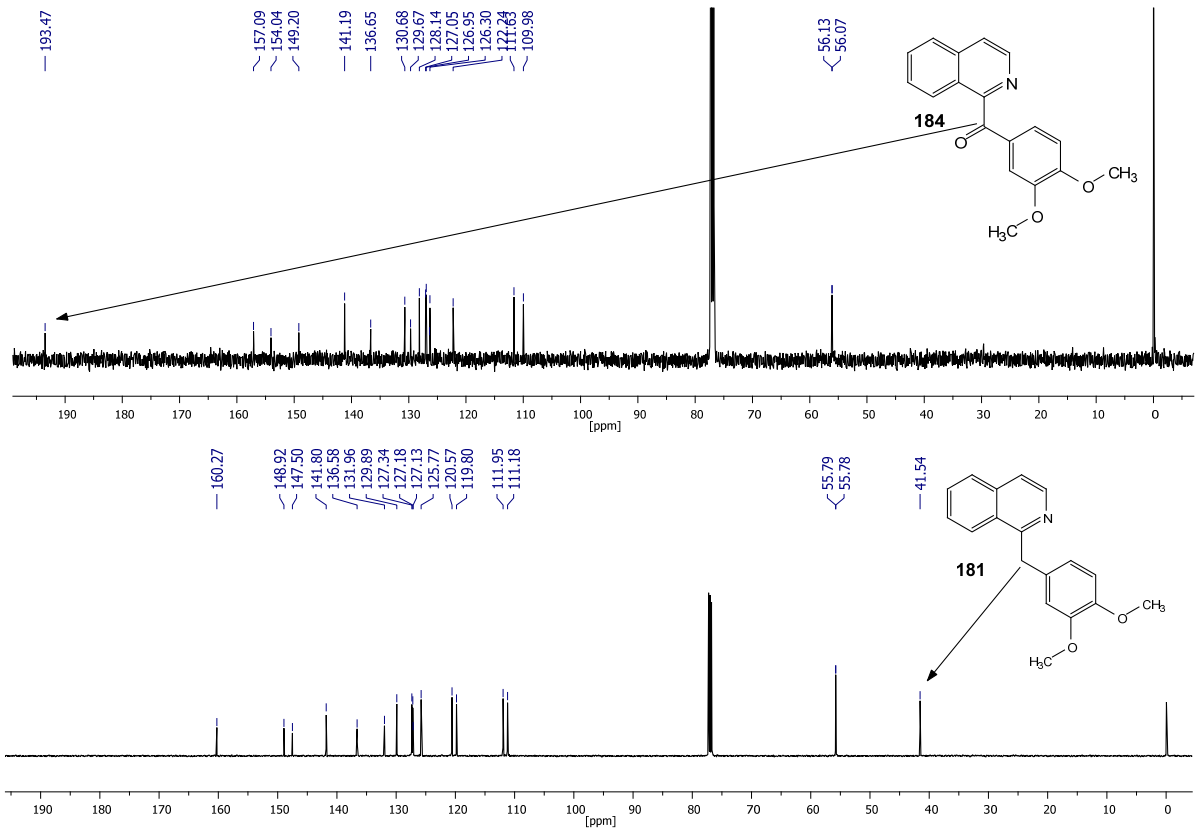
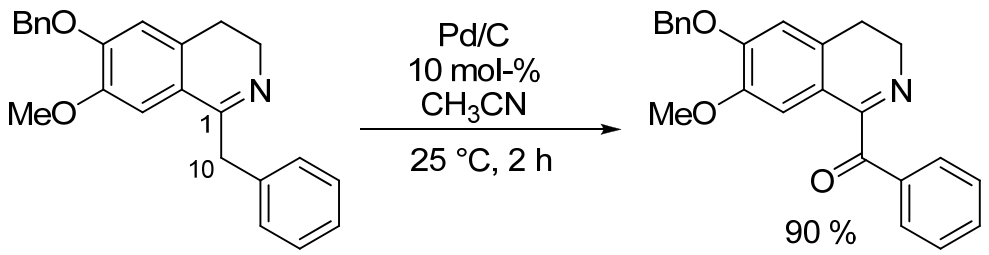


Abbildung 19 Vergleich der 13C NMR-Spektren der Verbindungen **181** und **184**.

Aufgrund der geringen Ausbeuten (< 5 %) und der Entstehung von Nebenprodukten besteht für die selektive Oxidation des B-Rings noch Optimierungsbedarf. Ein weiteres Problem der oben genannten Oxidationsmittel war der mögliche Bindungsbruch zwischen C1 und C10. So wurde auch bei der Reaktion mit MnO_2 in $CHCl_3$ (Schema **34**) der Dimethoxybenzaldehyd mit 3 % erhalten.

3.2.4 Synthese von 3,4-Dihydropapaveraldin-Derivaten

Ein weiterer Schwerpunkt dieser Arbeit lag in der Synthese von 3,4-Dihydropapaveraldin-Derivaten. Einige bereits bekannte Derivate mit elektronenreichem A-Ring zeigen zytostatische Wirkung durch ihren Einfluss in der G1-Phase der Zellteilung.[69] Eine Übertragung der in der Literatur vorgestellten Reaktionsbedingungen (Pd/C, Acetonitril, Luft) zur selektiven Oxidation der Methylengruppe an C10 lieferte allerdings selbst nach 3 Tagen keinen vollen Umsatz (Schema **35**).

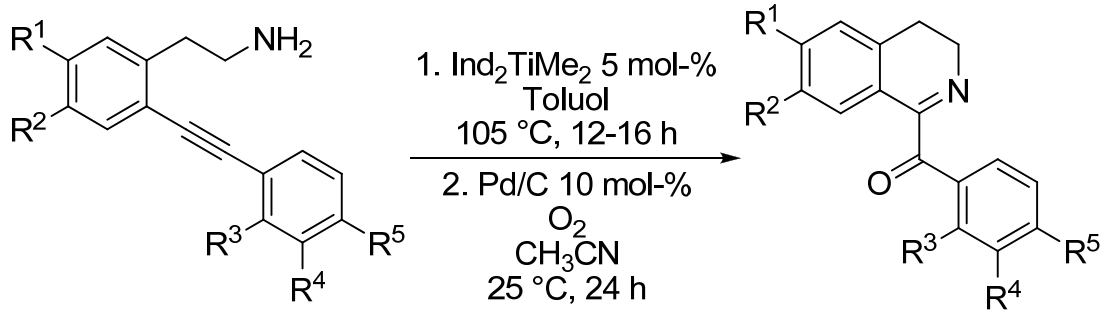


Schema 35 Ausgewählte Reaktion zur Literaturbekannte selektiven Oxidation der Methylengruppe an C10.[69]

Aus diesem Grund wurden die Bedingungen entsprechend modifiziert (Tabelle **6**). Nach der Hydroaminierung der Amine **119**-**146** erfolgte die Zugabe von Pd/C sowie Acetonitril zum Reaktionsgemisch. Anschließend wurde unter reiner Sauerstoffatmosphäre 24 h bei 25 °C gerührt (Tabelle **6**).

Verbindungen mit elektronenreichem C-Ring (**187**, **196**, **205**, **214**) wurden in geringeren Ausbeuten (36-55 %) gegenüber den elektronenarmen (z.B. **189** mit 73 %) oder elektronisch neutralen (z.B. **188** mit 88 %) Verbindungen erhalten. Dies wurde auf den bereits angesprochenen möglichen Bindungsbruch (siehe Schema **32**) zwischen dem Isochinolin- und dem Benyzl-Teil zurückgeführt, der bei elektronenreichem C-Ring vermehrt beobachtet wurde.

Tabelle 6 Ausbeuten der Papaveraldin-Derivate.

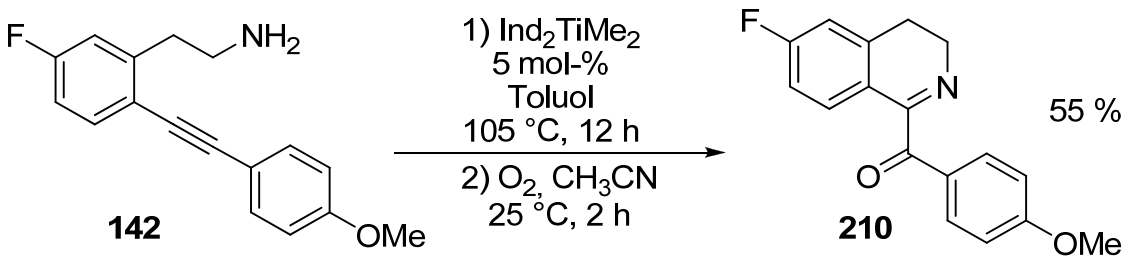


Nr.	Edukt	R^1	R^2	R^3	R^4	R^5	Produkt	Ausbeute [%][a]
1	**119**	H	H	H	OMe	OMe	**187**	55
2	**120**	H	H	H	H	Me	**188**	88
3	**121**	H	H	H	H	CF_3	**189**	73
4	**122**	H	H	H	H	F	**190**	78
5	**123**	H	H	H	H	Cl	**191**	76
6	**124**	H	H	H	H	OMe	**192**	81
7	**125**	H	H	Me	H	H	**193**	90
8	**126**	H	H	CF_3	H	H	**194**	65
9	**127**	H	H	OMe	H	H	**195**	74
10	**128**	CF_3	H	H	OMe	OMe	**196**	39
11	**129**	CF_3	H	H	H	Me	**197**	73
12	**130**	CF_3	H	H	H	CF_3	**198**	57
13	**131**	CF_3	H	H	H	F	**199**	83
14	**132**	CF_3	H	H	H	Cl	**200**	75
15	**133**	CF_3	H	H	H	OMe	**201**	49
16	**134**	CF_3	H	Me	H	H	**202**	84
17	**135**	CF_3	H	CF_3	H	H	**203**	76
18	**136**	CF_3	H	OMe	H	H	**204**	82
19	**137**	F	H	H	OMe	OMe	**205**	36
20	**138**	F	H	H	H	Me	**206**	67
21	**139**	F	H	H	H	CF_3	**207**	65
22	**140**	F	H	H	H	F	**208**	72
23	**141**	F	H	H	H	Cl	**209**	74
24	**142**	F	H	H	H	OMe	**210**	62
25	**143**	F	H	Me	H	H	**211**	77
26	**144**	F	H	CF_3	H	H	**212**	65
27	**145**	F	H	OMe	H	H	**213**	59
28	**146**	F	F	H	OMe	OMe	**214**	36

[a] Reaktionsbedingungen: 1) Bisarylaminoalkin (1 eq), Ind_2TiMe_2 (5 mol-%), Toluol, 105 °C, 12-16 h; 2) Pd/C (10 mol-%), CH_3CN; Isolierte Ausbeute.

Bei einer direkten Einleitung von Sauerstoff durch eine Kanüle in die Reaktionslösung nach der Hydroaminierung trat der Bindungsbruch verstärkt auf. Es konnte zwar ebenfalls das gewünschte 3,4-Dihydropapaveraldin-Derivat isoliert werden, allerdings waren bei Versuchen mit direkter Sauerstoffeinleitung ins

Reaktionsgemisch ohne Pd/C die Ausbeuten geringer (um 7 %) und es wurde vermehrt der substituierte Benzaldehyd detektiert (Schema **36**).

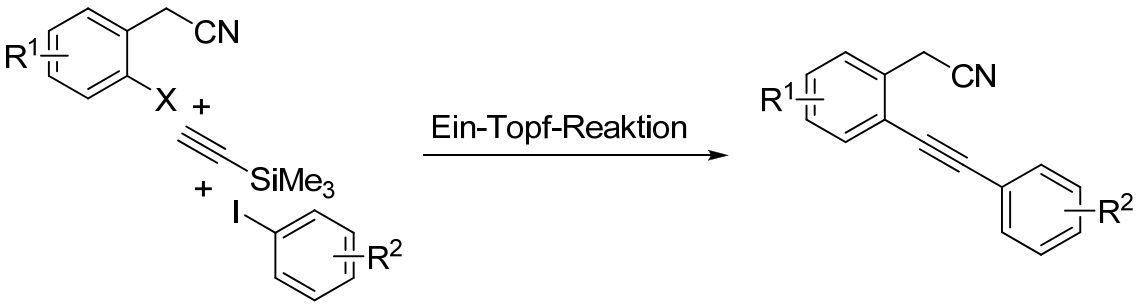


Schema 36 Testreaktion zur Oxidation der Benzylposition ohne Pd/C.

Dieser Versuch zeigte, dass eine kostengünstige Oxidation durch Sauerstoff prinzipiell möglich ist. Hierzu müssten allerdings die Reaktionsbedingungen weiter optimiert werden, um einen Bindungsbruch oder andere Nebenreaktionen vollständig zu unterdrücken.

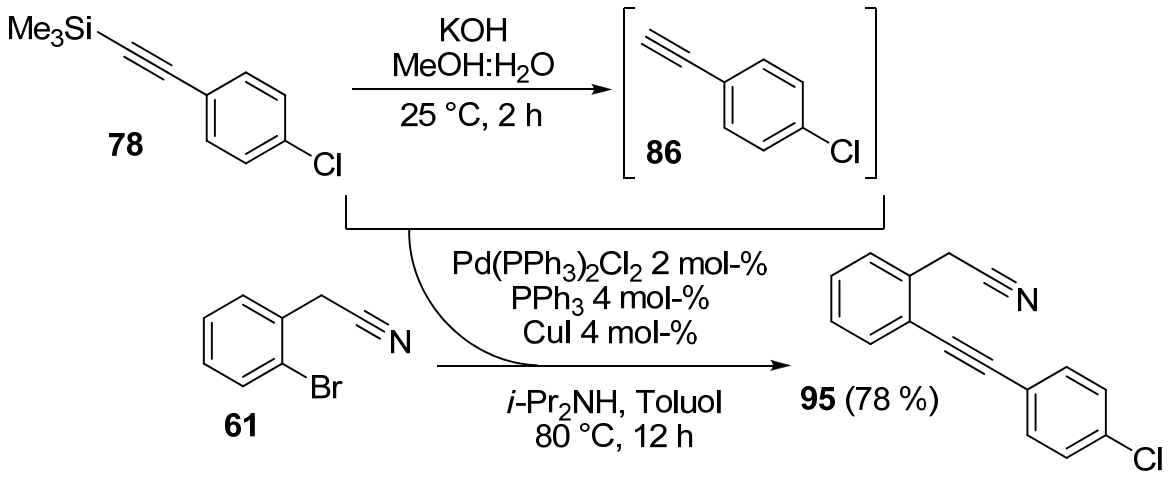
3.2.5 Ein-Topf-Synthese der benötigten Bisarylnitriloalkine

Die benötigten Bisarylnitriloalkine mit Hilfe einer Ein-Topf-Synthese herzustellen wurde bereits während der Totalsynthese von (*S*)-(+)-Laudanosin versucht. Bislang führten diese Untersuchungen jedoch nicht zu einem Ergebnis (Schema **37**).[75]



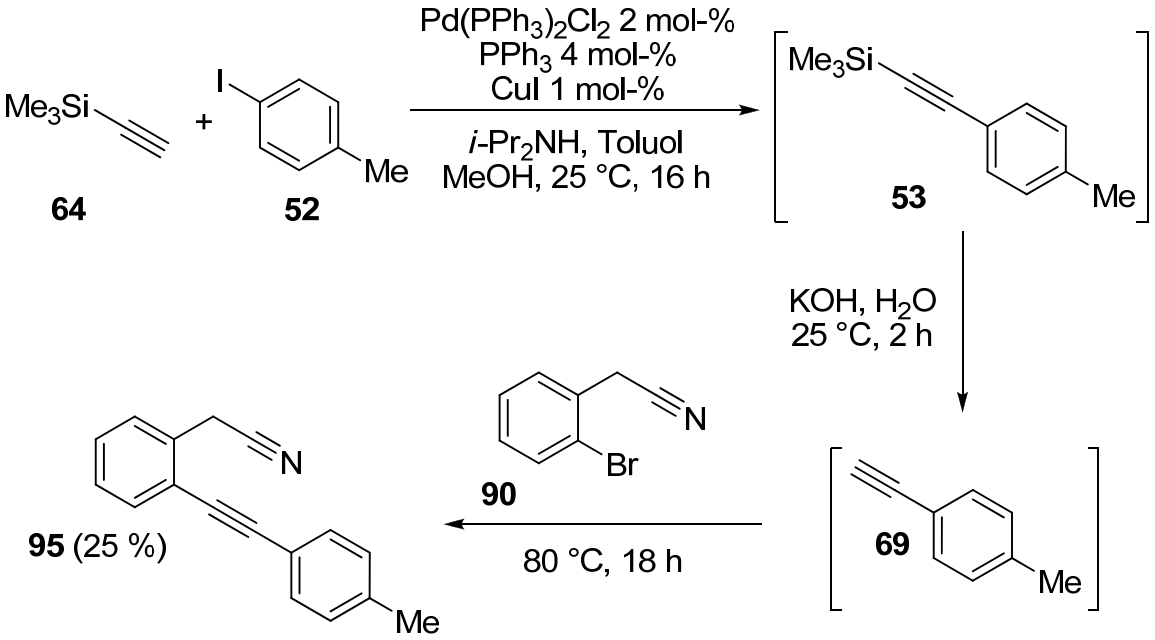
Schema 37 Gewünschte Ein-Topf-Reaktion zur Synthese von Bisarylnitriloalkinen

Auch der Versuch, die Entschützung mit Hilfe von Silbernitrat (Schema **23**) in die Ein-Topf-Synthese (Schema **37**) zu integrieren, schlug fehl. Ein entscheidender Fortschritt war die Optimierung der Bedingungen (Methanol und geringe Mengen an Wasser als Lösungsmittel und KOH als Base) zur Freilegung der terminalen Alkinfunktion (Schema **25**). Diese Reaktionsbedingungen sollten keinen Einfluss auf die anschließende Sonogashira-Reaktion haben. Um dies zu überprüfen, wurde in einer Testreaktion das kommerziell erhältliche Benzylnitril **61** mit der *in situ* entschützten Verbindung **86** unter Sonogashira-Bedingungen umgesetzt (Schema **38**).



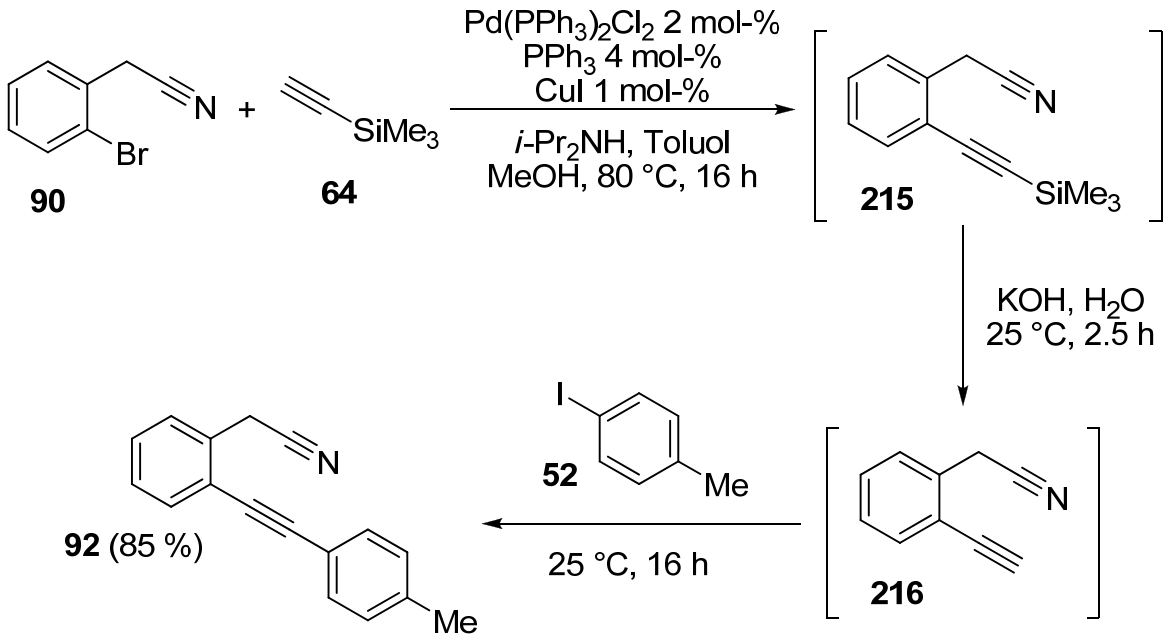
Schema 38 Sonogashira-Reaktion mit *in situ* Desilyierung des geschützten Arylalkins.

Die gute Ausbeute (Schema **38**, 78 %) bestätigte die oben genannte Vermutung. Der nächste logische Schritt war die vorangegangene Sonogashira-Reaktion (Schema **23** und Schema **24**) ebenfalls in den Prozess einzugliedern. Es folgte der erste Versuch, durch eine Ein-Topf-Reaktion die Verbindung **92** direkt zu synthetisieren (Schema **39**).



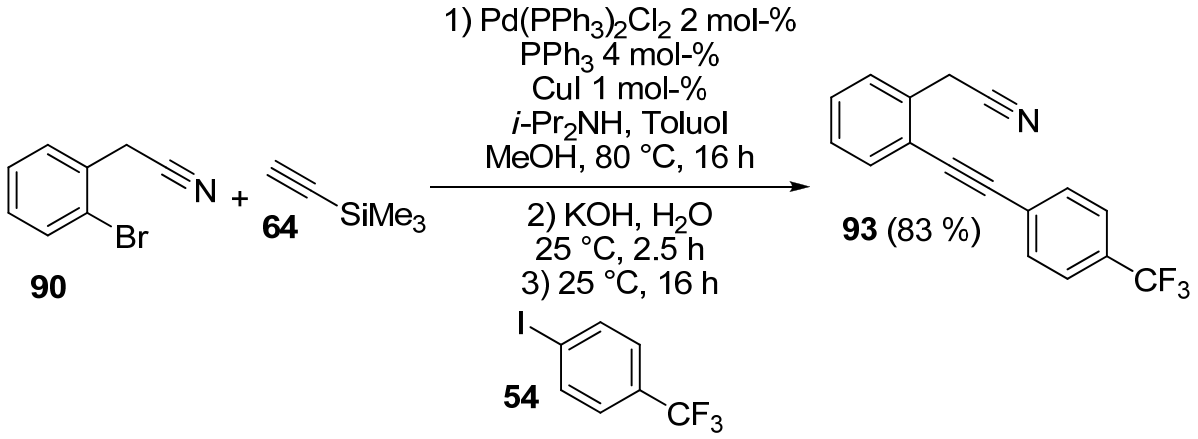
Schema 39 Syntheseversuch der Verbindung **92** durch Ein-Topf-Reaktion.

Die Teilschritte der Reaktion wurden mittels Gaschromatographie verfolgt und kontrolliert. Dabei fiel auf, dass im letzten Schritt, der zweiten Sonogashira-Reaktion diverse Nebenprodukte entstanden. Der Grund hierfür wurde auf die stark basischen Reaktionsbedingungen in Kombination mit der vermutlich zu hohen Temperatur von 80 °C zurückgeführt. Dadurch könnte ein nukleophiler Angriff auf die Nitrilfunktion nicht ausgeschlossen werden. Aus diesem Grund wurde in den folgenden Ein-Topf-Reaktionen erst das weniger reaktive Arylnitrilobromid mit Trimethylsilylacetylen umgesetzt. Nach anschließender Entschützung erfolgte die zweite Sonogashira-Reaktion bei Raumtemperatur. Mit Hilfe der entwickelten Ein-Topf-Reaktion konnte so die Gesamtausbeute für Verbindung **92** im Vergleich zur bisherigen Synthese um 29 % erhöht werden (Schema **40**).



Schema 40 Verbesserte Ein-Topf-Reaktion zur Synthese der Verbindung **92**.

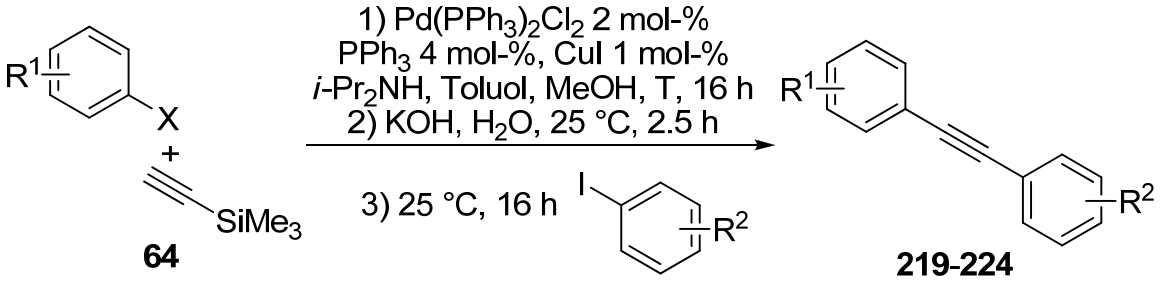
Durch diese Methode ließ sich auch das benötige Bisarylnitriloalkin **93** in einem Schritt mit einer sehr guten Ausbeute von 83 % synthetisieren (Schema **41**).

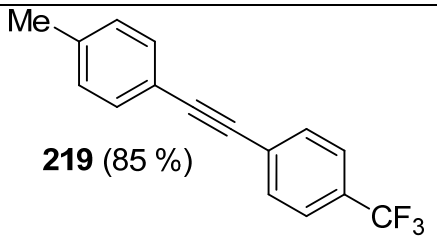
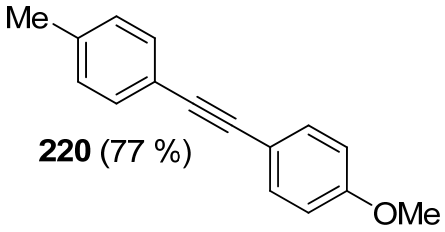
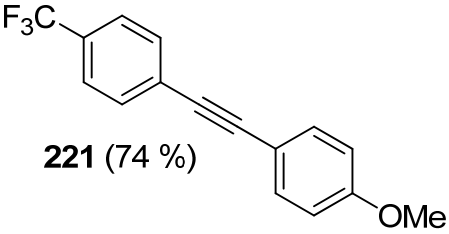
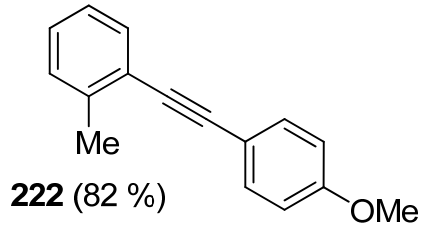
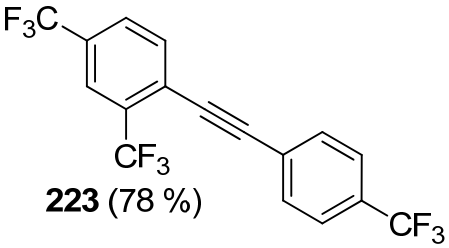
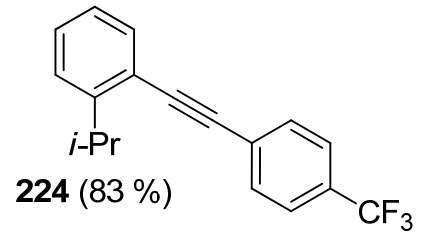


Schema 41 Verbesserte Ein-Topf-Reaktion zur Synthese der Verbindung **93**.

Um die Einsatzbreite der entwickelten Ein-Topf-Synthese zu testen, wurden zusätzlich verschiedene einfache Arylhalogenide eingesetzt, um unterschiedlich substituierte Bisarylalkine zu synthetisieren (Tabelle **7**). Neben der elektronischen Situation (Methoxy-, Alkyl- und Trifluormethylsubstituenten) wurde auch der sterische Anspruch der eingesetzten Arylhalogenide variiert. Neben einer *ortho*-Methyl Verbindung (**88**) wurden auch die räumlich anspruchsvollere *ortho*-trifluormethylsubstituierte Verbindung **217** sowie die *ortho*-isopropylsubstituierte Verbindung **218** eingesetzt.

Tabelle 7 Ausbeuten der Bisarylalkine aus der entwickelten Ein-Topf-Reaktion.



Nr.	R^1	X	T	Ar^1-X	R^2	Ar^2-X	Produkt (Ausbeute[a])
1	*p*-Me	I	25 °C	**67**	*p*-CF_3	**68**	 **219** (85 %)
2	*p*-Me	I	25 °C	**67**	*p*-OMe	**71**	 **220** (77 %)
3	*p*-OMe	I	25 °C	**71**	*p*-CF_3	**68**	 **221** (74 %)
4	*o*-Me	I	25 °C	**88**	*p*-OMe	**71**	 **222** (82 %)
5	*o/p*-$(CF_3)_2$	Br	80 °C	**217**	*p*-CF_3	**68**	 **223** (78 %)
6	*o*-*i*-Pr	I	25 °C	**218**	*p*-CF_3	**68**	 **224** (83 %)

[a] Reaktionsbedingungen: 1) Arylhalogenid (1 eq), Trimethylsilylacetylen (**64**) (1.2 eq)), $Pd(PPh_3)_2Cl_2$ (2 mol-%), PPh_3 (4 mol-%), CuI (2 mol-%), *i*-Pr_2NH, Toluol, T, 16 h. 2) KOH (2 eq), MeOH, 25 °C, 3 h. 3) Aryliodid (1 eq), 25 °C, 16 h. Isolierte Ausbeute.

Wie man aus Tabelle **7** erkennen kann, wurden die gewünschten Bisarylalkine in guten bis sehr guten Ausbeuten (74-85 %) erhalten. Beide Sonogashira-Kupplungen wurden mit einer einzigen, sehr geringen Katalysatorladung (2 mol-%) realisiert. Die *in situ* Entschützung erfolgte durch Zugabe von kostengünstigem wässrigen Methanol und Kaliumhydroxid bei Raumtemperatur. Diese Methode ist auch im Gramm-Maßstab (Tabelle **7**, Eintrag 5) anwendbar und zeichnet sich des Weiteren durch die guten Ausbeuten (74-85 %) aus.

4. Zusammenfassung und Ausblick

Zu Beginn der vorliegenden Arbeit wurden zwei Titanpentafullvenkomplexe und der homoleptische Titantetrabenzylkomplex der Arbeitsgruppe Beckhaus auf ihre Anwendung zur intramolekularen Hydroaminierung von Alkenen untersucht und mit bekannten Systemen verglichen. Dabei stellte sich heraus, dass alle Komplexe katalytische Aktivität bei der Umsetzung von Amino-2,2-diphenylpent-4-en zeigen. Durch Variation des eingesetzten Amins ließ sich feststellen, dass der neue homoleptische Komplex $TiBn_4$ ähnliche Aktivität wie der bereits bekannte $Ti(NMe_2)_4$ Komplex besitzt. Der untersuchte Benzofulvenkomplex mit Indenylliganden zeigte zum Ind_2TiMe_2 analoge Ergebnisse. Auch wenn die Pentafulvenkomplexe mit Cp-Liganden nur stark Thorpe-Ingold aktivierte Aminoalkene cyclisieren konnten, besitzen diese ebenfalls wie der Benzofulvenkomplex ein sehr hohes Potential für mechanistische Studien. Bereits bei Raumtemperatur erfolgt eine Reaktion des Katalysators mit dem Amin. Das entstandene Additionsprodukt konnte bereits kristallisiert werden und zeigt als Molekülstruktur eine Amido-Spezie.[91] Derzeit wird im Arbeitskreis Beckhaus versucht, weitere Zwischenprodukte aus dem postulierten Katalysezyklus zu erhalten. Da das katalytisch aktive Katalysatorsystem verwendet wurde, kann von den erhaltenen Molekülstrukturen direkt auf den Mechanismus der intramolekularen Hydroaminierung von Aminoalkenen geschlossen werden.

Der Hauptteil dieser Arbeit befasst sich mit der Synthese von 1-Benzylisochinolin-Derivaten mit elektronenarmem sowie elektronisch neutralem A-Ring. Des Weiteren wurde die Elektronendichte am C-Ring variiert. Die Einführung des A- und C-Rings erfolgte durch eine Sonogashira-Reaktion. Nach der Reduktion zum Amin wurden durch eine Kombination aus Hydroaminierung und Reduktion 28 Norlaudanosin-Derivate in guten (67 %) bis exzellenten (96 %) Ausbeuten synthetisiert (Abbildung **20**). Hierbei wurde ein Vertreter zum entsprechenden Laudanosin-Derivat transformiert. Eine weitere Transformation des Hydroaminierungsproduktes erfolgte durch Zugabe von Pd/C und Sauerstoff. So erfolgte eine Oxidation der Benzylposition. Die erhaltenen 28 3,4-Dihydropapaveraldin-Derivate ließen sich in moderaten (39 %) bis sehr guten (90 %) Ausbeuten isolieren.

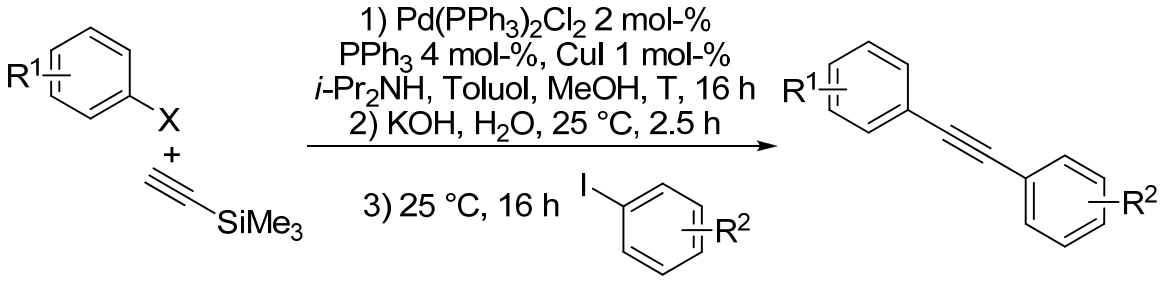
3,4-Dihydropapaveraldin-Derivate Norlaudanosin-Derivate

Abbildung 20 Synthetisierte Norlaudanosin- und Dihydropapaveraldin-Derivate.

Aufgrund des enthaltenen 1-Benzylisochinolin Grundgerüsts besitzen diese Verbindungen ein hohes pharmakologisches Potential. In der Vergangenheit standen bereits bekannte 1-Benzylisochinolin-Derivate im Mittelpunkt von Wirkstoffoptimierungsversuchen. Allerdings wurden in diesen nur Derivate mit elektronenreichem A-Ring untersucht.

In der vorliegenden Arbeit erfolgte ebenfalls die Untersuchung und der Nachweis der selektiven Oxidation des B-Rings zum Isochinolinsystem. Auf eine Optimierung der Oxidationsbedingungen zur selektiven Synthese der entsprechenden Papaverin-Derivate konnte jedoch aus Zeitgründen nicht näher eingegangen werden.

Eine deutliche Vereinfachung in der Synthese von 1-Benzylisochinolin-Derivaten ließ sich durch das entwickelte Ein-Topf-Verfahren erreichen (Schema **42**).



Schema 42 Entwickeltes Ein-Topf-Verfahren zur Synthese von Bisarylalkinen.

Mit diesem Protokoll wurden unterschiedlich substituierte Arylhalogenide mit Trimethylsilylacetylen zu den entsprechenden Bisarylalkinen synthetisiert. Die enthaltenen Sonogashira-Kupplungen wurden mit einer einzigen, sehr geringen Katalysatorladung (2 mol-%) realisiert. Die *in situ* Entschützung erfolgte durch Zugabe von kostengünstigem wässrigen Methanol und Kaliumhydroxid bei Raumtemperatur. Diese Methode ist auch im Gramm-Maßstab anwendbar und zeichnet sich des Weiteren durch die guten Ausbeuten (> 80 %) aus.

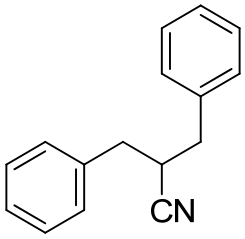
5. Experimenteller Teil

All reactions were performed under an inert atmosphere of argon in oven dried Duran glassware. Schlenk tube reactions were performed under an inert atmosphere of nitrogen in oven dried Schlenk tubes (Duran glassware, 100 mL, Ø 30 mm) equipped with Teflon stopcocks and magnetic stirring bars (15 × 4.5 mm). Toluene was distilled from molten sodium under argon or purchased (toluene extra dry (Molecular sieves) from Acros Organics. All other reagents were purchased from commercial sources and were used without further purification. Unless otherwise noted, yields refer to isolated yields of pure compounds as gauged by thin layer chromatography (TLC), ^{1}H and ^{13}C NMR. All products were characterized by ^{1}H NMR, ^{13}C NMR, infrared (IR) spectroscopy, and mass spectrometry (MS). Additional characterization data were obtained by high-resolution mass spectrometry (HRMS). NMR spectra were recorded on the following spectrometers: Bruker Avance DRX 500, Bruker Avance III, 500 MHz. All ^{1}H NMR spectra are reported in δ units ppm relative to the signal of TMS at 0.00 ppm. All ^{13}C NMR spectra are reported in δ units ppm relative to the central line of the triplet for $CDCl_3$ at 77.0 ppm. Infrared spectra were recorded on a Bruker Tensor 27 spectrometer using an attenuated total reflection (ATR) method. Mass spectra were recorded on a Finnigan TSQ 700 or a Finnigan MAT 95 spectrometer (EI) with an ionization potential of 70 eV or a Waters Micromass Q-Tof Premier spectrometer (ESI, 8 eV). Melting points are uncorrected. PE: light petroleum ether, b.p. 40-60 °C. MTBE: methyl *tert*-butyl ether. TLC analyses were performed with Polygram SIL G/UV254 plates from Macherey–Nagel. Detection of the compounds was achieved with UV light. For flash chromatography silica gel 60 from Fluka (230–400 mesh, particle size 0.040–0.063 mm) was used.

Preparation of a solution of monomeric formaldehyde in THF: A mixture of dry paraformaldehyde (3.00 g, dried for two days in a dry oven under vacuum at 80 °C), THF (100 mL) and a few drops of $BF_3 \cdot Et_2O$ was refluxed at 70 °C for 2 h. Then, the mixture was slowly distilled and collected in a two-necked flask cooled to −70 °C. The concentration of the solution is approximately 0.8 mol/L.

Hydroamination of volatile aminoalkenes and subsequent formation of benzoylamides; General procedure A: An oven dried Schlenk tube equipped with a Teflon stopcock and a magnetic stirring bar was transferred into a nitrogen-filled glovebox and charged with the catalyst (0.12 mmol, 5 mol-%), toluene (1.0 mL), the aminoalkene (2.40 mmol) and toluene (1.0 mL). Then, the tube was sealed, and the resulting mixture was heated to 105 °C for the appropriate time. After the mixture had been cooled to room temperature, CH_2Cl_2 (10.0 mL) and NEt_3 (1.0 mL, 7.2 mmol) was added in one portion, benzoylchloride (**43**, 0.3 mL, 2.64 mmol) were added dropwise under water cooling. The resulting mixture was stirred at 25 °C for 12 h. Then, the solution was diluted with CH_2Cl_2 (30 mL) and washed with saturated aqueous NH_4Cl solution. The aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL) and the combined organic layers were dried ($MgSO_4$) and concentration under vacuum in the presence of Celite®. The product was isolated by flash chromatography.

Hydroamination of non-volatile aminoalkenes; General procedure B: An oven dried Schlenk tube equipped with a Teflon stopcock and a magnetic stirring bar was transferred into a nitrogen-filled glovebox and charged with the catalyst (0.12 mmol, 5 mol-%), toluene (1.0 mL), the aminoalkene (2.40 mmol) and toluene (1.0 mL). Then, the tube was sealed, and the resulting mixture was heated to 105 °C for the appropriate time. After the mixture had been cooled to room temperature, the solution was diluted with CH_2Cl_2 (30 mL) and washed with saturated aqueous NH_4Cl solution. The aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL) and the combined organic layers were dried ($MgSO_4$) and concentration under vacuum in the presence of Celite®. The product was isolated by flash chromatography.



$C_{16}H_{15}N$
MW: 221.30

2-Benzyl-3-phenylpropanenitrile (**32**): 3-Phenylpropanenitrile (**33**, 20.1 g, 152 mmol) was added to a solution of LDA [generated in situ from *n*-BuLi (64 mL in hexanes, 2.5 M, 160 mmol) and diisopropylamine (10.4 g, 152 mmol) in THF (400 mL)] at −78 °C and stirred for 30 min. To the resulting solution (chloromethyl)benzene (**34**, 38.6 g, 305 mmol) was added. The solution was warmed to room temperature overnight with stirring. Et_2O (100 mL) was added and the resulting mixture was washed with 2 N HCl (2 × 100 mL). The combined aqueous layers were extracted with Et_2O (3 × 100 mL) and the combined organic layers were dried ($MgSO_4$) and concentrated under vacuum. The residue was purified by column chromatography (PE/EtOAc, 90:10, R_f = 0.28) to give **32** (32.2 g, 146 mmol, 95 %) as colorless crystals.

M.p.: 89 °C.

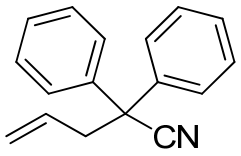
^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.90 (d, J = 7.1 Hz, 4 H), 2.97-3.05 (m, 1 H), 7.20-7.35 (m, 10 H) ppm.

^{13}C NMR (126 MHz, DEPT, $CDCl_3$): δ = 35.8 (CH_2), 37.9 (CH), 121.2 (C), 127.3 (CH), 128.7 (CH), 129.0 (CH), 136.8 (C) ppm.

IR (neat): $\tilde{\nu}$ = 3028, 2936, 2241, 1605, 1493, 1455, 1081, 1027, 914, 756, 737, 699 cm^{-1}.

MS (EI): *m/z* (%) = 221 (20) $[M]^+$, 91 (100), 65 (9).

HRMS: calcd. ($C_{16}H_{15}N$) 221.1204; found 221.1209.



$C_{17}H_{15}N$
MW: 233.31

2,2-Diphenylpent-4-enenitrile (**35**): 2,2-Diphenylacetonitrile (**6**, 45.7 g, 237 mmol) was added to a solution of LDA [generated in situ from *n*-BuLi (100 mL in hexanes, 2.5 M, 250 mmol) and diisopropylamine (23.9 g, 237 mmol) in THF (600 mL)] at −78 °C and stirred for 2 h. To the resulting solution allyl bromide (**28**, 57.2 g, 473 mmol) was added. The solution was warmed to room temperature overnight with stirring. Et_2O (100 mL) was added and the resulting mixture was washed with 2 N HCl (2 × 100 mL). The combined aqueous phase was extracted with Et_2O (3 × 100 mL) and the combined organic layers were dried ($MgSO_4$) and concentrated under vacuum. The residue was purified by Kugelrohr distillation (0.2 mbar, 170 °C) to give **35** (50.0 g, 214 mmol, 91 %) as a colorless oil.

B.p.: 170 °C (0.1 mbar).

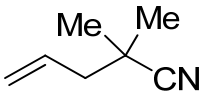
^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.12 (d, J = 7.0 Hz, 2 H), 5.15 (d, J = 10.2 Hz, 1 H), 5.19 (d, J = 17.0 Hz, 1 H), 5.70 (ddt, J = 17.1, 10.2, 7.0 Hz, 1 H), 7.25-7.41 (m, 12 H) ppm.

^{13}C NMR (126 MHz, DEPT, $CDCl_3$): δ = 43.9 (CH_2), 51.7 (C), 120.3 (CH_2), 121.9 (C), 127.0 (CH), 127.9 (CH), 128.8 (CH), 131.7 (CH), 139.7 (C) ppm.

IR (neat): $\tilde{\nu}$ = 3063, 3031, 2982, 1642, 1598, 1493, 1449, 1033, 991, 924, 752, 695 cm^{-1}.

MS (EI): *m/z* (%) = 233 (4) $[M]^+$, 192 (100), 165 (54).

HRMS: calcd. ($C_{17}H_{15}N$) 233.1204; found 233.1202.



$C_7H_{11}N$
MW: 109.17

2,2-Dimethyl-4-pentenenitrile (**36**): Isobutyronitrile (**30**, 16.9 g, 244 mmol) was added to a solution of LDA [generated in situ from *n*-BuLi (100 mL in hexanes, 2.5 M, 250 mmol) and diisopropylamine (24.7 g, 244 mmol) in THF (600 mL)] at −78 °C and stirred for 45 min. To the resulting solution allyl bromide (**28**, 59.0 g, 488 mmol) was added. The solution was warmed to room temperature overnight with stirring. Et_2O (100 mL) was added and the resulting mixture was washed with 2 N HCl (2 × 100 mL). The combined aqueous phase was extracted with Et_2O (3 × 100 mL) and the combined organic layers were dried ($MgSO_4$) and concentrated under vacuum. The residue was distilled under reduced pressure (31 mbar, 35 °C) to give **36** (17.5 g, 160 mmol, 66 %) as a colorless oil.

B.p.: 60 °C (31 mbar).

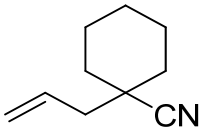
^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.34 (s, 6 H), 2.28 (d, J = 7.4 Hz, 2 H), 5.19 (d, J = 16.9 Hz, 1 H), 5.23 (d, J = 9.8 Hz, 1 H), 5.87 (ddt, J = 17.3, 10.1, 7.4 Hz, 1 H) ppm.

^{13}C NMR (126 MHz, J-MOD, $CDCl_3$): δ = 26.1 (CH_3), 32.1 (C), 45.0 (CH_2), 119.8 (CH_2), 124.6 (C), 132.1 (CH) ppm.

IR (neat): $\tilde{\nu}$ = 2983, 2939, 2237, 1646, 1471, 1393, 1373, 1282, 1195, 999, 926, 720 cm^{-1}.

MS (EI): *m/z* (%) = 109 (11) $[M]^+$, 94 (3), 68 (14), 41 (100).

HRMS: calcd. ($C_7H_{11}N$) 109.0891; found 109.0890.



$C_{10}H_{15}N$
MW: 149.23

1-Allylcyclohexanecarbonitrile (**37**): Cyclohexanecarbonitrile (**31**, 25.8 g, 237 mmol) was added to a solution of LDA [generated in situ from *n*-BuLi (100 mL in hexanes, 2.5 M, 250 mmol) and diisopropylamine (23.9 g, 244 mmol) in THF (600 mL)] at −78 °C and stirred for 2 h. To the resulting solution allyl bromide (**28**, 57.2 g, 473 mmol) was added. The solution was warmed to room temperature overnight with stirring. Et_2O (100 mL) was added and the resulting mixture was washed with 2 N HCl (2 × 100 mL). The combined aqueous layers were extracted with Et_2O (3 × 100 mL) and the combined organic layers were dried ($MgSO_4$) and concentrated under vacuum. The residue was distilled under reduced pressure (33 mbar, 88 °C) to give **37** (24.5 g, 164 mmol, 69 %) as a colorless liquid.

B.p.: 88 °C (33 mbar).

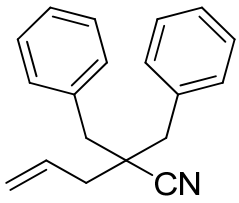
^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.11-1.30 (m, 3 H), 1.56-1.68 (m, 2 H), 1.68-1.78 (m, 3 H), 1.95 (d, *J* = 13.0 Hz, 2 H), 2.28 (d, *J* = 7.4 Hz, 2 H), 5.17 (d, *J* = 17.7 Hz, 1 H), 5.20 (d, *J* = 10.9 Hz, 1 H), 5.88 (ddt, *J* = 17.3, 10.3, 7.4 Hz, 1 H) ppm.

^{13}C NMR (126 MHz, DEPT, $CDCl_3$): δ = 22.9 (CH_2), 25.2 (CH_2), 35.2 (CH_2), 38.7 (C), 44.5 (CH_2), 119.4 (CH_2), 123.1 (C), 131.8 (CH) ppm.

IR (neat): $\tilde{\nu}$ = 2933, 2860, 1643, 1452, 996, 974, 821, 847, 714 cm^{-1}.

MS (EI): *m/z* (%) = 149 (82) $[M]^+$, 134 (15), 121 (24), 108 (56), 92 (11), 81 (100), 67 (36), 53 (16), 41 (63).

HRMS: calcd. ($C_{10}H_{19}N$) 149.1204; found 149.1205.



$C_{19}H_{19}N$
MW: 261.36

2,2-Dibenzylpent-4-enenitrile (**38**): 2-Benzyl-3-phenylpropanenitrile (**32**, 25.8 g, 237 mmol) was added to a solution of LDA [generated in situ from *n*-BuLi (100 mL in hexanes, 2.5 M, 250 mmol) and diisopropylamine (23.9 g, 237 mmol) in THF (600 mL)] at −78 °C and stirred for 2 h. To the resulting solution allyl bromide (**28**, 57.2 g, 473 mmol) was added. The solution was warmed to room temperature overnight with stirring. Et_2O (100 mL) was added and the resulting mixture was washed with 2 N HCl (2 × 100 mL). The combined aqueous layers were extracted with Et_2O (3 × 100 mL) and the combined organic layers were dried ($MgSO_4$) and concentrated under vacuum. The residue was purified by column chromatography (PE:EtOAc, 98:2) to give **38** (24.7 g, 94.5 mmol, 80 %) as a colorless oil.

B.p.: 160 °C (0.07 mbar).

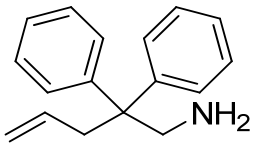
^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.28 (d, J = 7.2 Hz, 2 H), 2.83 (d, J = 13.9 Hz, 2 H), 2.86 (d, J = 13.7 Hz, 2 H), 5.21 (d, J = 17.0 Hz, 1 H), 5.28 (d, J = 10.1 Hz, 1 H), 5.91 (ddt, J = 17.0, 10.1, 7.2 Hz, 1 H), 7.26-7.36 (m, 10 H) ppm.

^{13}C NMR (126 MHz, DEPT, $CDCl_3$): δ = 40.4 (CH_2), 42.8 (CH_2), 42.8 (C), 120.5 (CH), 122.4 (C), 127.4 (CH), 128.4 (CH), 130.5 (CH), 132.0 (CH), 135.2 (C) ppm.

IR (neat): $\tilde{\nu}$ = 3030, 2935, 1643, 1604, 1496, 1454, 1088, 1028, 994, 922, 757, 699 cm^{-1}.

MS (EI): *m/z* (%) = 261 (4) $[M]^+$, 170 (1), 168 (1), 115 (2), 91 (100), 65 (6), 41 (1).

HRMS: calcd. ($C_{19}H_{19}N$) 261.1517; found 261.1514.



$C_{17}H_{19}N$
MW: 237.34

2,2-Diphenylpent-4-en-1-amine (**39**): 2,2-Diphenylpent-4-enenitrile (**35**, 50.0 g, 241 mmol) was added dropwise to a suspension of $LiAlH_4$ (13.7 g, 360 mmol) in dry Et_2O (300 mL) at 0 °C. The Reaction mixture was heated to 35 °C overnight, cooled to 0 °C and saturated aqueous K_2SO_4 (10 mL) and 5 N NaOH (10 mL) was added dropwise. The suspension was filtered and the aqueous layer was extracted with Et_2O (3 × 100 mL). The organic layer was dried ($MgSO_4$) and concentrated under vacuum. The residue was purified by Kugelrohr distillation (0.13 mbar, 144 °C) to give **39** (43.6 g, 184 mmol, 86 %) as a colorless oil.

B.p.: 144 °C (0.13 mbar).

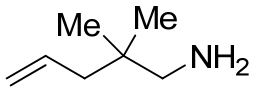
^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.02 (br. s, 2 H), 2.92 (d, *J* = 7.1 Hz, 2 H), 3.32 (s, 2 H), 4.97 (d, *J* = 10.2 Hz, 1 H), 5.05 (d, *J* = 17.0 Hz, 1 H), 5.39 (ddt, *J* = 17.0, 10.2, 7.2 Hz, 1 H), 7.15-7.22 (m, 6 H), 7.25-7.31 (m, 4 H) ppm.

^{13}C NMR (126 MHz, DEPT, $CDCl_3$): δ = 41.1 (CH_2), 48.5 (CH_2), 51.3 (C), 117.7 (CH_2), 126.1 (CH), 128.1 (CH), 128.2 (CH), 134.6 (CH), 146.2 (C) ppm.

IR (neat): $\tilde{\nu}$ = 3059, 3026, 2931, 2860, 1600, 1496, 1446, 1035, 1001, 916, 756, 698 cm^{-1}.

MS (EI): *m/z* (%) = 237 (1) $[M]^+$, 260 (35), 178 (16), 165 (26), 129 (100), 115 (11), 91 (81).

HRMS: calcd. ($C_{17}H_{19}N$) 153.1517; found 153.1521.



$C_7H_{15}N$
MW: 113.20

2,2-Dimethylpent-4-en-1-amine (**40**): 2,2-Dimethylpent-4-ene-1-nitrile (**36**, 17.5 g, 160 mmol) was added dropwise to a suspension of $LiAlH_4$ (9.10 g, 240 mmol) in dry Et_2O (200 mL) at 0 °C. The Reaction mixture was heated to 35 °C overnight, cooled to 0 °C and saturated aqueous K_2SO_4 (10 mL) and 5 N NaOH (10 mL) was added dropwise. The suspension was filtered and the aqueous layer was extracted with Et_2O (3 × 100 mL). The organic layer was dried ($MgSO_4$) and concentrated under vacuum. The residue was distilled under reduced pressure (40 mbar, 45 °C) to afford **40** (16.3 g, 144 mmol, 90 %) as a colorless liquid.

B.p.: 45 °C (40 mbar).

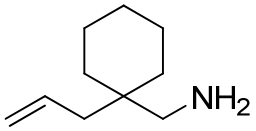
^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.86 (s, 6 H), 1.48 (br. s, 2 H), 1.97 (d, J = 7.5 Hz, 2 H), 2.45 (s, 2 H), 4.99-5.07 (m, 2 H), 5.76-5.87 (m, 1 H) ppm.

^{13}C NMR (126 MHz, DEPT, $CDCl_3$): δ = 24.5 (CH_3), 34.8 (C), 43.9 (CH_2), 52.5 (CH_2), 116.9 (CH_2), 135.2 (CH) ppm.

IR (neat): $\tilde{\nu}$ = 3075, 2956, 2606, 2868, 1638, 1471, 1388, 1364, 1261, 1062, 996, 911, 804, 741 cm^{-1}.

MS (EI): *m/z* (%) = 113 (6) $[M]^+$, 98 (58), 82 (5), 69 (6), 57 (100), 56 (25), 55 (11), 49 (6), 42 (12), 41 (22).

HRMS: calcd. ($C_7H_{15}N$) 113.1204; found 113.1207.



$C_{10}H_{19}N$
MW: 153.26

(1-Allylcyclohexyl)methanamine (**41**): 1-Allylcyclohexanecarbonitrile (**37**, 24.4 g, 164 mmol) was added dropwise to a suspension of $LiAlH_4$ (9.30 g, 245 mmol) in dry Et_2O (200 mL) at 0 °C. The Reaction mixture was heated to 35 °C overnight, cooled to 0 °C and saturated aqueous K_2SO_4 (10 mL) and 5 N NaOH (10 mL) was added dropwise. The suspension was filtered and the aqueous layer was extracted with Et_2O (3 × 100 mL). The organic layer was dried ($MgSO_4$) and concentrated under vacuum. The residue was distilled under reduced pressure (37 mbar, 121 °C) to afford **41** (13.0 g, 84.8 mmol, 52 %) as a colorless oil.

B.p.: 37 °C (121 mbar).

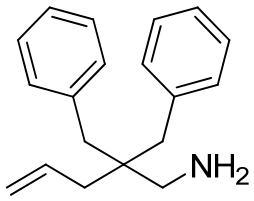
^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.07 (br. s, 2 H), 1.22-1.49 (m, 10 H), 2.07 (d, *J* = 7.6 Hz, 2 H), 2.52 (s, 2 H), 5.04 (d, *J* = 9.8 Hz, 1 H), 5.05 (d, *J* = 17.9 Hz, 1 H), 5.80 (ddt, *J* = 17.4, 10.0, 7.6 Hz, 1 H) ppm.

^{13}C NMR (126 MHz, DEPT, $CDCl_3$): δ = 21.4 (CH_2), 26.3 (CH_2), 33.2 (CH_2), 36.9 (C), 39.8 (CH_2), 48.7 (CH_2), 116.7 (CH_2), 134.9 (CH) ppm.

IR (neat): $\tilde{\nu}$ = 2922, 2849, 1637, 1454, 1068, 998, 909, 796, 728 cm^{-1}.

MS (EI): *m/z* (%) = 152 (1) $[M]^+$, 138 (49), 122 (17), 111 (26), 107 (15), 95 (21), 95 (13), 81 (100), 79 (20), 69 (14), 67 (35), 57 (12), 55 (19), 41 (29).

HRMS: calcd. ($C_{10}H_{19}N$) 153.1517; found 153.1517.



$C_{19}H_{23}N$
MW: 265.39

2,2-Dibenzylpent-4-en-1-amine (**42**): 2,2-Dibenzylpent-4-enenitrile (**38**, 7.50 g, 28.7 mmol) was added dropwise to a suspension of $LiAlH_4$ (1.6 g, 42.2 mmol) in dry Et_2O (110 mL) at 0 °C. The Reaction mixture was heated to 35 °C overnight, cooled to 0 °C and saturated aqueous K_2SO_4 (10 mL) and 5 N NaOH (10 mL) was added dropwise. The suspension was filtered and the aqueous layer was extracted with Et_2O (3 × 50 mL). The organic layer was dried ($MgSO_4$) and concentrated under vacuum. The residue was purified by column chromatography (MTBE/7 N NH_3 in MeOH 98:2, R_f = 0.64) to give **42** (6.63 g, 25.0 mmol, 86 %) as a colorless oil.

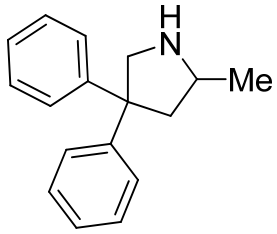
^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.07 (br. s, 2 H), 2.03 (d, *J* = 7.1 Hz, 2 H), 2.49 (s, 2 H), 2.65 (d, *J* = 13.6 Hz, 2 H), 2.69 (d, *J* = 13.5 Hz, 2 H), 5.10 (d, *J* = 17.0 Hz, 1 H), 5.15 (d, *J* = 10.2 Hz, 1 H), 6.01 (ddt, *J* = 17.0, 10.2, 7.2 Hz, 1 H), 7.17-7.30 (m, 10 H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$): δ = 38.5 (CH_2), 41.5 (CH_2), 42.5 (C), 46.7 (CH_2), 117.9 (CH_2), 126.0 (CH), 127.9 (CH), 130.6 (CH), 135.0 (CH), 138.5 (C) ppm.

IR (neat): $\tilde{\nu}$ = 3027, 2919, 2857, 1635, 1601, 1494, 1453, 1071, 1031, 994, 912, 748, 700 cm^{-1}.

MS (EI): *m/z* (%) = 264 (10) $[M]^+$, 207 (5), 193 (7), 174 (97), 157 (10), 143 (36), 129 (12), 115 (14), 91 (100), 65 (8).

HRMS: calcd. ($C_{19}H_{23}N$) 265.1830; found 265.1830.



$C_{17}H_{19}N$
MW: 237.34

2-Methyl-4,4-diphenylpyrrolidine (**44**): General procedure B was used to synthesize **44** from 2,2-diphenylpent-4-en-1-amine (**39**, 570 mg, 2.40 mmol). After chromatography (SiO_2, MTBE/7 N NH_3 in MeOH 95:5, R_f = 0.35), **44** was obtained as a colorless oil.

Entry	catalyst	time [h]	yield [mg]	yield [mmol]	yield [%]
1	**I**	24	525	2.21	92
2	**V**	24	517	2.18	90
3	**IV**	24	496	2.09	87
4	**VI**	24	502	2.12	88
5	**VII**	24	498	2.10	87
6	**VIII**	24	416	1.75	73

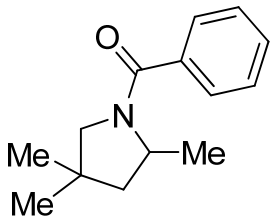
^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.20 (d, *J* = 6.7 Hz, 3 H), 2.03 (dd, *J* = 12.5, 8.9 Hz, 1 H), 2.10 (br. s, 1 H), 2.74 (dd, *J* = 12.5, 6.4 Hz, 1 H), 3.32-3.41 (m, 1 H), 3.47 (d, *J* = 11.0 Hz, 1 H), 3.67 (d, *J* = 11.6 Hz, 1 H), 7.14-7.18 (m, 2 H), 7.20-7.31 (m, 8 H) ppm.

^{13}C NMR (126 MHz, DEPT, $CDCl_3$): δ = 22.3 (CH_3), 47.0 (CH_2), 53.0 (CH), 57.2 (C), 57.9 (CH_2), 125.9 (CH), 125.9 (CH), 126.9 (CH), 127.0 (CH), 128.2 (CH), 128.3 (CH), 147.0 (C), 147.8 (C) ppm.

IR (neat): $\tilde{\nu}$ = 2960, 2869, 1599, 1494, 1447, 1374, 1099, 1034, 774, 756, 698 cm^{-1}.

MS (EI): *m/z* (%) = 237 (12) $[M]^+$, 178 (5), 165 (6), 115 (5), 91 (4), 57 (100), 56 (6).

HRMS: calcd. ($C_{17}H_{19}N$) 237.1517; found 237.1520.



$C_{14}H_{19}NO$
MW: 217.31

Phenyl(2,4,4-trimethylpyrrolidin-1-yl)methanone (**45**): General procedure A was used to synthesize **45** from 2,2-dimethylpent-4-en-1-amine (**40**, 272 mg, 2.40 mmol). After chromatography (SiO_2, PE/EtOAc, 80:20, R_f = 0.27) **45** was obtained as a colorless oil.

entry	catalyst	time [h]	yield [mg]	yield [mmol]	yield [%]
1	**I**	24	162	0.75	31
2		96	310	1.43	59
3	**V**	24	185	0.85	36
4		96	254	1.17	49
5	**IV**	24	178	0.82	34
6		96	308	1.42	59
7	**VI**	24	91	0.42	18
8		96	163	0.75	31
9	**VII**	24	0	0	0
10		96	24	0.11	5
11	**VIII**	24	0	0	0
12		96	0	0	0

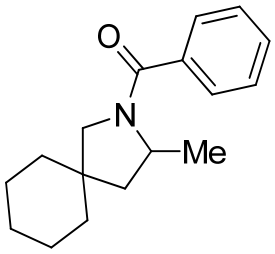
^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.91 (s, 3 H), 1.05 (s, 3 H), 1.37-1.45 (m, 4 H), 1.95 (dd, *J* = 12.8, 7.3 Hz, 1 H), 3.10 (d, *J* = 10.4 Hz, 1 H), 3.29 (d, *J* = 10.4 Hz, 1 H), 4.31-4.40 (m, 1 H), 7.36-7.55 (m, 5 H) ppm.

^{13}C NMR (126 MHz, DEPT, $CDCl_3$): δ = 20.2 (CH_3), 25.4 (CH_3), 25.7 (CH_3), 38.2 (C), 47.5 (CH_2), 52.9 (CH), 62.6 (CH_2), 127.5 (CH), 128.1 (CH), 129.9 (CH), 137.1 (C), 170.1 (C) ppm.

IR (neat): $\tilde{\nu}$ = 2957, 2868, 1716, 1626, 1577, 1447, 1403, 1372, 1352, 1290, 1213, 1136, 1074, 851, 792, 716, 698, 661 cm^{-1}.

MS (EI): *m/z* (%) = 217 (14) $[M]^+$, 174 (26), 105 (100), 77 (82), 56 (64), 55 (27), 51 (51), 50 (11), 42 (14), 41 (47).

HRMS: calcd. ($C_{14}H_{19}NO$) 217.1467; found 217.1464.



$C_{17}H_{23}NO$
MW: 257.37

Phenyl(2,4,4-trimethylpyrrolidin-1-yl)methanone (**46**): General procedure A was used to synthesize **46** from (1-allylcyclohexyl)methanamine (**41**, 368 mg, 2.40 mmol). After chromatography (SiO_2, PE/EtOAc 80:20, R_f = 0.57), **46** was obtained as a colorless oil.

entry	catalyst	time [h]	yield [mg]	yield [mmol]	yield [%]
1	**I**	24	545	2.12	88
2		96	573	2.23	93
3	**V**	24	450	1.75	73
4		96	554	2.15	90
5	**IV**	24	478	1.86	77
6		96	602	2.34	98
7	**VI**	24	433	1.68	70
8		96	547	2.13	89
9	**VII**	24	0	0	0
10		96	0	0	0
11	**VIII**	24	0	0	0
12		96	0	0	0

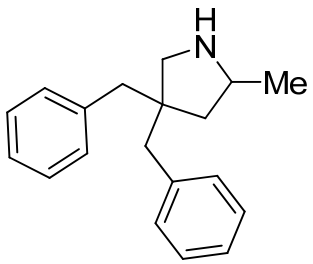
^{1}H NMR (500 MHz, $CDCl_3$, 50 °C): δ = 1.22-1.49 (m, 14 H), 2.12 (dd, J = 12.6, 7.5 Hz, 1 H), 3.16 (d, J = 11.0 Hz, 1 H), 3.29 (br. s, 1 H), 4.30 (br. s, 1 H), 7.33-7.41 (m, 3 H), 7.43-7.55 (m, 2 H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$, DEPT, 50 °C): δ = 20.3 (CH_3), 22.6 (CH_2), 23.7 (CH_2), 26.1 (CH_2), 33.7 (CH_2), 36.3 (CH_2), 42.2 (C), 44.8 (CH_2), 52.0 (CH), 60.2 (CH_2), 127.2 (CH), 128.1 (CH), 129.6 (CH), 137.5 (C), 170.1 (C) ppm.

IR (neat): $\tilde{\nu}$ = 2992, 2853, 1626, 1577, 1447, 1403, 1354, 1304, 1221, 1179, 1142, 1106, 792, 716, 698, 661 cm^{-1}.

MS (EI): *m/z* (%) = 257 (10) $[M]^+$, 242 (6), 161 (5), 160 (12), 106 (6), 105 (100), 77 (25), 56 (7), 41 (4).

HRMS: calcd. ($C_{17}H_{24}NO$) 258.1858; found 258.1864.



$C_{19}H_{23}N$
MW: 265.39

4,4-Dibenzyl-2-methylpyrrolidine (**47**): General procedure B was used to synthesize **47** from 2,2-dibenzylpent-4-en-1-amine (**42**, 637 mg, 2.40 mmol). After chromatography (SiO_2, MTBE/7 N NH_3 in MeOH 90:10, R_f = 0.32), **47** was obtained as a colorless oil.

entry	catalyst	time [h]	yield [mg]	yield [mmol]	yield [%]
1	**I**	24	550	2.07	86
2	**V**	24	588	2.22	92
3	**IV**	24	601	2.26	94
4	**VI**	24	593	2.23	93
5	**VII**	24	386	1.45	61
6	**VIII**	24	366	1.38	58

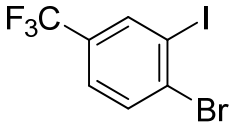
^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.97 (d, J = 6.7 Hz, 3 H), 1.30 (dd, J = 12.8, 9.2 Hz, 1 H), 1.44 (br. s, 1 H), 1.90 (dd, J = 12.8, 7.3 Hz, 1 H), 2.73 (d, J = 6.1 Hz, 4 H), 2.82 (d, J = 11.6 Hz, 1 H), 2.94 (d, J = 11.6 Hz, 1 H), 2.95-3.02 (m, 1 H), 7.14-7.25 (m, 6 H), 7.26-7.31 (m, 4 H) ppm.

^{13}C NMR (126 MHz, DEPT, $CDCl_3$): δ = 21.4 (CH_3), 43.9 (CH_2), 45.0 (CH_2), 45.3 (CH_2), 48.7 (C), 54.1 (CH), 56.2 (CH_2), 126.1 (CH), 126.1 (CH), 128.0 (CH), 130.4 (CH), 130.5 (CH), 139.0 (C), 139.1 (C) ppm.

IR (neat): $\tilde{\nu}$ = 3026, 2955, 2921, 2885, 1602, 1494, 1453, 1373, 1083, 1030, 750, 738, 700 cm^{-1}.

MS (EI): *m/z* (%) = 265 (6) [M]$^{+}$, 264 (14), 250 (12), 187 (14), 174 (51), 173 (53), 115 (12), 96 (37), 91 (92), 65 (13), 57 (100).

HRMS: calcd. ($C_{19}H_{23}N$) 265.1830; found 265.1827.



$C_7H_3BrF_3I$
MW: 350.90

1-Bromo-2-iodo-4-trifluoromethylbenzene (**49**): Concentrated H_2SO_4 (75 mL) was added dropwise to a solution of $NaIO_4$ (12.8 g, 60.0 mmol) and I_2 (15.2 g, 60.0 mmol) in a 2:1 mixture of AcOH and Ac_2O (75 mL) at 5-10 °C. Then, 1-bromo-4-(trifluoromethyl)benzene (**48**, 11.3 g, 50.0 mmol) was added dropwise at the same

temperature. After this had been stirred at 25 °C for 21 h, the mixture was poured into ice-water containing Na_2SO_3. After extraction with CH_2Cl_2 (3 × 50 mL), the combined organic layers were dried ($MgSO_4$) and concentrated under vacuum. The residue was purified by flash chromatography (SiO_2, PE, R_f = 0.56) to give **49** (16.9 g, 48.2 mmol, 96 %) as a yellow oil.

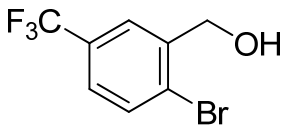
^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.45 (br. d, J = 8.2 Hz, 1 H), 7.74 (d, J = 8.4 Hz, 1 H), 8.09 (br. s, 1 H) ppm.

^{13}C NMR (75 MHz, DEPT, $CDCl_3$): δ = 101.4 (C), 122.6 (q, J = 273 Hz, CF_3), 126.1 (q, J = 4 Hz, CH), 130.6 (q, J = 34 Hz, C), 133.0 (CH), 134.1 (C), 137.0 (q, J = 4 Hz, CH) ppm.

IR (neat): $\tilde{\nu}$ = 1591, 1459, 1377, 1317, 1257, 1173, 1132, 1102, 1074, 1012, 893, 825, 800, 705 cm^{-1}.

MS (EI): m/z (%) = 352 (100) [M, ^{81}Br]$^+$, 350 (99) [M, ^{79}Br]$^+$, 333 (6), 331 (5), 225 (19), 223 (19), 144 (29).

HRMS: calcd. ($C_7H_3BrF_3I$) 349.8415; found 349.8409.



$C_8H_6BrF_3O$
MW: 255.03

(2-Bromo-5-(trifluoromethyl)phenyl)methanol (**50**)**:** At –20 °C, a solution of *i*-PrMgCl·LiCl in THF (12.5 mL, c = 2.0 mol/L, 25.0 mmol) was slowly added to a solution of 1-Bromo-2-iodo-4-trifluoromethylbenzene (**49**, 8.75 g, 25.0 mmol) in THF (13 mL). After the mixture had been stirred at –20 °C for 2 h, a solution of monomeric formaldehyde in THF (35 mL, $c \approx$ 0.8 mol/L, 28.0 mmol) was added. Then, the mixture was stirred for additional 1 h and water (50 mL) was subsequently added. After extraction with Et_2O (5 × 30 mL), the combined organic layers were dried ($MgSO_4$) and concentrated under vacuum. The residue was purified by flash

chromatography (SiO_2, PE/EtOAc, 90:10, R_f = 0.32) to give **50** (3.95 g, 15.5 mmol, 62 %) as a colorless solid.

M.p.: 67 °C.

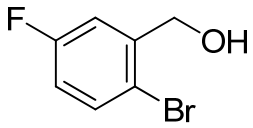
^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.37 (br. s, 1 H), 4.78 (s, 2 H), 7.40 (dd, J = 8.3, 1.9 Hz, 1 H), 7.65 (d, *J* = 8.3 Hz, 1 H), 7.79 (d, *J* = 1.3 Hz, 1 H).

^{13}C NMR (75 MHz, DEPT, $CDCl_3$): δ = 64.3 (CH_2), 123.8 (q, *J* = 272 Hz, CF_3), 125.1 (q, *J* = 4 Hz, CH), 125.5 (q, *J* = 4 Hz, CH), 125.7 (C), 130.1 (q, *J* = 33 Hz, C), 132.9 (CH), 140.8 (C) ppm.

IR (KBr): $\tilde{\nu}$ = 3300, 2913, 1605, 1583, 1474, 1413, 1372, 1330, 1257, 1184, 1120, 1083, 1057, 1023, 897, 834, 829, 745, 716 cm^{-1}.

MS (EI): *m/z* (%) = 256 (36) [M, ^{81}Br]$^+$, 254 (34) [M, ^{79}Br]$^+$, 237 (15), 235 (13), 175 (100), 145 (41), 127 (52), 113 (7).

HRMS: calcd. ($C_8H_6OBrF_3$) 253.9554; found 253.9559.



C_7H_6BrFO
MW: 205.02

(2-Bromo-5-fluorophenyl)methanol (**53**)**:** 2-Bromo-5-fluorobenzoic acid (**51**, 7.00 g, 32.0 mmol) was added in portions to a stirred suspension of $NaBH_4$ (1.09 g, 28.8 mmol) in dry diglyme (40 mL). Then, a solution of freshly distilled $BF_3{\cdot}Et_20$ (4.80 mL, 38.4 mmol) in diglyme (10 mL) was added over a period of 1 h. After this had been stirred at 25 °C for 4 h (TLC control) the reaction mixture was poured on ice. The precipitate was suction filtered and dried under vacuum to give **53** (4.80 g, 23.4 mmol, 73 %) as a colorless solid.

M.p.: 92 °C.

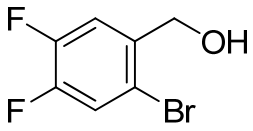
^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.02 (t, *J* = 5.5 Hz, 1 H), 4.65 (d, *J* = 4.8 Hz, 2 H), 6.81 (dt, *J* = 8.4, 3.1 Hz, 1 H), 7.19 (dd, *J* = 8.8, 3.3 Hz, 1 H), 7.41 (dd, *J* = 8.8, 5.3 Hz, 1 H) ppm.

^{13}C NMR (126 MHz, DEPT, $CDCl_3$): δ = 64.5 (CH_2), 115.6 (d, *J* = 24 Hz, CH), 115.7 (C), 115.8 (d, *J* = 23 Hz, CH), 133.6 (d, *J* = 8 Hz, CH), 142.0 (d, *J* = 7 Hz, C), 162.3 (d, *J* = 247 Hz, CF) ppm.

IR (neat): $\tilde{\nu}$ = 3272, 3180, 2357, 2338, 1580, 1464, 1439, 1410, 1361, 1266, 1219, 1149, 1106, 1065, 1025, 984, 950, 874, 809 cm^{-1}.

MS (EI): *m/z* (%) = 206 (44) [M, ^{81}Br]$^{+}$, 204 (47) [M, ^{79}Br]$^{+}$, 175 (15), 125 (100), 123 (18), 97 (89), 96 (64), 95 (55), 94 (26), 77 (74), 75 (56).

HRMS: calcd. (C_7H_6BrFO) 203.9586; found 203.9586.



$C_7H_5BrF_2O$
MW: 223.01

(2-Bromo-4,5-difluorophenyl)methanol (**54**)**:** 2-Bromo-4,5-difluorobenzoic acid (**52**, 2.00 g, 8.43 mmol) was added in portions to a stirred suspension of $NaBH_4$ (287 mg, 7.59 mmol) in dry diglyme (6.0 ml). Then, a solution of freshly distilled $BF_3{\cdot}Et_20$ (1.30 mL, 10.1 mmol) in dry diglyme (3.8 mL) was added over a period of 30 min. After this had been stirred at 25 °C for 4 h the mixture was poured on ice. The precipitate was suction filtered and dried under vacuum to **54** (1.50 g, 6.73 mmol, 77 %) as a colorless solid.

M.p.: 71 °C.

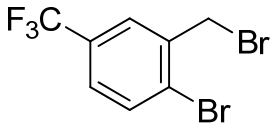
^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.08 (t, *J* = 5.8 Hz, 1 H), 4.68 (d, *J* = 5.3 Hz, 2 H), 7.34-7.42 (m, 2 H) ppm.

^{13}C NMR (75 MHz, DEPT, $CDCl_3$): δ = 63.9 (CH_2), 114.9 (dd, J = 8, 4 Hz, C), 117.0 (d, J = 19 Hz, CH), 121.3 (d, J = 20 Hz, CH), 136.8 (dd, J = 5, 4 Hz, C), 149.3 (dd, J = 251, 13 Hz, CF), 149.8 (dd, J = 249, 12 Hz, CF) ppm.

IR (neat): $\tilde{\nu}$ = 3303, 3061, 2917, 1614, 1600, 1494, 1474, 1443, 1399, 1362, 1293, 1219, 1185, 1138, 1066, 981, 881, 809 cm^{-1}.

MS (EI): *m/z* (%) = 224 (72) [M, ^{81}Br]$^+$, 222 (72) [M, ^{79}Br]$^+$, 207 (11), 203 (10), 193 (12), 162 (10), 143 (100), 141 (22), 126 (14), 125 (14), 115 (69), 114 (72), 113 (37), 112 (20), 95 (27), 63 (18).

HRMS: calcd. ($C_7H_5OBrF_2$) 221.9492; found 221.9491.



$C_8H_5Br_2F_3$
MW: 317.93

1-Bromo-2-(bromomethyl)-4-(trifluoromethyl)benzene (**55**)**:** PBr_3 (677 mg, 2.50 mmol) was added dropwise to a solution of (2-bromo-5-(trifluoromethyl)phenyl)methanol (**50**, 1.27 g, 5.00 mmol) in CH_2Cl_2 (25 mL). After the solution had been stirred at 25 °C for 24 h, saturated aqueous Na_2CO_3 solution (50 mL) was added. The mixture was extracted with CH_2Cl_2 (5 × 30 mL). The combined organic layers were dried ($MgSO_4$) and concentrated under vacuum. The residue was purified by flash chromatography (SiO_2, 180 g, PE) to give **55** (1.25 g, 3.93 mmol, 79 %) as a colorless oil.

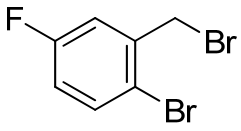
^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.61 (s, 2 H), 7.42 (dd, J = 8.4, 1.0 Hz, 1 H), 7.70-7.74 (m, 2 H) ppm.

^{13}C NMR (75 MHz, DEPT, $CDCl_3$): δ = 32.0 (CH_2), 123.4 (q, J = 272 Hz, CF_3), 126.6 (q, J = 4 Hz, CH), 127.9 (q, J = 4 Hz, CH), 128.3 (C), 130.5 (q, J = 33 Hz, C), 134.0 (CH), 138.1 (C) ppm.

IR (neat): $\tilde{\nu}$ = 2934, 1780, 1605, 1580, 1479, 1440, 1409, 1333, 1276, 1220, 1198, 1173, 1131, 1081, 1032, 949, 908, 829, 748, 728 cm^{-1}.

MS (EI): *m/z* (%) = 320 (8) [M, $^{81}Br/^{81}Br]^+$, 318 (16) [M, $^{81}Br/^{79}Br]^+$, 316 (10) [M, $^{79}Br/^{79}Br]^+$, 285 (17), 239 (100), 237 (100), 158 (42), 151 (12), 113 (8).

HRMS: calcd. ($C_8H_5Br_2F_3$) 315.8710; found 315.8703.



$C_7H_5Br_2F$
MW: 267.92

1-Bromo-2-(bromomethyl)-4-fluorobenzene (**56**): PBr_3 (1.90 g, 7.05 mmol) was added dropwise to a solution of (2-bromo-5-fluorophenyl)methanol (**53**, 2.89 g, 14.1 mmol) in CH_2Cl_2 (55 mL). After the mixture had been stirred at 25 °C for 24 h, saturated aqueous Na_2CO_3 solution (50 mL) was added. The mixture was extracted with CH_2Cl_2 (5 × 30 mL). The combined organic layers were dried ($MgSO_4$) and concentrated under vacuum. The residue was purified by flash chromatography (SiO_2, 480 g, PE) to give **56** (3.29 g, 12.2 mmol, 87 %) was isolated as a colorless oil.

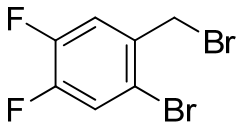
^1H NMR (500 MHz, $CDCl_3$): δ = 4.53 (s, 1 H), 6.90 (dt, *J* = 8.3, 3.0 Hz, 1 H), 7.18 (dd, *J* = 9.0, 3.0 Hz, 1 H), 7.51 (dd, *J* = 8.8, 5.3 Hz, 1 H) ppm.

^{13}C NMR (126 MHz, DEPT, $CDCl_3$): δ = 32.4 (CH_2), 117.3 (d, *J* = 22 Hz, CH), 118.1 (d, *J* = 24 Hz, CH), 118.4 (d, *J* = 3 Hz, C), 134.5 (d, *J* = 8 Hz, CH), 138.8 (d, *J* = 8 Hz, C), 161.8 (d, *J* = 248 Hz, CF) ppm.

IR (neat): $\tilde{\nu}$ = 3072, 2976, 1603, 1580, 1473, 1439, 1408, 1271, 1237, 1214, 1157, 1126, 1100, 1032, 960, 871, 813, 739, 713 cm^{-1}.

MS (EI): *m/z* (%) = 270 (6) [M, $^{81}Br/^{81}Br]^+$, 268 (14) [M, $^{81}Br/^{79}Br]^+$, 266 (7) [M, $^{79}Br/^{79}Br]^+$, 189 (83), 188 (13), 187 (100), 108 (25), 107 (24), 81 (13).

HRMS: calcd. ($C_7H_5Br_2F$) 265.8742; found 265.8742.



$C_7H_4Br_2F_2$
MW: 285.91

1-Bromo-2-(bromomethyl)-4,5-difluorobenzene (**57**): PBr_3 (1.49 g, 5.50 mmol) was added dropwise to a solution of (2-bromo-4,5-difluorophenyl)methanol (**54**, 2.45 g, 11.0 mmol) in CH_2Cl_2 (55 mL). After the mixture had been stirred at 25 °C for 24 h, saturated aqueous Na_2CO_3 solution (50 mL) was added. The mixture was extracted with CH_2Cl_2 (5 × 30 mL). The combined organic layers were dried ($MgSO_4$) and concentrated under vacuum. The residue was purified by flash chromatography (SiO_2, 350 g, PE) to give **57** (2.96 g, 10.3 mmol, 94 %) as a colorless oil.

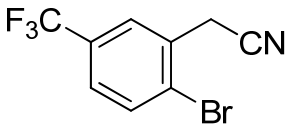
^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.51 (s, 2 H), 7.32 (dd, *J* = 10.4, 7.9 Hz, 1 H), 7.42 (dd, *J* = 9.6, 7.4 Hz, 1 H) ppm.

^{13}C NMR (75 MHz, DEPT, $CDCl_3$): δ = 31.7 (CH_2), 117.9 (dd, *J* = 8, 4 Hz, C), 119.5 (d, *J* = 18 Hz, CH), 122.2 (d, *J* = 20 Hz, CH), 133.9 (dd, *J* = 5, 4 Hz, C), 149.6 (dd, *J* = 250, 13 Hz, CF), 150.0 (dd, *J* = 255, 14 Hz, CF) ppm.

IR (neat): $\tilde{\nu}$ = 3051, 2977, 2590, 1736, 1602, 1499, 1441, 1395, 1306, 1289, 1218, 1193, 1152, 1115, 994, 883, 815, 737, 703 cm^{-1}.

MS (EI): *m/z* (%) = 288 (7) [M, ^{81}Br/^{81}Br]$^+$, 286 (11) [M, ^{81}Br/^{79}Br]$^+$, 284 (6) [M, ^{79}Br/^{79}Br]$^+$, 207 (97), 205 (100), 126 (33), 125 (19), 113 (8).

HRMS: calcd. ($C_7H_4Br_2F_2$) 283.8648; found 283.8633.



$C_9H_5BrF_3N$
MW: 264.04

2-(2-Bromo-5-(trifluoromethyl)phenyl)acetonitrile (**58**): **Procedure A**: A solution of NaCN (490 mg, 10.0 mmol) in DMSO (2.5 mL) was heated to 90 °C. The oil bath was removed and 1-bromo-2-(bromomethyl)-4-(trifluoromethyl)benzene (**55**, 1.59 g, 5.00 mmol) was slowly added. After the mixture had been allowed to reach 50 °C, water (25 mL) was added. The mixture was extracted with CH_2Cl_2 (5 × 40 mL) and the combined organic layers were dried ($MgSO_4$) and concentration under vacuum. The residue was purified by flash chromatography (SiO_2, 100 g, PE/EtOAc, 95:5) to give **58** (810 mg, 3.07 mmol, 61 %) as a colorless solid. **Procedure B**: To a solution of KCN (1.50 g, 23.1 mmol) in EtOH (23 mL) and Water (12.5) 1-bromo-2-(bromomethyl)-4-(trifluoromethyl)benzene (**55**, 6.68 g, 21.00 mmol) was added. After the mixture had been stirred at 65 °C for 1 h ice-water (100 mL) was added. The mixture was extracted with Et_2O (3 × 100 mL) and the combined organic layers were washed with saturated NaHCO3 solution (3 × 80 mL), water (2 × 80 mL) and satured NaCl solution (2 × 60 mL). After that the organic layer was dried ($MgSO_4$) and concentration under vacuum. The residue was purified by flash chromatography (SiO_2, 450 g, PE/EtOAc, 90:10) to give **58** (5.03 g, 19.1 mmol, 90 %) as a colorless solid.

M.p.: 62 °C.

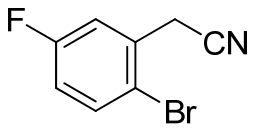
^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.90 (s, 2 H), 7.50 (dd, J = 8.3, 1.5 Hz, 1 H), 7.76 (d, J = 8.7 Hz, 1 H), 7.78 (s, 1 H) ppm.

^{13}C NMR (75 MHz, DEPT, $CDCl_3$): δ = 25.0 (CH_2), 116.0 (C), 123.3 (q, J = 273 Hz, CF_3), 126.5 (q, J = 4 Hz, CH), 126.7 (q, J = 4 Hz, CH), 127.6 (C), 130.8 (q, J = 33 Hz, C), 131.2 (C), 133.8 (CH) ppm.

IR (KBr): $\tilde{\nu}$ = 3080, 2914, 2252, 1607, 1476, 1425, 1403, 1331, 1322, 1286, 1263, 1187, 1167, 1129, 1085, 1032, 937, 877, 839, 747, 715 cm^{-1}.

MS (EI): *m/z* (%) = 265 (75) [M, $^{81}Br]^+$, 263 (78) [M, $^{79}Br]^+$, 246 (9), 244 (11), 184 (100), 183 (21), 157 (13), 134 (11), 114 (6).

HRMS: calcd. ($C_9H_5NBrF_3$) 262.9557; found 262.9533.



C_8H_5BrFN
MW: 214.03

2-(2-Bromo-5-fluorophenyl)acetonitrile (**59**): A solution of NaCN (1.76 g, 36.0 mmol) in DMSO (10 mL) was heated to 90 °C. The oil bath was removed and 1-bromo-2-(bromomethyl)-4-fluorobenzene (**56**, 4.82 g, 18.0 mmol) was slowly added. After the mixture had been allowed to reach 50 °C, water (100 mL) was added. The mixture was extracted with CH_2Cl_2 (5 × 200 mL) and the combined organic layers were dried ($MgSO_4$) and concentration under vacuum. The residue was purified by flash chromatography (SiO_2, 250 g, PE/EtOAc, 90:10) to give **59** (2.30 g, 10.8 mmol, 60 %) was isolated as a colorless solid. **Procedure B**: To a solution of KCN (2.97 g, 45.7 mmol) in EtOH (32 mL) and Water (21) bromo-2-(bromomethyl)-4-fluorobenzene (**56**, 11.11 g, 41.50 mmol) was added. After the mixture had been stirred at 65 °C for 1 h ice-water (100 mL) was added. The mixture was extracted with Et_2O (3 × 100 mL) and the combined organic layers were washed with saturated NaHCO3 solution (3 × 100 mL), water (2 × 100 mL) and satured NaCl solution (2 × 80 mL). After that the organic layer was dried ($MgSO_4$) and concentration under vacuum. The residue was purified by flash chromatography (SiO_2, 1000 g, PE/EtOAc, 90:10 to 95:5) to give **59** (8.11 g, 37.9 mmol, 91 %) as a colorless solid.

M.p.: 58 °C.

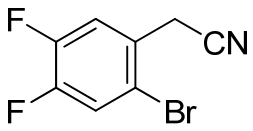
^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.83 (s, 2 H), 6.97 (dt, *J* = 8.4, 2.9 Hz, 1 H), 7.30 (dd, *J* = 8.7, 3.0 Hz, 1 H), 7.57 (dd, *J* = 8.7, 5.4 Hz, 1 H) ppm.

^{13}C NMR (126 MHz, DEPT, $CDCl_3$): δ = 24.9 (CH_2), 116.3 (C), 117.0 (d, *J* = 24 Hz, CH), 117.1 (d, *J* = 22 Hz, CH), 117.6 (d, *J* = 3 Hz, C), 131.9 (d, *J* = 7 Hz, C), 134.3 (*d*, *J* = 8 Hz, CH), 162.0 (d, *J* = 249 Hz, CF) ppm.

IR (neat): $\tilde{\nu}$ = 3096, 3075, 2939, 2916, 2264, 2247, 1898, 1727, 1608, 1576, 1465, 1416, 1398, 1321, 1266, 1212, 1151, 1102, 1030, 965, 934, 926, 851, 815, 741 cm^{-1}.

MS (EI): *m/z* (%) = 215 (71) [M, ^{81}Br]$^+$, 213 (76) [M, ^{79}Br]$^+$, 135 (17), 134 (100), 133 (45), 132 (22), 108 (17), 107 (69), 106 (17), 94 (5).

HRMS: calcd. (C_8H_5NBrF) 212.9589; found 212.9590.



$C_8H_4BrF_2N$
MW: 232.02

2-(2-Bromo-4,5-difluorophenyl)acetonitrile (**60**): A solution of NaCN (980 mg, 20.0 mmol) in DMSO (5.0 mL) was heated to 90 °C. The oil bath was removed and 1-bromo-2-(bromomethyl)-4,5-difluorobenzene (**57**, 2.86 g, 10.0 mmol) was slowly added. After the mixture had been allowed to reach 50 °C, water (25 mL) was added. The mixture was extracted with CH_2Cl_2 (5 × 40 mL) and the combined organic layers were ($MgSO_4$) and concentration under vacuum. The residue was purified by flash chromatography (SiO_2, 200 g, PE/EtOAc, 90:10) to give **60** (1.34 g, 5.78 mmol, 58 %) as a colorless solid.

M.p.: 54 °C.

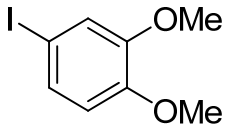
^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.79 (s, 2 H), 7.41 (dd, *J* = 10.1, 7.7 Hz, 1 H), 7.47 (dd, *J* = 9.4, 7.3 Hz, 1 H) ppm.

^{13}C NMR (75 MHz, DEPT, $CDCl_3$): δ = 24.3 (CH_2), 116.1 (C), 117.1 (dd, *J* = 7, 4 Hz, C), 118.5 (d, *J* = 20 Hz, CH), 122.2 (d, *J* = 20 Hz, CH), 126.8 (dd, *J* = 6, 4 Hz, C), 149.8 (dd, *J* = 252, 11 Hz, CF), 149.9 (dd, *J* = 255, 12 Hz, CF) ppm.

IR (KBr): $\tilde{\nu}$ = 3055, 2972, 2939, 2257, 1719, 1602, 1586, 1502, 1412, 1399, 1286, 1206, 1177, 1149, 993, 915, 887, 859, 805, 756 cm^{-1}.

MS (EI): *m/z* (%) = 233 (96) [M, $^{81}Br]^+$, 231 (97) [M, $^{79}Br]^+$, 152 (100), 125 (47), 113 (7).

HRMS: calcd. ($C_8H_4NBrF_2$) 230.9495; found 230.9488.



$C_8H_9IO_2$
MW: 264.06

4-Iodo-1,2-dimethoxy-benzene (**63**): A solution of veratrol (**62,** 20.7 g, 150 mmol), I_2 (15.2 g, 60.0 mmol), and HIO_3 (5.28 g, 30.0 mmol) in a 3:1 mixture of MeOH/H_2O (1.20 L) was heated to 85 °C for 72 h. Then, saturated aqueous Na_2SO_3 was added until the iodine color disappeared. The mixture was extracted with CH_2Cl_2 (3 × 150 mL) and the combined organic layers were dried ($MgSO_4$) and concentrated under vacuum. The residue was purified by Kugelrohr distillation to give **63** (35.3 g, 134 mmol, 89 %) as a yellow oil.

B.p.: 70 °C (0.2 mbar).

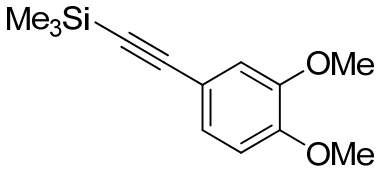
^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.84 (s, 3 H), 3.85 (s, 3 H), 6.61 (d, *J* = 8.5 Hz, 1 H), 7.11 (d, *J* = 1.8 Hz, 1 H), 7.22 (dd, *J* = 8.5, 1.8 Hz, 1 H) ppm.

^{13}C NMR (126 MHz, DEPT, $CDCl_3$): δ = 55.9 (CH_3), 56.1 (CH_3), 82.3 (C), 113.2 (CH), 120.4 (CH), 129.8 (CH), 149.2 (C), 149.9 (C) ppm.

IR (neat): $\tilde{\nu}$ = 2955, 2930, 2836, 1583, 1503, 1460, 1439, 1393, 1321, 1250, 1229, 1177, 1157, 1022, 838, 797, 762, 614 cm^{-1}.

MS (EI): *m/z* (%) = 264 (83) $[M]^+$, 249 (26), 221 (31), 218 (18), 203 (17), 122 (19), 94 (100), 79 (33), 77 (23), 66 (24).

HRMS: calcd. ($C_8H_9IO_2$) 263.9647; found 263.9647.



$C_{13}H_{18}O_2Si$
MW: 234.37

((3,4-Dimethoxyphenyl)ethynyl)trimethylsilane (**65**): $Pd(PPh_3)_2Cl_2$ (1.35 g, 1.92 mmol, 2 mol-%), CuI (731 mg, 3.84 mmol, 4 mol-%), PPh_3 (1.01 g, 3.84 mmol, 4 mol-%), *i*Pr_2NH (400 mL) and CH_2Cl_2 (200 mL) were placed in an oven dried and argon-filled Schlenk flask. After addition of 4-iodo-1,2-dimethoxy-benzene (**63,** 25.4 g, 96.0 mmol), the mixture was stirred at 25 °C for 30 minutes, and trimethylsilylacetylene (**64**, 9.90 g, 101 mmol) was added. After this mixture had been stirred at 25 °C for an additional 16 h, a saturated NH_4Cl solution (200 mL) was added. The mixture was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic layers were dried ($MgSO_4$) and concentrated under vacuum. The residue was purified by flash chromatography (SiO_2, 600 g, PE/EtOAc, 75:25, R_f = 0.41) to give **65** (21.1 g, 90.1 mmol, 94 %) as a yellow oil.

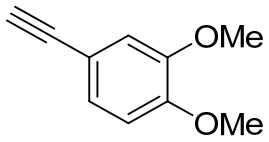
^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.24 (s, 9 H), 3.87 (s, 3 H), 3.87 (s, 3 H), 6.76 (d, *J* = 8.3 Hz, 1 H), 6.96 (d, *J* = 1.8 Hz, 1 H), 7.07 (dd, *J* = 8.3, 1.9 Hz, 1 H) ppm.

^{13}C NMR (126 MHz, DEPT, $CDCl_3$): δ = 0.0 (CH_3), 55.8 (CH_3), 55.9 (CH_3), 92.3 (C), 105.2 (C), 110.8 (CH), 114.6 (CH), 115.3 (C), 125.4 (CH), 148.5 (C), 149.7 (C) ppm.

IR (neat): $\tilde{\nu}$ = 3001, 2958, 2835, 2156, 1599, 1577, 1514, 1464, 1442, 1409, 1322, 1266, 1243, 1197, 1163, 1137, 1027, 951, 855, 765 cm^{-1}.

MS (EI): *m*/*z* (%) = 234 (58) $[M]^+$, 219 (100), 203 (11), 162 (14), 151 (13), 138 (10), 113 (10), 109 (4), 95 (4), 77 (8).

HRMS: calcd. ($C_{13}H_{18}O_2Si$) 234.1076; found 234.1058.



$C_{10}H_{10}O_2$
MW: 162.19

4-Ethynyl-1,2-dimethoxybenzene (**66**): Water (50 mL) and $AgNO_3$ (1.09 g, 6.40 mmol) were added to a solution of ((3,4-dimethoxyphenyl)ethynyl)trimethylsilane (**65**, 7.50 g, 32 mmol) in acetone (200 mL) and the resulting mixture was stirred in the dark at 25 °C for 18 h. Then it was poured into a saturated aqueous NaCl solution (300 mL) and extracted (MTBE (3×200 mL). The combined organic layers were dried ($MgSO_4$) and concentrated under vacuum. The residue was purified by flash chromatography (SiO_2, 300 g, PE/EtOAc, 80:20, R_f = 0.32) to give **66** (4.90 g, 6.17 mmol, 94 %) as a white crystalline solid.

M.p.: 70 °C.

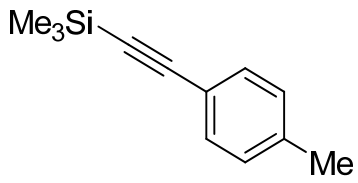
^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.00 (s, 1 H), 3.87 (s, 3 H), 3.88 (s, 3 H), 6.79 (d, *J* = 8.3 Hz, 1 H), 6.98 (d, *J* = 1.8 Hz, 1 H), 7.10 (dd, *J* = 8.3, 1.8 Hz, 1 H) ppm.

^{13}C NMR (125 MHz, DEPT, $CDCl_3$): δ = 55.9 (CH_3), 75.6 (CH), 83.7 (C), 110.9 (CH), 114.2 (C), 114.7 (CH), 125.4 (CH), 148.6 (C), 149.9 (C) ppm.

IR (neat): $\tilde{\nu}$ = 3428, 3259, 3250, 3007, 2971, 2939, 2843, 1597, 1579, 1511, 1452, 1446, 1408, 1323, 1263, 1240, 1152, 1138, 1035, 1026, 860, 821, 810, 730, 621 cm^{-1}.

MS (EI): *m*/*z* (%) = 162 (100) $[M]^+$, 147 (21), 119 (10), 91 (14), 76 (8), 65 (6).

HRMS: calcd. ($C_{10}H_{10}O_2$) 162.0681; found 162.0659.



$C_{12}H_{16}Si$
MW: 188.34

Trimethyl(p-tolylethynyl)silane (**75**): $Pd(PPh_3)_2Cl_2$ (702 mg, 1.00 mmol, 2 mol-%), CuI (381 mg, 2.00 mmol, 4 mol-%), PPh_3 (525 mg, 2.00 mmol, 4 mol-%), *i*Pr_2NH (150 mL) and CH_2Cl_2 (80 mL) were placed in an oven dried and argon-filled Schlenk flask. After addition of 1-iodo-4-methylbenzene (**67**, 10.9 g, 50.0 mmol), the mixture was stirred at 25 °C for 30 minutes, and trimethylsilylacetylene (**64**, 5.16 g, 52.5 mmol) was added. After this mixture had been stirred at 25 °C for an additional 16 h, a saturated NH_4Cl solution (100 mL) was added. The mixture was extracted with CH_2Cl_2 (3 × 80 mL). The combined organic layers were dried ($MgSO_4$) and concentrated under vacuum. The residue was purified by flash chromatography (SiO_2, 250 g, PE, R_f = 0.35) to give **75** (9.21 g, 48.9 mmol, 98 %) as a colorless liquid.

B.p.: 116 °C (20 mbar).

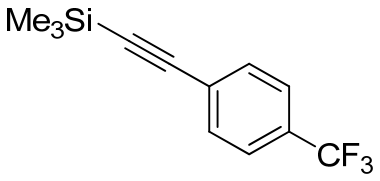
^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.24 (s, 9 H), 2.33 (s, 3 H), 7.09 (d, *J* = 7.9 Hz, 2 H), 7.35 (d, *J* = 8.1 Hz, 2 H) ppm.

^{13}C NMR (126 MHz, DEPT, $CDCl_3$): δ = 0.0 (CH_3), 21.5 (CH_3), 93.2 (C), 105.3 (C), 120.0 (C), 128.9 (CH), 131.8 (CH), 138.6 (C) ppm.

IR (neat): $\tilde{\nu}$ = 2959, 2157, 1507, 1250, 1222, 862, 839, 815, 758 cm^{-1}.

MS (EI): *m/z* (%) = 188 (21) $[M]^+$, 175 (5), 174 (17), 173 (100), 143 (5).

HRMS: calcd. ($C_{12}H_{16}Si$) 188.1021; found 188.1025.



$C_{12}H_{13}F_3Si$
MW: 242.31

Trimethyl((4-(trifluoromethyl)phenyl)ethynyl)silane (**76**): $Pd(PPh_3)_2Cl_2$ (702 mg, 1.00 mmol, 2 mol-%), CuI (381 mg, 2.00 mmol, 4 mol-%), PPh_3 (525 mg, 2.00 mmol, 4 mol-%), *i*Pr_2NH (150 mL) and CH_2Cl_2 (80 mL) were placed in an oven dried and argon-filled Schlenk flask. After addition of 1-iodo-4-(trifluoromethyl)benzene (**68**, 13.6 g, 50.0 mmol), the mixture was stirred at 25 °C for 30 minutes, and trimethylsilylacetylene (**64**, 5.16 g, 52.5 mmol) was added. After this mixture had been stirred at 25 °C for an additional 16 h, a saturated NH_4Cl solution (200 mL) was added. The mixture was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic layers were dried ($MgSO_4$) and concentrated under vacuum. The residue was purified by flash chromatography (SiO_2, 250 g, PE, R_f = 0.54) to **76** (11.5 g, 47.6 mmol, 95 %) as a light yellow liquid.

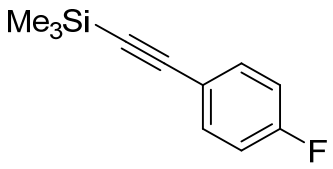
^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.26 (s, 9 H), 7.56 (br. s, 4 H) ppm.

^{13}C NMR (126 MHz, DEPT, $CDCl_3$): δ = −0.3 (CH_3), 97.1 (C), 103.5 (C), 124.0 (q, *J* = 272 Hz, CF_3), 125.1 (d, *J* = 4 Hz, CH), 127.1 (C), 130.3 (q, *J* = 32 Hz, C), 132.2 (CH) ppm.

IR (neat): $\tilde{\nu}$ = 2962, 2163, 1614, 1406, 1320, 1251, 1167, 1127, 1067, 837 cm^{-1}.

MS (EI): *m/z* (%) = 242 (15) $[M]^+$, 229 (5), 228 (22), 227 (100), 233 (4), 197 (8), 164 (4).

HRMS: calcd. ($C_{12}H_{13}F_3Si$) 242.0739; found 242.0742.



$C_{11}H_{13}FSi$
MW: 192.30

((4-Fluorophenyl)ethynyl)trimethylsilane (**77**): $Pd(PPh_3)_2Cl_2$ (1.26 mg, 1.80 mmol, 3 mol-%), CuI (686 mg, 3.60 mmol, 6 mol-%), PPh_3 (944 mg, 3.60 mmol, 6 mol-%), *i*Pr_2NH (160 mL) and toluene (40 mL) were placed in an oven dried and argon-filled Schlenk flask. After addition of 1-bromo-4-fluorobenzene (**69**, 10.5 g, 60.0 mmol), the mixture was stirred at 25 °C for 30 minutes, and trimethylsilylacetylene (**64**, 6.78 g, 69.0 mmol) was added. After this mixture had been stirred at 80 °C for an additional 16 h, a saturated NH_4Cl solution (200 mL) was added. The mixture was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic layers were dried ($MgSO_4$) and concentrated under vacuum. The residue was purified by flash chromatography (SiO_2, 400 g, PE, R_f = 0.48) to give **77** (11.4 g, 59.0 mmol, 98 %) as a light yellow liquid.

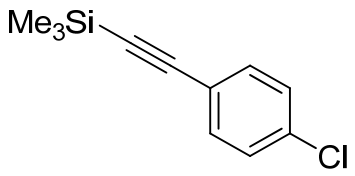
^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.24 (s, 9 H), 6.97 (t, *J* = 8.6 Hz, 2 H), 7.43 (dd, *J* = 8.4, 5.6 Hz, 2 H) ppm.

^{13}C NMR (126 MHz, DEPT, $CDCl_3$): δ = 0.1 (CH_3), 93.8 (C), 104.0 (C), 115.5 (CH, d, *J* = 22 Hz), 119.3 (C, d, *J* = 3 Hz), 133.9 (CH, d, *J* = 8 Hz), 162.6 (CF, d, *J* = 249 Hz) ppm.

IR (neat): $\tilde{\nu}$ = 2960, 2161, 1600, 1504, 1251, 1232, 1213, 1155, 865, 83 cm^{-1}.

MS (EI): *m/z* (%) = 192 (13) $[M]^+$, 178 (12), 177 (100), 147 (6), 47 (5).

HRMS: calcd. ($C_{11}H_{13}FSi$) 192.0771; found 192.0753.



$C_{11}H_{13}ClSi$
MW: 208.76

((4-Chlorophenyl)ethynyl)trimethylsilane (**78**): $Pd(PPh_3)_2Cl_2$ (702 mg, 1.00 mmol, 2 mol-%), CuI (381 mg, 2.00 mmol, 4 mol-%), PPh_3 (525 mg, 2.00 mmol, 4 mol-%), *i*Pr_2NH (200 mL) and CH_2Cl_2 (80 mL) were placed in an oven dried and argon-filled Schlenk flask. After addition of 1-chloro-4-iodobenzene (**70**, 11.9 g, 50.0 mmol), the mixture was stirred at 25 °C for 30 minutes, and trimethylsilylacetylene (**64**, 5.16 g, 52.5 mmol) was added. After this mixture had been stirred at 25 °C for an additional 16 h, a saturated NH_4Cl solution (200 mL) was added. The mixture was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic layers were dried ($MgSO_4$) and concentrated under vacuum. The residue was purified by flash chromatography (SiO_2, 250 g, PE, R_f = 0.35) to give **78** (9.71 g, 46.5 mmol, 93 %) as colorless crystals.

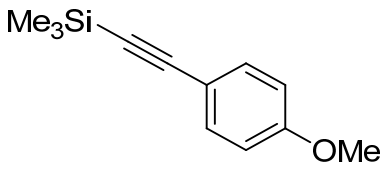
^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.24 (s, 5 H), 7.26 (d, *J* = 8.5 Hz, 1 H), 7.38 (d, *J* = 8.5 Hz, 1 H) ppm.

^{13}C NMR (126 MHz, DEPT, $CDCl_3$): δ = −0.1 (CH_3), 95.3 (C), 103.8 (C), 121.6 (C), 128.5 (CH), 133.2 (CH), 134.5 (C) ppm.

IR (neat): $\tilde{\nu}$ = 2956, 2156, 1589, 1484, 1471, 1247, 1213, 1089, 1014, 842, 819, 755 cm^{-1}.

MS (EI): *m/z* (%) = 210 (5) [M, $^{37}Cl]^+$, 208 (16) [M, $^{35}Cl]^+$, 195 (33), 194 (14), 193 (100), 44 (7).

HRMS: calcd. ($C_{11}H_{13}ClSi$) 208.0475; found 208.0473.



$C_{12}H_{16}OSi$
MW: 204.34

((4-Methoxyphenyl)ethynyl)trimethylsilane (**79**): $Pd(PPh_3)_2Cl_2$ (702 mg, 1.00 mmol, 2 mol-%), CuI (381 mg, 2.00 mmol, 4 mol-%), PPh_3 (525 mg, 2.00 mmol, 4 mol-%), *i*Pr_2NH (200 mL) and CH_2Cl_2 (80 mL) were placed in an oven dried and argon-filled Schlenk flask. After addition of 1-iodo-4-methoxybenzene (**71**, 11.7 g, 50.0 mmol), the mixture was stirred at 25 °C for 30 minutes, and trimethylsilylacetylene (**64**, 5.16 g, 52.5 mmol) was added. After this mixture had been stirred at 25 °C for an additional 16 h, a saturated NH_4Cl solution (200 mL) was added. The mixture was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic layers were dried ($MgSO_4$) and concentrated under vacuum. The residue was purified by flash chromatography (SiO_2, 250 g, PE/EtOAc, 95:5, R_f = 0.28) to give **79** (10.1 g, 49.2 mmol, 97 %) as a light red liquid.

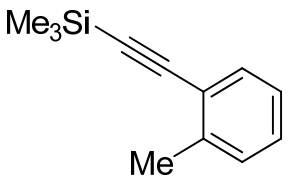
^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.24 (s, 9 H), 3.78 (s, 3 H), 6.80 (d, *J* = 8.5 Hz, 2 H), 7.39 (d, *J* = 8.5 Hz, 2 H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$): δ = 0.0 (CH_3), 55.2 (CH_3), 92.4 (C), 105.2 (C), 113.8 (CH), 115.3 (C), 133.4 (CH), 159.8 (C) ppm.

IR (neat): $\tilde{\nu}$ = 2958, 2155, 1605, 1506, 1464, 1442, 1292, 1245, 1171, 1033, 861, 828, 754 cm^{-1}.

MS (EI): *m/z* (%) = 204 (30) $[M]^+$, 190 (15), 189 (100), 174 (6), 146 (7).

HRMS: calcd. ($C_{12}H_{16}OSi$) 204.0970; found 204.0968.



$C_{12}H_{16}Si$
MW: 188.34

Trimethyl(o-tolylethynyl)silane (**80**): $Pd(PPh_3)_2Cl_2$ (702 mg, 1.00 mmol, 2 mol-%), CuI (381 mg, 2.00 mmol, 4 mol-%), PPh_3 (525 mg, 2.00 mmol, 4 mol-%), *i*Pr_2NH (200 mL) and CH_2Cl_2 (80 mL) were placed in an oven dried and argon-filled Schlenk flask. After addition of 1-iodo-2-methylbenzene (**72**, 11.9 g, 50.0 mmol), the mixture was stirred at 25 °C for 30 minutes, and trimethylsilylacetylene (**64**, 5.16 g, 52.5 mmol) was added. After this mixture had been stirred at 25 °C for an additional 16 h, a saturated NH_4Cl solution (200 mL) was added. The mixture was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic layers were dried ($MgSO_4$) and concentrated under vacuum. The residue was purified by flash chromatography (SiO_2, 250 g, PE, R_f = 0.49) to give **80** (9.0 g, 48.0 mmol, 96 %) as a colorless liquid.

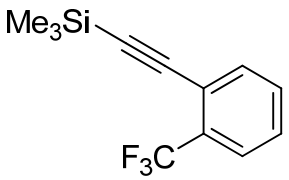
^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.26 (s, 9 H), 2.43 (s, 3 H), 7.11 (t, *J* = 7.0 Hz, 1 H), 7.16-7.23 (m, 2 H), 7.42 (d, *J* = 7.9 Hz, 1 H) ppm.

^{13}C NMR (126 MHz, DEPT, $CDCl_3$): δ = 0.0 (CH_3), 20.6 (CH_3), 98.2 (C), 104.0 (C), 122.9 (C), 125.4 (CH), 128.4 (CH), 129.3 (CH), 132.1 (CH), 140.6 (C) ppm.

IR (neat): $\tilde{\nu}$ = 2961, 2157, 1485, 1251, 1196, 113, 1046, 869, 837, 756 cm^{-1}.

MS (EI): *m/z* (%) = 188 (24) $[M]^+$, 174 (17), 173 (100), 145 (10), 143 (6).

HRMS: calcd. ($C_{12}H_{16}Si$) 188.1021; found 188.1018.



$C_{12}H_{13}F_3Si$
MW: 242.31

Trimethyl((2-(trifluoromethyl)phenyl)ethynyl)silane (**81**): $Pd(PPh_3)_2Cl_2$ (562 mg, 0.80 mmol, 2 mol-%), CuI (305 mg, 1.60 mmol, 4 mol-%), PPh_3 (420 mg, 1.60 mmol, 4 mol-%), *i*Pr_2NH (160 mL) and CH_2Cl_2 (40 mL) were placed in an oven dried and argon-filled Schlenk flask. After addition of 1-iodo-2-(trifluoromethyl)benzene (**73**, 10.9 g, 40.0 mmol), the mixture was stirred at 25 °C for 30 minutes, and trimethylsilylacetylene (**64**, 4.13 g, 42.0 mmol) was added. After this mixture had been stirred at 25 °C for an additional 16 h, a saturated NH_4Cl solution (100 mL) was added. The mixture was extracted with CH_2Cl_2 (3 × 80 mL). The combined organic layers were dried ($MgSO_4$) and concentrated under vacuum. The residue was purified by flash chromatography (SiO_2, 250 g, PE, R_f = 0.46) to give **81** (9.42 g, 38.9 mmol, 97 %) as a colorless liquid.

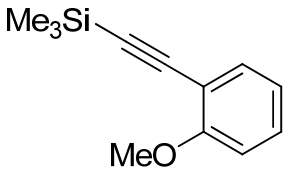
^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.28 (d, *J* = 1.8 Hz, 9 H), 7.39 (t, *J* = 7.9 Hz, 1 H), 7.47 (t, *J* = 7.6 Hz, 1 H), 7.58-7.66 (m, 2 H) ppm.

^{13}C NMR (126 MHz, DEPT, $CDCl_3$): δ = −0.4 (CH_3), 100.5 (C), 100.9 (C), 121.4 (C), 123.5 (q, *J* = 273 Hz, CF_3), 125.7 (q, *J* = 5 Hz, CH), 128.2 (CH), 131.3 (CH), 132.1 (q, *J* = 31 Hz, C), 134.1 (CH) ppm

IR (neat): $\tilde{\nu}$ = 2963, 2165, 1489, 1450, 1316, 1251, 1169, 1134, 111, 1058, 1034, 862, 840, 760 cm^{-1}.

MS (EI): *m/z* (%) = 242 (16) $[M]^+$, 228 (14), 227 (100), 146 (49), 127 (35), 126 (21), 106 (14), 101 (16), 81 (33), 77 (29).

HRMS: calcd. ($C_{12}H_{13}F_3Si$) 242.0739; found 242.0739.



$C_{12}H_{16}OSi$
MW: 204.34

((2-Methoxyphenyl)ethynyl)trimethylsilane (**82**): $Pd(PPh_3)_2Cl_2$ (702 mg, 1.00 mmol, 2 mol-%), CuI (381 mg, 2.00 mmol, 4 mol-%), PPh_3 (525 mg, 2.00 mmol, 4 mol-%), *i*Pr_2NH (200 mL) and CH_2Cl_2 (80 mL) were placed in an oven dried and argon-filled Schlenk flask. After addition of 1-iodo-2-methoxybenzene (**71**, 11.7 g, 50.0 mmol), the mixture was stirred at 25 °C for 30 minutes, and trimethylsilylacetylene (**64**, 5.16 g, 52.5 mmol) was added. After this mixture had been stirred at 25 °C for an additional 16 h, a saturated NH_4Cl solution (200 mL) was added. The mixture was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic layers were dried ($MgSO_4$) and concentrated under vacuum. The residue was purified by flash chromatography (SiO_2, 250 g, PE/EtOAc, 95:5, R_f = 0.35) to give **82** (9.90 g, 48.4 mmol, 97 %) as a light brown liquid.

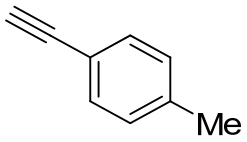
^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.26 (s, 9 H), 3.86 (s, 3 H), 6.83 (d, *J* = 8.4 Hz, 1 H), 6.87 (t, *J* = 7.5 Hz, 1 H), 7.26 (td, *J* = 7.7, 1.3 Hz, 1 H), 7.43 (dd, *J* = 7.5, 1.6 Hz, 1 H) ppm.

^{13}C NMR (126 MHz, DEPT, $CDCl_3$): δ = 0.0 (CH_3), 55.7 (CH_3), 98.4 (C), 101.2 (C), 110.6 (CH), 112.2 (C), 120.3 (CH), 129.9 (CH), 134.1 (CH), 160.2 (C) ppm.

IR (neat): $\tilde{\nu}$ = 2959, 2157, 1595, 1490, 1464, 1292, 1249, 1113, 1025, 862, 837, 748 cm^{-1}.

MS (EI): *m/z* (%) = 204 (54) $[M]^+$, 119 (55), 189 (100), 161 (23), 159 (31), 115 (19).

HRMS: calcd. ($C_{12}H_{16}OSi$) 204.0970; found 204.1007.



C_9H_8
MW: 116.16

1-Ethynyl-4-methylbenzene (**83**): To a solution of trimethyl(p-tolylethynyl)silane (**75**, 5.65 g, 30.0 mmol) in methanol (100 mL) KOH (34 mg, 0.60 mmol) in 1 mL of water was added. The solution was stirred at 25 °C for 1 h until GC analysis indicated that the reaction was complete. The reaction mixture was diluted with water (200 mL) and extracted with *n*-pentane (50 mL). The combined organic layers were dried ($MgSO_4$) and the solvent was removed under vacuum. The residue was purified by flash chromatography (SiO_2, 150 g, *n*-pentane, R_f = 0.64) to give **83** (2.78 g, 23.9 mmol, 80 %) as a colorless liquid.

B.p.: 65 °C (20 mbar).

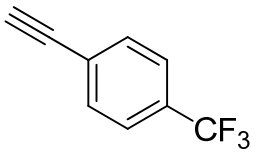
^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.33 (s, 4 H), 3.02 (s, 1 H), 7.11 (d, J = 7.9 Hz, 2 H), 7.38 (d, J = 7.9 Hz, 2 H) ppm.

^{13}C NMR (126 MHz, DEPT, $CDCl_3$): δ = 21.4 (CH_3), 76.4 (CH), 83.8 (C), 119.0 (C), 129.0 (CH), 132.0 (CH), 138.9 (C) ppm.

IR (neat): $\tilde{\nu}$ = 3291, 2108, 1507, 1215, 1176, 1021, 815 cm^{-1}.

MS (EI): *m*/*z* (%) = 116 (79) $[M]^+$, 115 (100), 89 (9), 86 (6), 84 (10), 63 (9), 62 (4), 49 (14).

HRMS: calcd. (C_9H_8) 116.0626; found 116.0627.



$C_9H_5F_3$
MW: 170.13

1-Ethynyl-4-(trifluoromethyl)benzene (**84**): To a solution of trimethyl((4-(trifluoromethyl)phenyl)ethynyl)silane (**76**, 7.75 g, 32.0 mmol) in methanol (120 mL) KOH (34 mg, 0.60 mmol) in 1 mL of water was added. The solution was stirred at 25 °C for 1 h until GC analysis indicated that the reaction was complete. The reaction mixture was diluted with water (100 mL) and extracted with *n*-pentane (4 × 60 mL). The combined organic layers were dried ($MgSO_4$) and the solvent was removed under vacuum. The residue was purified by flash chromatography (SiO_2, 150 g, *n*-pentane) to give **84** (3.55 g, 20.9 mmol, 65 %) as a colorless liquid.

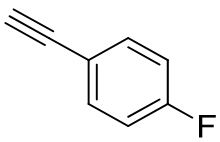
^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.09 (s, 1 H), 7.48 (br. s, 4 H) ppm.

^{13}C NMR (126 MHz, DEPT, $CDCl_3$): δ = 79.5 (CH), 82.2 (C), 123.9 (q, J = 272 Hz, CF_3), 125.3 (d, J = 3 Hz, CH), 126.0 (C), 130.7 (q, J = 32 Hz, C), 132.4 (CH) ppm.

IR (neat): $\tilde{\nu}$ = 3308, 1626, 1614, 1410, 1321, 1168, 1125, 1106, 1067, 1019, 842, 735 cm^{-1}.

MS (EI): *m*/*z* (%) = 170 (100) [M]$^+$, 169 (21), 151 (30), 120 (23), 75 (13), 74 (10), 50 (7).

HRMS: calcd. ($C_9H_5F_3$) 170.0343; found 170.0340.



C_8H_5F
MW: 120.12

1-Ethynyl-4-fluorobenzene (**85**): To a solution of trimethyl((4-(trifluoromethyl)phenyl)ethynyl)silane (**77**, 10.77 g, 56.0 mmol) in methanol (120 mL) KOH (63 mg, 1.12 mmol) in 1 mL of water was added. The solution was stirred at 25

°C for 1 h until GC analysis indicated that the reaction was complete. The reaction mixture was diluted with water (100 mL) and extracted with *n*-pentane (4 × 60 mL). The combined organic layers were dried ($MgSO_4$) and the solvent was removed under vacuum. The residue was purified by flash chromatography (SiO_2, 120 g, *n*-pentane) to give **85** (3.71 g, 30.9 mmol, 55 %) as a light yellow liquid.

M.p.: 25 °C.

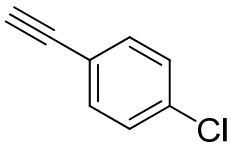
^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.04 (s, 1 H), 7.02 (t, J = 8.5 Hz, 2 H), 7.47 (dd, J = 8.2, 5.8 Hz, 2 H) ppm.

^{13}C NMR (126 MHz, DEPT, $CDCl_3$): δ = 76.9 (CH), 82.6 (C), 115.6 (d, J = 22 Hz, CH), 118.2 (d, J = 3 Hz, C), 134.1 (d, J = 9 Hz, CH), 162.8 (d, J = 250 Hz, CF) ppm.

IR (neat): $\tilde{\nu}$ = 3297, 2957, 1601, 1504, 1249, 1230, 1156, 833 cm^{-1}.

MS (EI): *m*/*z* (%) = 120 (100) $[M]^+$, 100 (4), 94 (9), 74 (6).

HRMS: calcd. (C_8H_5F) 120.0375; found 120.0373.



C_8H_5Cl
MW: 136.58

1-Chloro-4-ethynylbenzene (**86**): To a solution of ((4-chlorophenyl)ethynyl)trimethylsilane (**78**, 5.24 g, 25.0 mmol) in methanol (90 mL) KOH (28 mg, 0.50 mmol) in 1 mL of water was added. The solution was stirred at 25 °C for 1 h until GC analysis indicated that the reaction was complete. The reaction mixture was diluted with water (150 mL) and extracted with *n*-pentane (4 × 100 mL). The combined organic layers were dried ($MgSO_4$) and the solvent was removed under vacuum. The residue was purified by flash chromatography (SiO_2, 120 g, *n*-pentane) to give **86** (2.95 g, 21.6 mmol, 54 %) as colorless crystals.

M.p.: 43 °C.

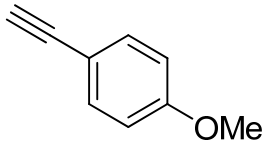
^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.10 (s, 1 H), 7.29 (d, J = 7.9 Hz, 2 H), 7.41 (d, J = 7.9 Hz, 2 H) ppm.

^{13}C NMR (126 MHz, J-MOD, $CDCl_3$): δ = 78.2 (CH), 82.5 (C), 120.6 (C), 128.7 (CH), 133.3 (CH), 134.9 (CCl) ppm.

IR (neat): $\tilde{\nu}$ = 3261, 1591, 1486, 1472, 1396, 1248, 1087, 1013, 823 cm^{-1}.

MS (EI): m/z (%) = 138 (32) [M, ^{37}Cl]$^{+}$, 136 (100) [M, ^{35}Cl]$^{+}$, 101 (21), 75 (13), 74 (11), 50 (10).

HRMS: calcd. (C_8H_5Cl) 136.0080; found 136.0083.



C_9H_8O
MW: 132.16

1-Ethynyl-4-methoxybenzene (**87**): To a solution of ((4-methoxyphenyl)ethynyl)trimethylsilane (**79**, 9.91 g, 49.0 mmol) in methanol (120 mL) KOH (54 mg, 0.97 mmol) in 1 mL of water was added. The solution was stirred at 25 °C for 1 h until GC analysis indicated that the reaction was complete. The reaction mixture was diluted with water (100 mL) and extracted with *n*-pentane (4 × 50 mL). The combined organic layers were dried ($MgSO_4$) and the solvent was removed under vacuum. The residue was purified by flash chromatography (SiO_2, 120 g, *n*-pentane) to give **87** (5.51 g, 41.7 mmol, 86 %) as colorless crystals.

M.p.: 27 °C.

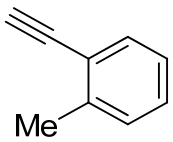
^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.00 (s, 1 H), 3.75 (s, 3 H), 6.81 (d, J = 9.2 Hz, 2 H), 7.41 (d, J = 8.5 Hz, 2 H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$): δ = 55.1 (CH_3), 75.8 (CH), 83.6 (C), 113.8 (CH), 114.1 (C), 133.5 (CH), 159.8 (C) ppm.

IR (neat): $\tilde{\nu}$ = 3257, 3004, 2972, 2941, 2844, 1607, 1508, 1508, 1291, 1243, 1174, 1028, 840, 822, 704 cm^{-1}.

MS (EI): *m*/*z* (%) = 132 (100) $[M]^+$, 115 (100), 89 (9), 74 (3), 63 (9).

HRMS: calcd. (C_9H_8O) 132.0575; found 132.0573.



C_9H_8
MW: 116.16

1-Ethynyl-2-methylbenzene (**88**): **Procedure A**: To a solution of trimethyl(o-tolylethynyl)silane (**80**, 9.51 g, 51.0 mmol) in methanol (120 mL) KOH (57 mg, 1.01 mmol) in 1 mL of water was added. The solution was stirred at 25 °C for 1 h until GC analysis indicated that the reaction was complete. The reaction mixture was diluted with water (100 mL) and extracted with *n*-pentane (4 × 50 mL). The combined organic layers were dried ($MgSO_4$) and the solvent was removed under vacuum. The residue was purified by flash chromatography (SiO_2, 150 g, *n*-pentane) to give **88** (5.21 g, 44.9 mmol, 94 %) as a light yellow liquid.

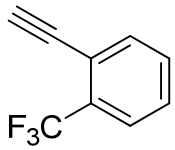
^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.44 (s, 3 H), 3.24 (s, 1 H), 7.11 (t, *J* = 7.3 Hz, 1 H), 7.16-7.24 (m, 2 H), 7.45 (d, *J* = 7.9 Hz, 1 H) ppm.

^{13}C NMR (126 MHz, J-MOD, $CDCl_3$): δ = 20.5 (CH_3), 80.9 (CH), 82.5 (C), 121.9 (C), 125.5 (CH), 128.7 (CH), 129.4 (CH), 132.5 (CH), 140.7 (C) ppm.

IR (neat): $\tilde{\nu}$ = 3290, 1484, 1456, 1108, 1043, 841, 755 cm^{-1}.

MS (EI): *m*/*z* (%) = 116 (78) $[M]^+$, 131 (75), 103 (15), 89 (42), 78 (8), 77 (8), 63 (21), 62 (10).

HRMS: calcd. (C_9H_8) 116.0626; found 116.0625.



$C_9H_5F_3$
MW: 170.13

1-Ethynyl-2-(trifluoromethyl)benzene (**89**): To a solution of trimethyl((2-(trifluoromethyl)phenyl)ethynyl)silane (**81**, 9.21 g, 38.0 mmol) in methanol (120 mL) KOH (43 mg, 0.76 mmol) in 1 mL of water was added. The solution was stirred at 25 °C for 1 h until GC analysis indicated that the reaction was complete. The reaction mixture was diluted with water (100 mL) and extracted with *n*-pentane (3 × 50 mL). The combined organic layers were dried ($MgSO_4$) and the solvent was removed under vacuum. The residue was purified by flash chromatography (SiO_2, 150 g, *n*-pentane) to give 1-ethynyl-2-(trifluoromethyl)benzene **89** (4.82 g, 28.3 mmol, 74 %) as a colorless liquid.

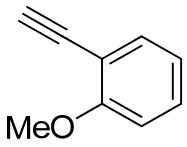
^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.34 (s, 2 H), 7.39 (t, *J* = 7.6 Hz, 1 H), 7.45 (t, *J* = 7.6 Hz, 1 H), 7.61 (d, *J* = 7.9 Hz, 1 H), 7.63 (d, *J* = 7.7 Hz, 1 H) ppm.

^{13}C NMR (126 MHz, DEPT, $CDCl_3$): δ = 79.4 (C), 82.9 (CH), 120.4 (d, *J* = 2 Hz, C), 123.4 (q, *J* = 273 Hz, CF_3), 125.8 (d, *J* = 4 Hz, CH), 128.6 (CH), 131.4 (CH), 132.2 (q, *J* = 31 Hz, C), 134.7 (CH) ppm.

IR (neat): $\tilde{\nu}$ = 3303, 1576, 1490, 1450, 1315, 1265, 1165, 1129, 1106, 1055, 1033, 764 cm^{-1}.

MS (EI): *m*/*z* (%) = 170 (100) $[M]^+$, 169 (73), 151 (52), 120 (9), 75 (8).

HRMS: calcd. ($C_9H_5F_3$) 170.0343; found 170.0343.



C_9H_8O
MW: 132.16

1-Ethynyl-2-methoxybenzene (**90**): To a solution of ((2-methoxyphenyl)ethynyl)trimethylsilane (**82**, 9.81 g, 48.0 mmol) in methanol (120 mL) KOH (54 mg, 0.96 mmol) in 1 mL of water was added. The solution was stirred at 25 °C for 1 h until GC analysis indicated that the reaction was complete. The reaction mixture was diluted with water (100 mL) and extracted with *n*-pentane (4 × 50 mL). The combined organic layers were dried ($MgSO_4$) and the solvent was removed under vacuum. The residue was purified by flash chromatography (SiO_2, 120 g, *n*-pentane) to give **90** (3.15 g, 23.8 mmol, 50 %) as a light red liquid.

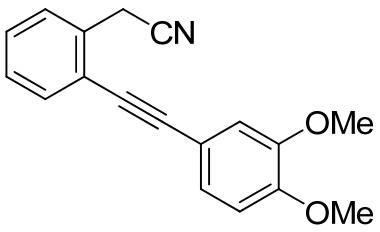
^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.30 (s, 1 H), 3.87 (s, 3 H), 6.84-6.91 (m, 2 H), 7.29 (t, J = 7.9 Hz, 1H), 7.45 (d, J = 7.3, 1 H) ppm.

^{13}C NMR (126 MHz, DEPT, $CDCl_3$): δ = 55.6 (CH_3), 79.9 (CH), 81.0 (C), 110.4 (CH), 111.0 (C), 120.3 (CH), 130.1 (CH), 134.0 (CH), 160.4 (C) ppm.

IR (neat): $\tilde{\nu}$ = 3281, 2964, 1596, 1489, 1464, 1434, 1289, 1279, 1250, 1110, 1023, 749 cm^{-1}.

MS (EI): *m*/*z* (%) = 132 (100) $[M]^+$, 131 (75), 103 (15), 89 (42), 78 (8), 77 (8), 63 (21), 62 (10).

HRMS: calcd. (C_9H_8O) 132.0575; found 132.0573.



$C_{18}H_{15}NO_2$
MW: 277.32

2-(2-((3,4-Dimethoxyphenyl)ethynyl)phenyl)acetonitrile (**91**): $Pd(PPh_3)_2Cl_2$ (449 mg, 0.64 mmol, 2 mol-%), CuI (61 mg, 0.32 mmol, 1 mol-%), PPh_3 (336 mg, 1.28 mmol, 4 mol-%), *i*Pr_2NH (41 mL) and toluene (27 mL) were placed in an oven dried and argon-filled Schlenk flask. After addition of 2-(2-bromophenyl)acetonitrile (**61**, 6.27 g, 32.0 mmol), the mixture was stirred at 25 °C for 30 minutes, and 4-ethynyl-1,2-dimethoxybenzene (**66**, 5.71 g, 35.2 mmol) was added. After this mixture had been stirred at 80 °C for an additional 16 h, a saturated NH_4Cl solution (200 mL) was added. The mixture was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic layers were dried ($MgSO_4$) and concentrated under vacuum. The residue was purified by flash chromatography (SiO_2, 600 g, PE/EtOAc, 80:20, R_f = 0.18) to give **91** (7.84 g, 28.3 mmol, 88 %) as a yellow solid.

M.p.: 81 °C.

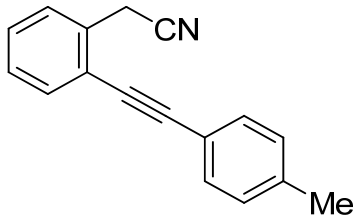
^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.92 (s, 6 H), 3.98 (s, 2 H), 6.86 (d, *J* = 8.3 Hz, 1 H), 7.06 (s, 1 H), 7.17 (d, *J* = 8.3 Hz, 1 H), 7.31-7.40 (m, 2 H), 7.50 (d, *J* = 7.4 Hz, 1 H), 7.56 (d, *J* = 7.3 Hz, 1 H) ppm.

^{13}C NMR (126 MHz, DEPT, $CDCl_3$) δ = 22.8 (CH_2), 55.9 (CH_3), 55.9 (CH_3), 84.6 (C), 95.9 (C), 111.1 (CH), 114.1 (CH), 114.6 (C), 117.5 (C), 123.0 (C), 125.0 (CH), 128.1 (CH), 128.2 (CH), 128.7 (CH), 131.5 (C), 132.2 (CH), 148.7 (C), 149.9 (C) ppm.

IR (neat): $\tilde{\nu}$ = 3010, 2937, 2913, 2839, 2207, 1595, 1577, 1512, 1455, 1409, 1333, 1248, 1229, 1130, 1019, 857, 759 cm^{-1}.

MS (EI): *m/z* (%) = 277 (100) $[M]^+$, 262 (19), 234 (16), 207 (20), 190 (20), 164 (14) 139 (6), 81 (6).

HRMS: calcd. ($C_{18}H_{15}NO_2$) 277.1103; found 277.1095.



$C_{17}H_{13}N$
MW: 231.29

2-(2-(p-Tolylethynyl)phenyl)acetonitrile (**92**): **Procedure A**: $Pd(PPh_3)_2Cl_2$ (688 mg, 0.98 mmol, 4 mol-%), CuI (373 mg, 1.96 mmol, 8 mol-%), PPh_3 (514 mg, 1.96 mmol, 8 mol-%), *i*Pr_2NH (60 mL) and toluene (25 mL) were placed in an oven dried and argon-filled Schlenk flask. After addition of 2-(2-bromophenyl)acetonitrile (**61**, 4.80 g, 24.5 mmol), the mixture was stirred at 25 °C for 30 minutes, and 1-ethynyl-4-methylbenzene (**83**, 2.99 g, 25.7 mmol) was added. After this mixture had been stirred at 80 °C for an additional 16 h, a saturated NH_4Cl solution (100 mL) was added. The mixture was extracted with CH_2Cl_2 (4 × 75 mL). The combined organic layers were dried ($MgSO_4$) and concentrated under vacuum. The residue was purified by flash chromatography (SiO_2, 400 g, PE/EtOAc, 90:10, R_f = 0.34) to give **92** (4.04 g, 17.47 mmol, 71 %) as a light yellow solid. **Procedure B**: $Pd(PPh_3)_2Cl_2$ (70 mg, 0.10 mmol, 2 mol-%), CuI (19 mg, 0.10 mmol, 2 mol-%), PPh_3 (52 mg, 0.20 mmol, 4 mol-%), *i*Pr_2NH (2 mL) and toluene (15 mL) were placed in an oven dried and argon-filled Schlenk flask. After addition of 2-(2-bromophenyl)acetonitrile (**61**, 980 mg, 5.00 mmol), the mixture was stirred at 25 °C for 30 minutes, and ethynyltrimethylsilane (**64**, 501 mg, 5.10 mmol) was added. After this the mixture had been stirred at 80 °C for an additional 16 h, then cooled to room temperature. KOH (561 mg, 10 mmol), water (0,5 mL) and methanol (15 mL) was added in one portion followed after stirring 2.5 h at room temperature by the addition of 1-iodo-4-methylbenzene (**67**, 970 mg, 5.00 mmol). After another 16 h of stirring a saturated NH_4Cl solution (60 mL) was added. The mixture was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were washed with HCl (2 N, 50 mL), water (50 mL) and saturated NaCl solution (50 mL). The organic layer was dried ($MgSO_4$) and concentrated under vacuum. The residue was purified by flash chromatography

(SiO_2, 190 g, PE/EtOAc, 90:10, R_f = 0.34) to give **92** (975 mg, 4.22 mmol, 85 %) as a light yellow solid.

M.p.: 69 °C.

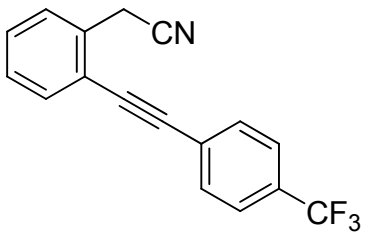
^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.37 (s, 3 H), 3.95 (s, 2 H), 7.17 (d, *J* = 8.0 Hz, 2 H), 7.29-7.38 (m, 2 H), 7.44 (d, *J* = 8.1 Hz, 2 H), 7.49 (d, *J* = 7.4 Hz, 1 H), 7.55 (dd, *J* = 7.4, 1.1 Hz, 2 H) ppm.

^{13}C NMR (126 MHz, DEPT, $CDCl_3$) δ = 21.5 (CH_3), 22.7 (CH_2), 85.3 (C), 95.9 (C), 117.4 (C), 119.3 (C), 122.9 (C), 128.0 (CH), 128.1 (CH), 128.8 (CH), 129.2 (CH), 131.4 (CH), 131.5 (C), 132.2 (CH), 139.1 (C) ppm.

IR (neat): $\tilde{\nu}$ = 3026, 2941, 2921, 2246, 2218, 1598, 1512, 1484, 1450, 1408, 948, 824, 753 cm^{-1}.

MS (EI): *m/z* (%) = 231 (100) $[M]^+$, 230 (60), 228 (9), 213 (49), 203 (18), 189 (13), 101 (5).

HRMS: calcd. ($C_{17}H_{13}N$) 231.1048; found 231.1046.



$C_{17}H_{10}F_3N$
MW: 285.26

2-(2-((4-(Trifluoromethyl)phenyl)ethynyl)phenyl)acetonitrile (**93**): **Procedure A**: $Pd(PPh_3)_2Cl_2$ (77 mg, 0.11 mmol, 2 mol-%), CuI (10 mg, 0.06 mmol, 1 mol-%), PPh_3 (58 mg, 0.22 mmol, 4 mol-%), *i*Pr_2NH (20 mL) and toluene (15 mL) were placed in an oven dried and argon-filled Schlenk flask. After addition of 2-(2-bromophenyl)acetonitrile (**61**, 1.08 g, 5.50 mmol), the mixture was stirred at 25 °C for 30 minutes, and 1-ethynyl-4-(trifluoromethyl)benzene (**84**, 1.29 g, 6.05 mmol) was

added. After this mixture had been stirred at 80 °C for an additional 16 h, a saturated NH_4Cl solution (100 mL) was added. The mixture was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were washed with HCl (2 N, 50 mL), water (50 mL) and saturated NaCl solution (50 mL). After that the combined organic layers were dried ($MgSO_4$) and concentrated under vacuum. The residue was purified by flash chromatography (SiO_2, 120 g, PE/EtOAc, 90:10, R_f = 0.24) to give **93** (1.29 g, 4.52 mmol, 82 %) as a light brown solid. **Procedure B**: $Pd(PPh_3)_2Cl_2$ (70 mg, 0.10 mmol, 2 mol-%), CuI (19 mg, 0.10 mmol, 2 mol-%), PPh_3 (52 mg, 0.20 mmol, 4 mol-%), *i*Pr_2NH (2 mL) and toluene (15 mL) were placed in an oven dried and argon-filled Schlenk flask. After addition of 2-(2-bromophenyl)acetonitrile (**61**, 980 g, 5.52 mmol), the mixture was stirred at 25 °C for 30 minutes, and ethynyltrimethylsilane (**64**, 501 mg, 5.10 mmol) was added. After this the mixture had been stirred at 80 °C for an additional 16 h, then cooled to room temperature. KOH (561 mg, 10 mmol), water (0,5 mL) and methanol (15 mL) was added in one portion followed after stirring 2.5 h at room temperature by the addition of 1-iodo-4-(trifluoromethyl)benzene (**68**, 1.36 g, 5.00 mmol). After another 16 h of stirring a saturated NH_4Cl solution (60 mL) was added. The mixture was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were washed with HCl (2 N, 50 mL), water (50 mL) and saturated NaCl solution (50 mL). The organic layer was dried ($MgSO_4$) and concentrated under vacuum. The residue was purified by flash chromatography (SiO_2, 145 g, PE/EtOAc, 90:10, R_f = 0.24) to give **93** (1.17 g, 4.10 mmol, 83 %) as a light brown solid.

M.p.: 76 °C.

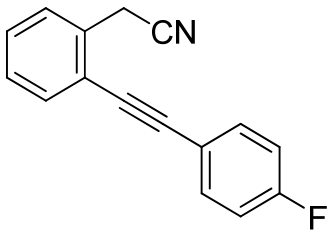
^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.96 (s, 2 H), 7.36 (t, *J* = 7.5 Hz, 1 H), 7.41 (t, *J* = 7.4 Hz, 1 H), 7.50 (d, *J* = 7.6 Hz, 1 H), 7.59 (d, *J* = 7.4 Hz, 1 H), 7.62 (d, *J* = 8.4 Hz, 2 H), 7.66 (d, *J* = 8.3 Hz, 2 H) ppm.

^{13}C NMR (126 MHz, DEPT, $CDCl_3$): δ = 22.8 (CH_2), 88.2 (C), 94.0 (C), 117.2 (C), 122.1 (C), 123.8 (q, *J* = 272 Hz, CF_3), 125.4 (q, *J* = 4 Hz, CH), 126.2 (C), 128.3 (CH), 128.4 (CH), 129.6 (CH), 130.4 (q, *J* = 33 Hz, C), 131.8 (CH), 131.9 (C), 132.6 (CH) ppm.

IR (neat): $\tilde{\nu}$ = 3065, 1613, 1484, 1451, 1403, 1320, 1153, 1121, 1063, 842, 761 cm^{-1}.

MS (EI): *m/z* (%) = 285 (100) $[M]^+$, 265 (41), 245 (10), 216 (35), 189 (15), 140 (6).

HRMS: (CI) calcd. ($C_{17}H_{11}F_3N$) 286.0844; found 286.0841.



$C_{16}H_{10}FN$
MW: 235.26

2-(2-((4-Fluorophenyl)ethynyl)phenyl)acetonitrile (**94**): **Procedure A**: $Pd(PPh_3)_2Cl_2$ (98 mg, 0.14 mmol, 2 mol-%), CuI (13 mg, 0.07 mmol, 1 mol-%), PPh_3 (73 mg, 0.28 mmol, 4 mol-%), *i*Pr_2NH (30 mL) and toluene (20 mL) were placed in an oven dried and argon-filled Schlenk flask. After addition of 2-(2-bromophenyl)acetonitrile (**61**, 1.37 g, 7.00 mmol), the mixture was stirred at 25 °C for 30 minutes, and 1-ethynyl-4-fluorobenzene (**85**, 925 g, 7.70 mmol) was added. After this mixture had been stirred at 80 °C for an additional 16 h, a saturated NH_4Cl solution (100 mL) was added. The mixture was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were washed with HCl (2 N, 50 mL), water (50 mL) and saturated NaCl solution (50 mL). After that the combined organic layers were dried ($MgSO_4$) and concentrated under vacuum. The residue was purified by flash chromatography (SiO_2, 150 g, PE/EtOAc, 95:5, R_f = 0.13) to give **94** (1.45 g, 6.15 mmol, 88 %) as a orange solid.

M.p.: 74 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.93 (s, 2 H), 7.06 (t, *J* = 8.6 Hz, 2 H), 7.29-7.40 (m, 2 H), 7.45-7.58 (m, 4 H) ppm.

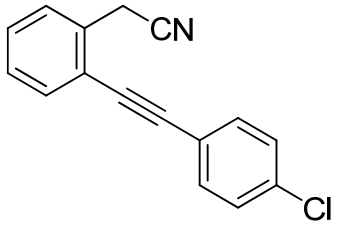
^{13}C NMR (126 MHz, DEPT, $CDCl_3$): δ = 22.7 (CH_2), 85.7 (C), 94.6 (C), 115. 8 (d, *J* = 22 Hz, CH), 117.3 (C), 118.6 (d, *J* = 3 Hz, C), 122.7 (C), 128.2 (CH), 128.2 (CH),

129.1 (CH), 131.7 (C), 132.3 (CH), 133.5 (d, *J* = 8 Hz, CH), 162.8 (d, *J* = 251 Hz, CF) ppm.

IR (neat): $\tilde{\nu}$ = 2947, 2247, 2216, 1596, 1505, 1408, 1216, 1153, 1099, 835, 809, 759 cm^{-1}.

MS (EI): *m/z* (%) = 235 (100) $[M]^+$, 234 (57), 232 (11), 214 (21), 207 (62), 103 (6).

HRMS: (CI) calcd. ($C_{16}H_{11}FN$) 236.0876; found 236.0877.



$C_{16}H_{10}ClN$
MW: 251.71

2-(2-((4-Chlorophenyl)ethynyl)phenyl)acetonitrile (**95**): $Pd(PPh_3)_2Cl_2$ (98 mg, 0.14 mmol, 2 mol-%), CuI (13 mg, 0.07 mmol, 1 mol-%), PPh_3 (73 mg, 0.28 mmol, 4 mol-%), *i*Pr_2NH (30 mL) and toluene (20 mL) were placed in an oven dried and argon-filled Schlenk flask. After addition of 2-(2-bromophenyl)acetonitrile (**61**, 1.37 g, 7.00 mmol), the mixture was stirred at 25 °C for 30 minutes, and 1-chloro-4-ethynylbenzene (**86**, 1.14 g, 8.40 mmol) was added. After this mixture had been stirred at 80 °C for an additional 16 h, a saturated NH_4Cl solution (100 mL) was added. The mixture was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were washed with HCl (2 N, 50 mL), water (50 mL) and saturated NaCl solution (50 mL). After that the combined organic layers were dried ($MgSO_4$) and concentrated under vacuum. The residue was purified by flash chromatography (SiO_2, 150 g, PE/EtOAc, 90:10, R_f = 0.29) to give **95** (1.65 g, 6.54 mmol, 93 %) as a colorless solid.

M.p.: 85 °C.

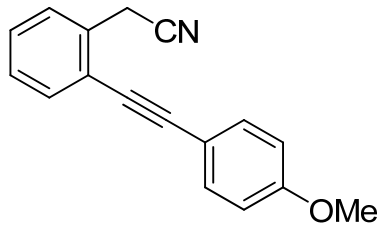
^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.93 (s, 2 H), 7.31-7.35 (m, 3 H), 7.38 (dt, *J* = 7.5, 1.2 Hz, 1 H), 7.45-7.50 (m, 3 H), 7.55 (dd, *J* = 7.5, 1.3 Hz, 1 H) ppm.

^{13}C NMR (126 MHz, DEPT, $CDCl_3$) δ = 22.8 (CH_2), 86.9 (C), 94.5 (C), 117.2 (C), 121.0 (C), 122.5 (C), 128.2 (CH), 128.3 (CH), 128.8 (CH), 129.2 (CH), 131.7 (C), 132.4 (CH), 132.8 (CH), 134.9 (CCl) ppm.

IR (neat): $\tilde{\nu}$ = 3058, 3023, 2941, 2912, 2243, 2216, 1589, 1492, 1408, 1400, 1089, 1011, 828, 758 cm^{-1}.

MS (EI): *m/z* (%) = 253 (22) [M, $^{37}Cl]^+$, 251 (66) [M, $^{35}Cl]^+$, 216 (100), 214 (30), 189 (27), 94 (8).

HRMS: calcd. ($C_{16}H_{10}ClN$) 251.0502; found 251.0500.



$C_{17}H_{13}NO$
MW: 247.29

2-(2-((4-Methoxyphenyl)ethynyl)phenyl)acetonitrile (**96**): **Procedure A**: $Pd(PPh_3)_2Cl_2$ (98 mg, 0.14 mmol, 2 mol-%), CuI (13 mg, 0.07 mmol, 1 mol-%), PPh_3 (73 mg, 0.28 mmol, 4 mol-%), *i*Pr_2NH (30 mL) and toluene (20 mL) were placed in an oven dried and argon-filled Schlenk flask. After addition of 2-(2-bromophenyl)acetonitrile (**61**, 1.37 g, 7.00 mmol), the mixture was stirred at 25 °C for 30 minutes, and 1-ethynyl-4-methoxybenzene (**87**, 1.02 g, 7.70 mmol) was added. After this mixture had been stirred at 80 °C for an additional 16 h, a saturated NH_4Cl solution (100 mL) was added. The mixture was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were washed with HCl (2 N, 50 mL), water (50 mL) and saturated NaCl solution (50 mL). After that the combined organic layers were dried ($MgSO_4$) and concentrated under vacuum. The residue was purified by flash

chromatography (SiO_2, 180 g, PE/EtOAc, 90:10, R_f = 0.27) to give **96** (1.49 g, 6.03 mmol, 86 %) as a yellow solid.

M.p.: 61 °C.

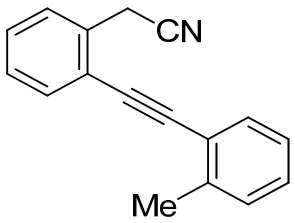
^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.82 (s, 3 H), 3.95 (s, 2 H), 6.86-6.91 (m, 2 H), 7.28-7.37 (m, 2 H), 7.45-7.51 (m, 3 H), 7.54 (dd, *J* = 7.3, 1.7 Hz, 1 H) ppm.

^{13}C NMR (126 MHz, DEPT, $CDCl_3$) δ = 22.8 (CH_2), 55.3 (CH_3), 84.8 (C), 95.8 (C), 114.1 (CH), 114.5 (C), 117.5 (C), 123.1 (C), 128.1 (CH), 128.1 (CH), 128.7 (CH), 131.4 (C), 132.1 (CH), 133.1 (CH), 160.0 ppm.

IR (neat): $\tilde{\nu}$ = 2966, 2926, 2839, 2253, 2209, 1605, 1508, 1443, 1285, 1245, 1173, 1173, 1106, 1022, 831, 758 cm^{-1}.

MS (EI): *m/z* (%) = 247 (100) $[M]^+$, 232 (37), 204 (28), 176 (24), 151 (7).

HRMS: calcd. ($C_{17}H_{13}NO$) 247.0997; found 247.1002.



$C_{17}H_{13}N$
MW: 231.29

2-(2-(o-Tolylethynyl)phenyl)acetonitrile (**97**): **Procedure A**: $Pd(PPh_3)_2Cl_2$ (98 mg, 0.14 mmol, 2 mol-%), CuI (13 mg, 0.07 mmol, 1 mol-%), PPh_3 (73 mg, 0.28 mmol, 4 mol-%), *i*Pr_2NH (30 mL) and toluene (20 mL) were placed in an oven dried and argon-filled Schlenk flask. After addition of 2-(2-bromophenyl)acetonitrile (**61**, 1.37 g, 7.00 mmol), the mixture was stirred at 25 °C for 30 minutes, and 1-ethynyl-2-methylbenzene (**88**, 976 mg, 8.40 mmol) was added. After this mixture had been stirred at 80 °C for an additional 16 h, a saturated NH_4Cl solution (100 mL) was added. The mixture was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic

layers were washed with HCl (2 N, 50 mL), water (50 mL) and saturated NaCl solution (50 mL). After that the combined organic layers were dried ($MgSO_4$) and concentrated under vacuum. The residue was purified by flash chromatography (SiO_2, 180 g, PE/EtOAc, 95:5, R_f = 0.19) to give **97** (1.46 g, 6.42 mmol, 92 %) as a light yellow solid.

M.p.: 40 °C.

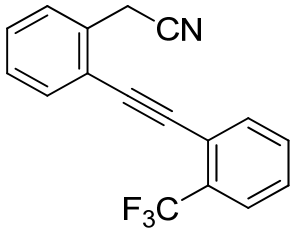
^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.53 (s, 3 H), 3.98 (s, 2 H), 7.17-7.22 (m, 1 H), 7.23-7.30 (m, 2 H), 7.33-7.36 (m, 1 H), 7.38 (dt, *J* = 7.6, 1.5 Hz, 1 H), 7.52 (d, *J* = 7.5 Hz, 2 H), 7.58 (dd, *J* = 7.6, 1.2 Hz, 1 H) ppm.

^{13}C NMR (126 MHz, DEPT, $CDCl_3$) δ = 20.9 (CH_3), 22.8 (CH_2), 89.8 (C), 94.6 (C), 117.4 (C), 122.3 (C), 123.0 (C), 125.7 (CH), 128.1 (CH), 128.2 (CH), 128.9 (CH), 128.9 (CH), 129.6 (CH), 131.4 (C), 132.0 (CH), 132.4 (CH), 140.0 (C) ppm.

IR (neat): $\tilde{\nu}$ = 3062, 2921, 1492, 1451, 1409, 1110, 1042 cm^{-1}.

MS (EI): *m/z* (%) = 231 (72) [M]$^+$, 230 (100), 203 (37), 189 (6), 101 (9).

HRMS: calcd. ($C_{17}H_{13}N$) 231.1048; found 231.1050.



$C_{17}H_{10}F_3N$
MW: 285.26

2-(2-((2-(Trifluoromethyl)phenyl)ethynyl)phenyl)acetonitrile (**98**): **Procedure A**: $Pd(PPh_3)_2Cl_2$ (98 mg, 0.14 mmol, 2 mol-%), CuI (13 mg, 0.07 mmol, 1 mol-%), PPh_3 (73 mg, 0.28 mmol, 4 mol-%), *i*Pr_2NH (20 mL) and toluene (15 mL) were placed in an oven dried and argon-filled Schlenk flask. After addition of 2-(2-bromophenyl)acetonitrile (**61**, 1.37 g, 7.00 mmol), the mixture was stirred at 25 °C for

30 minutes, and 1-ethynyl-2-(trifluoromethyl)benzene (**89**, 1.43 g, 8.40 mmol) was added. After this mixture had been stirred at 80 °C for an additional 16 h, a saturated NH_4Cl solution (100 mL) was added. The mixture was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were washed with HCl (2 N, 50 mL), water (50 mL) and saturated NaCl solution (50 mL). After that the combined organic layers were dried ($MgSO_4$) and concentrated under vacuum. The residue was purified by flash chromatography (SiO_2, 180 g, PE/EtOAc, 90:10, R_f = 0.29) to give **98** (1.92 g, 6.72 mmol, 96 %) as a orange solid.

M.p.: 54 °C.

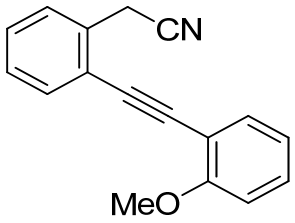
^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.98 (s, 2 H), 7.34 (t, *J* = 7.6 Hz, 1 H), 7.38-7.47 (m, 2 H), 7.51-7.56 (m, 2 H), 7.59 (d, *J* = 7.6 Hz, 1 H), 7.70 (d, *J* = 7.8 Hz, 2 H) ppm.

^{13}C NMR (126 MHz, DEPT, $CDCl_3$): δ = 22.4 (CH_2), 91.2 (C), 91.4 (C), 117.3 (C), 120.8 (C), 122.1 (C), 123.6 (q, *J* = 273 Hz, CF_3), 126.0 (q, *J* = 5 Hz, CH), 128.1 (CH), 128.1 (CH), 128.5 (CH), 129.6 (CH), 131.2 (q, *J* = 31 Hz, C), 131.6 (CH), 132.1 (C), 132.7 (CH), 134.0 (CH) ppm.

IR (neat): $\tilde{\nu}$ = 3037, 2931, 2911, 2246, 2222, 1603, 1572, 1497, 1481, 1455, 1403, 1310, 1261, 1169, 1124, 1089, 1058, 1030, 757 cm^{-1}.

MS (EI): *m/z* (%) = 285 (100) $[M]^+$, 264 (34), 245 (85), 238 (12), 213 (9), 142 (4).

HRMS: calcd. ($C_{17}H_{10}F_3N$) 285.0765; found 285.0770.



$C_{17}H_{13}NO$
MW: 247.29

2-(2-((2-Methoxyphenyl)ethynyl)phenyl)acetonitrile (**99**): **Procedure A**: $Pd(PPh_3)_2Cl_2$ (98 mg, 0.14 mmol, 2 mol-%), CuI (13 mg, 0.07 mmol, 1 mol-%), PPh_3 (73 mg, 0.28 mmol, 4 mol-%), *i*Pr_2NH (20 mL) and toluene (15 mL) were placed in an oven dried and argon-filled Schlenk flask. After addition of 2-(2-bromophenyl)acetonitrile (**61**, 1.37 g, 7.00 mmol), the mixture was stirred at 25 °C for 30 minutes, and 1-ethynyl-2-methoxybenzene (**90**, 1.11 g, 8.40 mmol) was added. After this mixture had been stirred at 80 °C for an additional 16 h, a saturated NH_4Cl solution (100 mL) was added. The mixture was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were washed with HCl (2 N, 50 mL), water (50 mL) and saturated NaCl solution (50 mL). After that the combined organic layers were dried ($MgSO_4$) and concentrated under vacuum. The residue was purified by flash chromatography (SiO_2, 180 g, PE/EtOAc, 90:10, R_f = 0.23) to give **99** (1.66 g, 6.71 mmol, 96 %) as a light yellow solid.

M.p.: 83 °C.

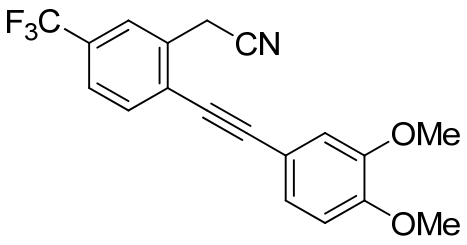
^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.93 (s, 3 H), 4.06 (s, 2 H), 6.92 (d, *J* = 8.4 Hz, 1 H), 6.96 (t, *J* = 7.5 Hz, 1 H), 7.30-7.39 (m, 3 H), 7.49 (dd, *J* = 7.6, 1.4 Hz, 1 H), 7.53 (d, *J* = 7.5 Hz, 1 H), 7.57 (dd, *J* = 7.4, 0.8 Hz, 1 H) ppm.

^{13}C NMR (126 MHz, DEPT, $CDCl_3$) δ = 22.5 (CH_2), 55.8 (CH_3), 90.3 (C), 92.2 (C), 110.6 (CH), 111.7 (C), 117.8 (C), 120.5 (CH), 123.1 (C), 127.9 (CH), 128.0 (CH), 128.8 (CH), 130.3 (CH), 131.9 (CH), 131.9 (C), 133.0 (CH), 160.1 (C) ppm.

IR (neat): $\tilde{\nu}$ = 2925, 2841, 1592, 1572, 1497, 1456, 1433, 1403, 1275, 1249, 1163, 1112, 1043, 1021, 742 cm^{-1}.

MS (EI): *m/z* (%) = 247 (100) $[M]^+$, 219 (51), 203 (20), 191 (12), 176 (20), 150 (8), 131 (8).

HRMS: calcd. ($C_{17}H_{13}NO$) 247.0997; found 247.0991.



$C_{19}H_{14}F_3NO_2$
MW: 345.32

2-(2-((3,4-Dimethoxyphenyl)ethynyl)-5-(trifluoromethyl)phenyl)acetonitrile (**100**): $Pd(PPh_3)_2Cl_2$ (85 mg, 0.12 mmol, 4 mol-%), CuI (46 mg, 0.24 mmol, 8 mol-%), PPh_3 (63 mg, 0.24 mmol, 8 mol-%), *i*Pr_2NH (6 mL) and DMF (6 mL) were placed in an oven dried and argon-filled Schlenk flask. After addition of 2-(2-bromo-5-(trifluoromethyl)phenyl)acetonitrile (**58**, 789 mg, 3.00 mmol), the mixture was stirred at 25 °C for 30 minutes, and 4-ethynyl-1,2-dimethoxybenzene (**66**, 486 mg, 3.00 mmol) was added. After this mixture had been stirred at 80 °C for an additional 16 h, a saturated NH_4Cl solution (200 mL) was added. The mixture was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic layers were dried ($MgSO_4$) and concentrated under vacuum. The residue was purified by flash chromatography (SiO_2, 120 g, PE/EtOAc, 80:20, R_f = 0.20) to give **100** (994 g, 2.88 mmol, 96 %) as a colorless solid.

M.p.: 80 °C.

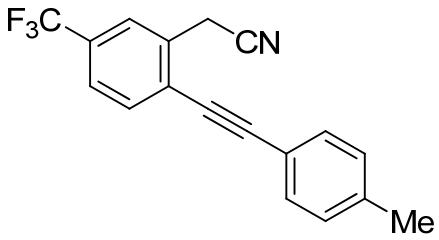
^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.92 (s, 6 H), 4.01 (s, 2 H), 6.87 (d, *J* = 8.3 Hz, 1 H), 7.06 (d, *J* = 1.9 Hz, 1 H), 7.20 (dd, *J* = 8.3, 1.9 Hz, 1 H), 7.60 (d, *J* = 8.1 Hz, 1 H), 7.67 (d, *J* = 8.1 Hz, 1 H), 7.74 (s, 1 H) ppm.

^{13}C NMR (75 MHz, DEPT, $CDCl_3$): δ = 22.9 (CH_2), 56.0 (CH_3), 56.0 (CH_3), 83.6 (C), 98.7 (C), 111.1 (CH), 113.8 (C), 114.2 (CH), 116.6 (C), 123.5 (q, *J* = 272 Hz, CF_3), 125.1 (q, *J* = 4 Hz, CH), 125.4 (CH), 127.0 (C), 130.4 (q, *J* = 33 Hz, CH), 132.3 (C), 132.5 (CH), 149.9 (C), 150.4 (C) ppm.

IR (KBr): $\tilde{\nu}$ = 3079, 2972, 2942, 2915, 2842, 2249, 2208, 1600, 1578, 1518, 1499, 1463, 1442, 1426, 1320, 1273, 1251, 1229, 1165, 1137, 1105, 1075, 1020, 871, 834, 817 cm^{-1}.

MS (EI): *m/z* (%) = 345 (100) $[M]^+$, 330 (6), 302 (8), 275 (13), 259 (4), 258 (3), 190 (6), 173 (3), 151 (5).

HRMS: calcd. ($C_{19}H_{14}NO_2F_3$) 345.0977; found 345.1010.



$C_{18}H_{12}F_3N$
MW: 299.29

2-(2-(p-Tolylethynyl)-5-(trifluoromethyl)phenyl)acetonitrile (**101**): $Pd(PPh_3)_2Cl_2$ (84 mg, 0.12 mmol, 2 mol-%), CuI (11 mg, 0.06 mmol, 1 mol-%), PPh_3 (84 mg, 0.12 mmol, 4 mol-%), *i*Pr_2NH (30 mL) and toluene (20 mL) were placed in an oven dried and argon-filled Schlenk flask. After addition of 2-(2-bromo-5-(trifluoromethyl)phenyl)acetonitrile (**58**, 1.58 g, 6.00 mmol), the mixture was stirred at 25 °C for 30 minutes, and 1-ethynyl-4-methylbenzene (**83**, 767 mg, 1.10 mmol) was added. After this mixture had been stirred at 80 °C for an additional 16 h, a saturated NH_4Cl solution (100 mL) was added. The mixture was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were washed with HCl (2 N, 50 mL), water (50 mL) and saturated NaCl solution (50 mL). After that the combined organic layers were dried ($MgSO_4$) and concentrated under vacuum. The residue was purified by flash chromatography (SiO_2, 90 g, PE/EtOAc, 70:30, R_f = 0.34) to give **101** (1.36 g, 4.34 mmol, 79 %) as a colorless solid.

M.p.: 89 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.39 (s, 3 H), 4.00 (s, 2 H), 7.19 (d, *J* = 8.0 Hz, 2 H), 7.46 (d, *J* = 8.1 Hz, 2 H), 7.58 (d, *J* = 8.1 Hz, 1 H), 7.66 (d, *J* = 8.1 Hz, 1 H), 7.74 (s, 1 H) ppm.

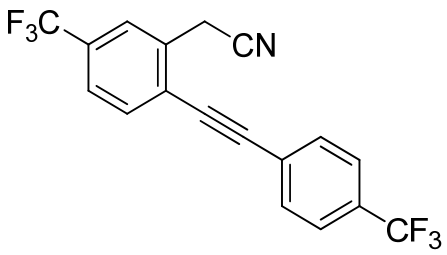
^{13}C NMR (126 MHz, DEPT, $CDCl_3$): δ = 21.6 (CH_3), 22.8 (CH_2), 84.2 (C), 98.6 (C), 116.6 (C), 118.6 (C), 123.5 (q, *J* = 272 Hz, CF_3), 125.0 (q, *J* = 4 Hz, CH), 125.1 (q, *J*

= 4 Hz, CH), 126.9 (CH), 129.3 (CH), 130.5 (q, *J* = 33 Hz, C), 131.6 (CH), 132.4 (C), 132.6 (CH), 139.9 (C) ppm.

IR (neat): $\tilde{\nu}$ = 2946, 2917, 2250, 2216, 1617, 1519, 1427, 1406, 1331, 1265, 1162, 1115, 1100, 1076, 938, 823 cm^{-1}.

MS (EI): *m/z* (%) = 299 (100) $[M]^+$, 297 (27), 284 (37), 230 (48), 227 (12), 214 (14), 206 (14), 202 (17), 149 (9), 115 (7).

HRMS: calcd. ($C_{18}H_{12}F_3N$) 299.0922; found 299.0926.



$C_{18}H_9F_6N$
MW: 353.26

2-(2-(p-Tolylethynyl)-5-(trifluoromethyl)phenyl)acetonitrile (**102**): $Pd(PPh_3)_2Cl_2$ (77 mg, 0.11 mmol, 2 mol-%), CuI (10 mg, 0.06 mmol, 1 mol-%), PPh_3 (58 mg, 0.22 mmol, 4 mol-%), *i*Pr_2NH (20 mL) and toluene (15 mL) were placed in an oven dried and argon-filled Schlenk flask. After addition of 2-(2-bromo-5-(trifluoromethyl)phenyl)acetonitrile (**58**, 1.45 g, 5.50 mmol), the mixture was stirred at 25 °C for 30 minutes, and 1-ethynyl-4-(trifluoromethyl)benzene (**84**, 1.03 mg, 6.05 mmol) was added. After this mixture had been stirred at 80 °C for an additional 16 h, a saturated NH_4Cl solution (100 mL) was added. The mixture was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were washed with HCl (2 N, 50 mL), water (50 mL) and saturated NaCl solution (50 mL). After that the combined organic layers were dried ($MgSO_4$) and concentrated under vacuum. The residue was purified by flash chromatography (SiO_2, 180 g, PE/EtOAc, 95:5, R_f = 0.19) to give **102** (1.67 g, 4.73 mmol, 86 %) as a light brown solid.

M.p.: 92 °C.

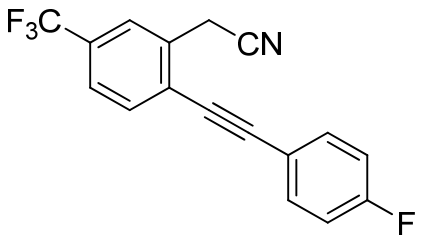
^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.01 (s, 2 H), 7.61-7.77 (m, 7 H) ppm.

^{13}C NMR (126 MHz, DEPT $CDCl_3$): δ = 22.9 (CH_2), 86.8 (C), 96.5 (C), 116.3 (C), 123.4 (q, J = 273 Hz, CF_3), 123.7 (q, J = 272 Hz, CF_3), 125.3 (q, J = 4 Hz, CH), 125.4 (q, J = 4 Hz, CH), 125.5 (q, J = 3 Hz, CH), 126.0 (C), 128.4 (C), 131.1 (q, J = 33 Hz, C), 131.4 (q, J = 33 Hz, C), 132.0 (CH), 132.8 (C), 133.0 (CH) ppm.

IR (neat): $\tilde{\nu}$ = 2957, 2255, 1616, 1405, 1324, 1122, 1103, 1065, 844 cm^{-1}.

MS (EI): *m/z* (%) = 353 (100) $[M]^+$, 352 (13), 334 (21), 333 (38), 285 (14), 284 (70), 283 (10), 257 (10), 214 (10).

HRMS: calcd. ($C_{18}H_9F_6N$) 353.0639; found 353.0635.



$C_{17}H_9F_4N$
MW: 303.25

2-(2-((4-Fluorophenyl)ethynyl)-5-(trifluoromethyl)phenyl)acetonitrile (**103**): $Pd(PPh_3)_2Cl_2$ (98 mg, 0.14 mmol, 2 mol-%), CuI (13 mg, 0.07 mmol, 1 mol-%), PPh_3 (73 mg, 0.28 mmol, 4 mol-%), *i*Pr_2NH (30 mL) and toluene (20 mL) were placed in an oven dried and argon-filled Schlenk flask. After addition of 2-(2-bromo-5-(trifluoromethyl)phenyl)acetonitrile (**58**, 1.85 g, 7.00 mmol), the mixture was stirred at 25 °C for 30 minutes, and 1-ethynyl-4-fluorobenzene (**85**, 925 mg, 7.70 mmol) was added. After this mixture had been stirred at 80 °C for an additional 16 h, a saturated NH_4Cl solution (100 mL) was added. The mixture was extracted with CH_2Cl_2 (4 × 50 mL). The combined organic layers were washed with HCl (2 N, 50 mL), water (50 mL) and saturated NaCl solution (50 mL). After that the combined organic layers were dried ($MgSO_4$) and concentrated under vacuum. The residue was purified by flash chromatography (SiO_2, 180 g, PE/EtOAc, 95:5, R_f = 0.14) to give **103** (1.68 g, 5.54 mmol, 79 %) as a orange solid.

M.p.: 61 °C.

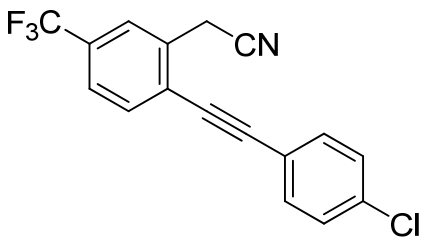
^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.00 (s, 2 H), 7.05-7.13 (m, 2 H), 7.54-7.59 (m, 2 H), 7.61 (d, *J* = 8.2 Hz, 1 H), 7.68 (d, *J* = 8.1 Hz, 1 H), 7.74 (s, 1 H) ppm.

^{13}C NMR (126 MHz, DEPT, $CDCl_3$): δ = 22.9 (CH_2), 84.5 (C), 97.2 (C), 116.0 (d, *J* = 22 Hz, CH), 116.5 (C), 117.8 (d, *J* = 4 Hz, C), 123.4 (q, *J* = 273 Hz, CF_3), 125.2 (q, *J* = 4 Hz, CH), 125.2 (q, *J* = 3 Hz, CH), 126.5 (C), 130.8 (q, *J* = 33 Hz, C), 132.5 (C), 132.7 (CH), 133.8 (d, *J* = 9 Hz, CH), 163.1 (d, *J* = 252 Hz, CF) ppm.

IR (neat): $\tilde{\nu}$ = 2938, 2219, 1601, 1516, 1497, 1426, 1333, 1325, 1266, 1239, 1229, 1134, 1074, 842, 835 cm^{-1}.

MS (CI): *m/z* (%) = 304 (78) $[M + H]^+$, 303 (100), 284 (6), 234 (24), 207 (6).

HRMS: (CI) calcd. ($C_{17}H_{10}F_4N$) 304.0749; found 304.0747.



$C_{17}H_9ClF_3N$
MW: 319.71

2-(2-((4-Chlorophenyl)ethynyl)-5-(trifluoromethyl)phenyl)acetonitrile (**104**): $Pd(PPh_3)_2Cl_2$ (98 mg, 0.14 mmol, 2 mol-%), CuI (13 mg, 0.07 mmol, 1 mol-%), PPh_3 (73 mg, 0.28 mmol, 4 mol-%), *i*Pr_2NH (30 mL) and toluene (20 mL) were placed in an oven dried and argon-filled Schlenk flask. After addition of 2-(2-bromo-5-(trifluoromethyl)phenyl)acetonitrile (**58**, 1.85 g, 7.00 mmol), the mixture was stirred at 25 °C for 30 minutes, and 1-chloro-4-ethynylbenzene (**86**, 1.14 g, 8.40 mmol) was added. After this mixture had been stirred at 80 °C for an additional 16 h, a saturated NH_4Cl solution (100 mL) was added. The mixture was extracted with CH_2Cl_2 (4 × 50 mL). The combined organic layers were washed with HCl (2 N, 50 mL), water (50 mL) and saturated NaCl solution (50 mL). After that the combined organic layers

were dried ($MgSO_4$) and concentrated under vacuum. The residue was purified by flash chromatography (SiO_2, 170 g, PE/EtOAc, 80:20, R_f = 0.47) to give **104** (2.06 g, 6.43 mmol, 92 %) as a light brown solid.

M.p.: over 230 °C.

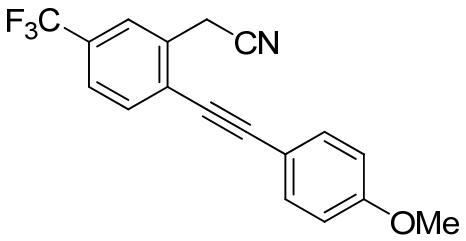
^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.99 (s, 2 H), 7.37 (d, *J* = 8.5 Hz, 2 H), 7.51 (d, *J* = 8.5 Hz, 2 H), 7.61 (d, *J* = 8.1 Hz, 1 H), 7.68 (d, *J* = 8.1 Hz, 1 H), 7.74 (s, 1 H) ppm.

^{13}C NMR (126 MHz, DEPT, $CDCl_3$): δ = 22.9 (CH_2), 85.6 (C), 97.0 (C), 116.5 (C), 120.2 (C), 123.4 (q, *J* = 273 Hz, CF_3), 125.2 (q, *J* = 3 Hz, CH), 125.2 (q, *J* = 4 Hz, CH), 126.4 (C), 129.0 (CH), 130.9 (q, *J* = 33 Hz, C), 132.5 (C), 132.8 (CH), 132.9 (CH), 135.6 (C) ppm.

IR (neat): $\tilde{\nu}$ = 2947, 2214, 1618, 1505, 1484, 1405, 1330, 1265, 1168, 1111, 1086, 1010, 829 cm^{-1}.

MS (EI): *m/z* (%) = 321 (23) [M, ^{37}Cl]$^+$, 319 (76) [M, ^{35}Cl]$^+$, 284 (100), 252 (11), 250 (38), 214 (38), 187 (7).

HRMS: calcd. ($C_{17}H_9ClF_3N$) 319.0376; found 319.0375.



$C_{18}H_{12}F_3NO$
MW: 315.29

2-(2-((4-Methoxyphenyl)ethynyl)-5-(trifluoromethyl)phenyl)acetonitrile (**105**): $Pd(PPh_3)_2Cl_2$ (84 mg, 0.12 mmol, 2 mol-%), CuI (11 mg, 0.06 mmol, 1 mol-%), PPh_3 (63 mg, 0.24 mmol, 4 mol-%), *i*Pr_2NH (30 mL) and toluene (20 mL) were placed in an oven dried and argon-filled Schlenk flask. After addition of 2-(2-bromo-5-(trifluoromethyl)phenyl)acetonitrile (**58**, 1.58 g, 6.00 mmol), the mixture was stirred at

25 °C for 30 minutes, and 1-ethynyl-4-methoxybenzene (**87**, 872 mg, 6.60 mmol) was added. After this mixture had been stirred at 80 °C for an additional 16 h, a saturated NH_4Cl solution (100 mL) was added. The mixture was extracted with CH_2Cl_2 (4 × 50 mL). The combined organic layers were washed with HCl (2 N, 50 mL), water (50 mL) and saturated NaCl solution (50 mL). After that the combined organic layers were dried ($MgSO_4$) and concentrated under vacuum. The residue was purified by flash chromatography (SiO_2, 200 g, PE/EtOAc, 70:30, R_f = 0.38) to give **105** (1.67 g, 5.31 mmol, 88 %) as a yellow-orange solid.

M.p.: 78 °C.

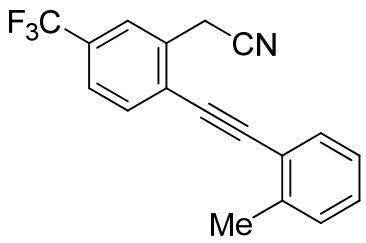
^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.84 (s, 3 H), 3.99 (s, 2 H), 6.88-6.93 (m, 2 H), 7.48-7.53 (m, 2 H), 7.58 (d, *J* = 7.9 Hz, 1 H), 7.65 (d, *J* = 8.1 Hz, 1 H), 7.73 (s, 1 H) ppm.

^{13}C NMR (126 MHz, DEPT, $CDCl_3$): δ = 22.8 (CH_2), 55.3 (CH_3), 83.8 (C), 98.7 (C), 113.8 (C), 114.3 (CH), 116.6 (CN), 123.5 (q, *J* = 272 Hz, CF_3), 125.0 (d, *J* = 4 Hz, CH), 125.1 (d, *J* = 4 Hz, CH), 127.1 (C), 130.3 (q, *J* = 33 Hz, C), 132.3 (C), 132.5 (CH), 133.3 (CH), 160.6 (C) ppm.

IR (neat): $\tilde{\nu}$ = 3001, 2950, 2848, 2001, 1678, 1599, 1515, 1469, 1336, 1291, 1247, 1172, 1123, 1100, 1023, 933, 836 cm^{-1}.

MS (EI): *m/z* (%) = 315 (100) $[M]^+$, 300 (23), 272 (15), 252 (12), 246 (36), 203 (17), 176 (6).

HRMS: calcd. ($C_{18}H_{12}F_3NO$) 315.0871; found 315.0876.



$C_{18}H_{12}F_3N$
MW: 299.29

2-(2-(o-Tolylethynyl)-5-(trifluoromethyl)phenyl)acetonitrile (**106**): $Pd(PPh_3)_2Cl_2$ (98 mg, 0.14 mmol, 2 mol-%), CuI (13 mg, 0.07 mmol, 1 mol-%), PPh_3 (73 mg, 0.28 mmol, 4 mol-%), *i*Pr_2NH (30 mL) and toluene (15 mL) were placed in an oven dried and argon-filled Schlenk flask. After addition of 2-(2-bromo-5-(trifluoromethyl)phenyl)acetonitrile (**58**, 1.85 g, 7.00 mmol), the mixture was stirred at 25 °C for 30 minutes, and 1-ethynyl-2-methylbenzene (**88**, 976 mg, 8.40 mmol) was added. After this mixture had been stirred at 80 °C for an additional 16 h, a saturated NH_4Cl solution (100 mL) was added. The mixture was extracted with CH_2Cl_2 (4 × 50 mL). The combined organic layers were washed with HCl (2 N, 50 mL), water (50 mL) and saturated NaCl solution (50 mL). After that the combined organic layers were dried ($MgSO_4$) and concentrated under vacuum. The residue was purified by flash chromatography (SiO_2, 160 g, PE/EtOAc, 95:5, R_f = 0.20) to give **106** (2.01 g, 6.71 mmol, 95 %) as a yellow solid.

M.p.: 80 °C.

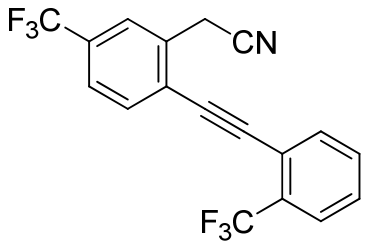
^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.53 (s, 3 H), 4.02 (s, 0 H), 7.22 (t, *J* = 7.5 Hz, 1 H), 7.26-7.33 (m, 2 H), 7.54 (d, *J* = 7.5 Hz, 1 H), 7.61 (d, *J* = 8.0 Hz, 1 H), 7.69 (d, *J* = 8.1 Hz, 1 H), 7.76 (s, 1 H) ppm.

^{13}C NMR (126 MHz, DEPT, $CDCl_3$): δ = 20.9 (CH_3), 22.9 (CH_2), 88.6 (C), 97.2 (C), 116.6 (C), 121.6 (C), 123.5 (q, *J* = 272 Hz, CF_3), 125.1 (q, *J* = 5 Hz, CH), 125.1 (q, *J* = 4 Hz, CH), 125.9 (CH), 126.9 (C), 129.5 (CH), 129.7 (CH), 130.6 (q, *J* = 33 Hz, C), 132.3 (CH), 132.3 (C), 132.8 (CH), 140.3 (C) ppm.

IR (neat): $\tilde{\nu}$ = 2937, 2211, 1614, 1480, 1425, 1397, 1324, 1262, 1159, 1124, 1097, 846 cm^{-1}.

MS (EI): *m/z* (%) = 299 (70) $[M]^+$, 298 (100), 271 (10), 251 (5), 230 (20), 202 (30), 101 (5).

HRMS: calcd. ($C_{18}H_{12}F_3N$) 299.0922; found 299.0926.



$C_{18}H_9F_6N$
MW: 353.26

2-(5-(Trifluoromethyl)-2-((2-(trifluoromethyl)phenyl)ethynyl)phenyl)acetonitrile (**107**): $Pd(PPh_3)_2Cl_2$ (98 mg, 0.14 mmol, 2 mol-%), CuI (13 mg, 0.07 mmol, 1 mol-%), PPh_3 (73 mg, 0.28 mmol, 4 mol-%), *i*Pr_2NH (20 mL) and toluene (15 mL) were placed in an oven dried and argon-filled Schlenk flask. After addition of 2-(2-bromo-5-(trifluoromethyl)phenyl)acetonitrile (**58**, 1.85 g, 7.00 mmol), the mixture was stirred at 25 °C for 30 minutes, and 1-ethynyl-2-(trifluoromethyl)benzene (**89**, 1.43 g, 8.40 mmol) was added. After this mixture had been stirred at 80 °C for an additional 16 h, a saturated NH_4Cl solution (100 mL) was added. The mixture was extracted with CH_2Cl_2 (4 × 50 mL). The combined organic layers were washed with HCl (2 N, 50 mL), water (50 mL) and saturated NaCl solution (50 mL). After that the combined organic layers were dried ($MgSO_4$) and concentrated under vacuum. The residue was purified by flash chromatography (SiO_2, 180 g, PE/EtOAc, 90:10, R_f = 0.25) to give **107** (2.16 g, 6.13 mmol, 88 %) as a light yellow solid.

M.p.: 84 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.04 (s, 2 H), 7.52 (t, *J* = 7.7 Hz, 1 H), 7.57-7.65 (m, 2 H), 7.70-7.76 (m, 3 H), 7.80 (s, 1 H) ppm.

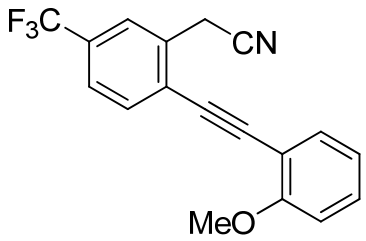
^{13}C NMR (126 MHz, DEPT, $CDCl_3$): δ = 22.5 (CH_2), 89.9 (C), 93.5 (C), 116.5 (C), 120.0 (C), 123.4 (q, *J* = 273 Hz, CF_3), 123.5 (q, *J* = 273 Hz, CF_3), 125.1 (q, *J* = 4 Hz, CH), 125.1 (q, *J* = 4 Hz, CH), 125.9 (C), 126.1 (q, *J* = 5 Hz, CH), 129.2 (CH), 131.4

(q, *J* = 33 Hz, C), 131.5 (q, *J* = 31 Hz, C), 131.7 (CH), 133.0 (C), 133.1 (CH), 134.2 (CH) ppm.

IR (neat): $\tilde{\nu}$ = 2952, 2920, 1410, 1325, 1310, 1263, 1162, 1100, 1078, 1056, 1035, 835 cm^{-1}.

MS (EI): *m/z* (%) = 353 (100) $[M]^+$, 334 (15), 313 (39), 284 (17), 264 (74), 245 (13), 214 (7), 142 (5).

HRMS: calcd. ($C_{18}H_9F_6N$) 353.0639; found 353.0644.



$C_{18}H_{12}F_3NO$
MW: 315.29

2-(2-((2-Methoxyphenyl)ethynyl)-5-(trifluoromethyl)phenyl)acetonitrile (**108**): $Pd(PPh_3)_2Cl_2$ (98 mg, 0.14 mmol, 2 mol-%), CuI (13 mg, 0.07 mmol, 1 mol-%), PPh_3 (73 mg, 0.28 mmol, 4 mol-%), *i*Pr_2NH (20 mL) and toluene (15 mL) were placed in an oven dried and argon-filled Schlenk flask. After addition of 2-(2-bromo-5-(trifluoromethyl)phenyl)acetonitrile (**58**, 1.85 g, 7.00 mmol), the mixture was stirred at 25 °C for 30 minutes, and 1-ethynyl-2-methoxybenzene (**90**, 1.11 g, 8.40 mmol) was added. After this mixture had been stirred at 80 °C for an additional 16 h, a saturated NH_4Cl solution (100 mL) was added. The mixture was extracted with CH_2Cl_2 (4 × 50 mL). The combined organic layers were washed with HCl (2 N, 50 mL), water (50 mL) and saturated NaCl solution (50 mL). After that the combined organic layers were dried ($MgSO_4$) and concentrated under vacuum. The residue was purified by flash chromatography (SiO_2, 190 g, PE/EtOAc, 90:10, R_f = 0.23) to give **108** (2.07 g, 6.56 mmol, 94 %) as a orange-yellow solid.

M.p.: 105 °C.

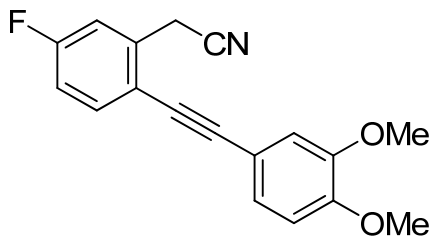
^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.94 (s, 3 H), 4.10 (s, 2 H), 6.94 (d, *J* = 8.4 Hz, 0 H), 6.97 (t, *J* = 7.4 Hz, 1 H), 7.38 (dt, *J* = 7.9, 1.6 Hz, 1 H), 7.50 (dd, *J* = 7.6, 1.5 Hz, 1 H), 7.59 (d, *J* = 8.1 Hz, 1 H), 7.67 (d, *J* = 8.1 Hz, 1 H), 7.77 (s, 1 H) ppm.

^{13}C NMR (126 MHz, DEPT, $CDCl_3$): δ = 22.5 (CH_2), 55.8 (CH_3), 89.1 (C), 95.0 (C), 110.6 (CH), 111.00 (C), 116.9 (C), 120.6 (CH), 123.5 (q, *J* = 272 Hz, CF_3), 124.9 (q, *J* = 4 Hz, CH), 125.0 (q, *J* = 4 Hz, CH), 127.0 (C), 130.4 (q, *J* = 33 Hz, C), 131.0 (CH), 132.1 (CH), 132.7 (C), 133.2 (CH), 160.4 (C) ppm.

IR (neat): $\tilde{\nu}$ = 2931, 1432, 1325, 1248, 1158, 1116, 1022, 836 cm^{-1}.

MS (EI): *m/z* (%) = 315 (100) [M]$^+$, 287 (61), 252 (11), 246 (14), 218 (14), 203 (19), 176 (10), 131 (6).

HRMS: calcd. ($C_{18}H_{12}F_3NO$) 315.0871; found 315.0867.



$C_{18}H_{14}FNO_2$
MW: 295.31

2-(2-((3,4-Dimethoxyphenyl)ethynyl)-5-fluorophenyl)acetonitrile (**109**): $Pd(PPh_3)_2Cl_2$ (62 mg, 0.09 mmol, 4 mol-%), CuI (34 mg, 0.18 mmol, 8 mol-%), PPh_3 (46 mg, 0.18 mmol, 8 mol-%), *i*Pr_2NH (10 mL) and DMF (8 mL) were placed in an oven dried and argon-filled Schlenk flask. After addition of 2-(2-bromo-5-fluorophenyl)acetonitrile (**59**, 942 mg, 4.40 mmol), the mixture was stirred at 25 °C for 30 minutes, and 4-ethynyl-1,2-dimethoxybenzene (**66**, 714 mg, 4.40 mmol) was added. After this mixture had been stirred at 80 °C for an additional 16 h, a saturated NH_4Cl solution (200 mL) was added. The mixture was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic layers were dried ($MgSO_4$) and concentrated under vacuum. The residue was purified by flash chromatography (SiO_2, 120 g, PE/EtOAc, 80:20, R_f = 0.17) to give **109** (1.12 g, 3.81 mmol, 87 %) as a colorless solid.

M.p.: 117 °C.

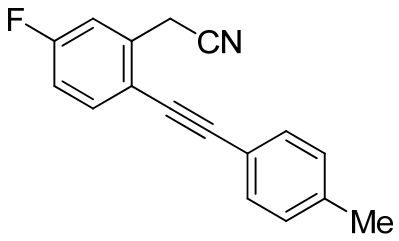
^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.91 (s, 6 H), 3.96 (s, 2 H), 6.85 (d, *J* = 8.2 Hz, 1 H), 7.02-7.07 (m, 2 H), 7.15 (dd, *J* = 8.3, 1.8 Hz, 1 H), 7.23 (dd, *J* = 8.9, 2.4 Hz, 1 H), 7.53 (dd, *J* = 8.5, 5.6 Hz, 1 H) ppm.

^{13}C NMR (126 MHz, DEPT, $CDCl_3$): δ = 22.8 (CH_2), 55.9 (CH_3), 55.9 (CH_3), 83.6 (C), 95.6 (C), 111.1 (CH), 114.1 (CH), 114.4 (C), 115.4 (d, *J* = 22 Hz, CH), 115.7 (d, *J* = 24 Hz, CH), 116.8 (C), 119.1 (d, *J* = 4 Hz, C), 125.0 (CH), 133.9 (d, *J* = 8 Hz, C), 134.0 (d, *J* = 9 Hz, CH), 148.8 (C), 150.0 (C), 162.3 (d, *J* = 251 Hz, CF).

IR (neat): $\tilde{\nu}$ = 3106, 3014, 2997, 2940, 2915, 2839, 2247, 2211, 1608, 1579, 1516, 1492, 1468, 1457, 1439, 1426, 1411, 1335, 1279, 1251, 1232, 1203, 1151, 1130, 1081, 1023, 969, 939, 929, 883, 849, 819, 798, 764, 731 cm^{-1}.

MS (EI): *m/z* (%) = 295 (100) $[M]^+$, 280 (16), 252 (27), 225 (18), 222 (7), 209 (13), 208 (20), 182 (12), 158 (5).

HRMS: calcd. ($C_{18}H_{14}NO_2F$) 295.1009; found 295.1008.



$C_{17}H_{12}FN$
MW: 249.28

2-(5-Fluoro-2-(p-tolylethynyl)phenyl)acetonitrile (**110**): $Pd(PPh_3)_2Cl_2$ (98 mg, 0.14 mmol, 2 mol-%), CuI (13 mg, 0.07 mmol, 1 mol-%), PPh_3 (73 mg, 0.28 mmol, 4 mol-%), *i*Pr_2NH (30 mL) and toluene (20 mL) were placed in an oven dried and argon-filled Schlenk flask. After addition of 2-(2-bromo-5-fluorophenyl)acetonitrile (**59**, 1.50 g, 7.00 mmol), the mixture was stirred at 25 °C for 30 minutes, and 1-ethynyl-4-methylbenzene (**83**, 894 mg, 7.10 mmol) was added. After this mixture had been stirred at 80 °C for an additional 16 h, a saturated NH_4Cl solution (100 mL) was

added. The mixture was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were washed with HCl (2 N, 50 mL), water (50 mL) and saturated NaCl solution (50 mL). After that the combined organic layers were dried ($MgSO_4$) and concentrated under vacuum. The residue was purified by flash chromatography (SiO_2, 90 g, PE/EtOAc, 90:10, R_f = 0.36) to give **110** (1.50 g, 6.01 mmol, 86 %) as a light yellow solid.

M.p.: 98 °C.

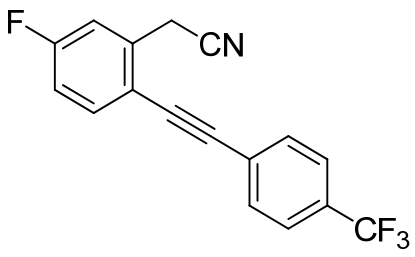
^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.38 (s, 3 H), 3.95 (s, 2 H), 7.01-7.06 (m, 1 H), 7.18 (d, *J* = 7.9 Hz, 2 H), 7.22-7.26 (m, 1 H), 7.42 (d, *J* = 8.0 Hz, 2 H), 7.50-7.56 (m, 1 H) ppm.

^{13}C NMR (126 MHz, DEPT, $CDCl_3$): δ = 21.5 (CH_3), 22.8 (CH_2), 84.3 (C), 95.6 (C), 115.5 (d, *J* = 18 Hz, CH), 115.6 (d, *J* = 20 Hz, CH), 116.9 (C), 119.1 (d, *J* = 3 Hz, C), 119.2 (C), 129.3 (CH), 131.4 (CH), 134.0 (d, *J* = 9 Hz, C), 134.0 (d, *J* = 9 Hz, CH), 139.2 (C), 162.3 (d, *J* = 251 Hz, CF) ppm.

IR (neat): $\tilde{\nu}$ = 2919, 2215, 1609, 1582, 1512, 1487, 1426, 1406, 1275, 1216, 1202, 1153, 966, 867, 814 cm^{-1}.

MS (EI): *m/z* (%) = 249 (100) $[M]^+$, 248 (52), 234 (46), 221 (20), 207 (13), 183 (3), 109 (5).

HRMS: calcd. ($C_{17}H_{12}FN$) 249.0954; found 249.0951.



$C_{17}H_9F_4N$
MW: 303.25

2-(5-Fluoro-2-((4-(trifluoromethyl)phenyl)ethynyl)phenyl)acetonitrile (**111**): $Pd(PPh_3)_2Cl_2$ (77 mg, 0.11 mmol, 2 mol-%), CuI (10 mg, 0.06 mmol, 1 mol-%), PPh_3 (58 mg, 0.22 mmol, 4 mol-%), *i*Pr_2NH (20 mL) and toluene (15 mL) were placed in an oven dried and argon-filled Schlenk flask. After addition of 2-(2-bromo-5-fluorophenyl)acetonitrile (**59**, 1.18 g, 5.50 mmol), the mixture was stirred at 25 °C for 30 minutes, and 1-ethynyl-4-(trifluoromethyl)benzene (**84**, 1.03 mg, 6.05 mmol) was added. After this mixture had been stirred at 80 °C for an additional 16 h, a saturated NH_4Cl solution (100 mL) was added. The mixture was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were washed with HCl (2 N, 50 mL), water (50 mL) and saturated NaCl solution (50 mL). After that the combined organic layers were dried ($MgSO_4$) and concentrated under vacuum. The residue was purified by flash chromatography (SiO_2, 180 g, PE/EtOAc, 95:5, R_f = 0.19) to give **111** (1.22 g, 4.02 mmol, 73 %) as a light brown solid.

M.p.: 82 °C.

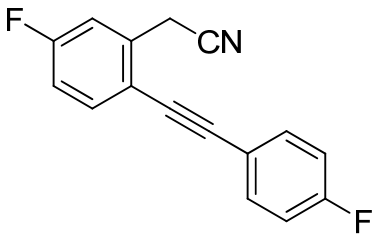
^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.96 (s, 2 H), 7.09 (dt, *J* = 8.3, 2.6 Hz, 1 H), 7.26 (dd, *J* = 8.7, 2.6 Hz, 1 H), 7.59 (dd, *J* = 8.6, 5.6 Hz, 1 H), 7.62-7.67 (m, 5 H) ppm.

^{13}C NMR (126 MHz, DEPT, $CDCl_3$): δ = 22.9 (CH_2), 87.2 (C), 93.8 (C), 115.8 (d, *J* = 22 Hz, CH), 116.0 (d, *J* = 24 Hz, CH), 116.6 (C), 118.3 (d, *J* = 4 Hz, C), 123.8 (q, *J* = 272 Hz, CF_3), 125.5 (q, *J* = 4 Hz, CH), 126.1 (C), 130.7 (q, *J* = 33 Hz, C), 131.8 (CH), 134.4 (d, *J* = 8 Hz, C), 134.5 (d, *J* = 9 Hz, CH), 162.8 (d, *J* = 253 Hz, CF) ppm.

IR (neat): $\tilde{\nu}$ = 2940, 2247, 2216, 1605, 1583, 1487, 1405, 1320, 1163, 1125, 1104, 1063, 1015, 842, 824 cm^{-1}.

MS (EI): *m/z* (%) = 303 (100) $[M]^+$, 302 (20), 284 (13), 283 (41), 234 (22), 232 (10), 207 (10).

HRMS: calcd. ($C_{17}H_9F_4N$) 303.0671; found 303.0676.



$C_{16}H_9F_2N$
MW:253,25

2-(5-Fluoro-2-((4-fluorophenyl)ethynyl)phenyl)acetonitrile (**112**): $Pd(PPh_3)_2Cl_2$ (98 mg, 0.14 mmol, 2 mol-%), CuI (13 mg, 0.07 mmol, 1 mol-%), PPh_3 (73 mg, 0.28 mmol, 4 mol-%), *i*Pr_2NH (30 mL) and toluene (20 mL) were placed in an oven dried and argon-filled Schlenk flask. After addition of 2-(2-bromo-5-fluorophenyl)acetonitrile (**59**, 1.50 g, 7.00 mmol), the mixture was stirred at 25 °C for 30 minutes, and 1-ethynyl-4-fluorobenzene (**85**, 925 mg, 7.70 mmol) was added. After this mixture had been stirred at 80 °C for an additional 16 h, a saturated NH_4Cl solution (100 mL) was added. The mixture was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were washed with HCl (2 N, 50 mL), water (50 mL) and saturated NaCl solution (50 mL). After that the combined organic layers were dried ($MgSO_4$) and concentrated under vacuum. The residue was purified by flash chromatography (SiO_2, 150 g, PE/EtOAc, 95:5, R_f = 0.14) to give **112** (1.68 g, 6.63 mmol, 95 %) as a orange solid.

M.p.: 103 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.94 (s, 2 H), 7.02-7.10 (m, 3 H), 7.23 (dd, *J* = 8.9, 2.0 Hz, 1 H), 7.49-7.56 (m, 3 H) ppm.

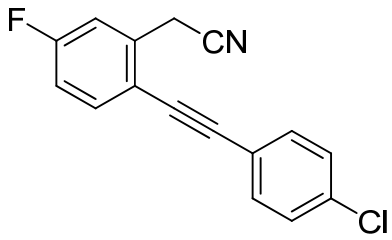
^{13}C NMR (126 MHz, DEPT, $CDCl_3$): δ = 22.8 (CH_2), 84.7 (C), 94.3 (C), 115.5 (d, *J* = 22 Hz, CH), 115.8 (d, *J* = 24 Hz, CH), 115.8 (d, *J* = 22 Hz, CH), 116.7 (C), 118.4 (d, *J*

= 4 Hz, C), 118.8 (d, *J* = 4 Hz, C), 133.5 (d, *J* = 9 Hz, CH), 134.1 (d, *J* = 8 Hz, C), 134.1 (d, *J* = 8 Hz, CH), 162.5 (d, *J* = 252 Hz, CF), 162.8 (d, *J* = 251 Hz, CF) ppm.

IR (neat): $\tilde{\nu}$ = 2946, 2246, 1908, 1608, 1598, 1582, 1506, 1487, 1426, 1405, 1276, 1222, 1213, 1203, 1153, 1097, 967, 867, 840, 824 cm^{-1}.

MS (CI): *m/z* (%) = 254 (45) $[M + H]^+$, 253 (100), 253 (13), 225 (6).

HRMS: (CI) calcd. ($C_{16}H_{10}F_2N$) 254.0781; found 254.0780.



$C_{16}H_9ClFN$
MW: 269.70

2-(2-((4-Chlorophenyl)ethynyl)-5-fluorophenyl)acetonitrile (**113**): $Pd(PPh_3)_2Cl_2$ (98 mg, 0.14 mmol, 2 mol-%), CuI (13 mg, 0.07 mmol, 1 mol-%), PPh_3 (73 mg, 0.28 mmol, 4 mol-%), *i*Pr_2NH (30 mL) and toluene (20 mL) were placed in an oven dried and argon-filled Schlenk flask. After addition of 2-(2-bromo-5-fluorophenyl)acetonitrile (**59**, 1.50 g, 7.00 mmol), the mixture was stirred at 25 °C for 30 minutes, and 1-chloro-4-ethynylbenzene (**86**, 1.14 g, 8.40 mmol) was added. After this mixture had been stirred at 80 °C for an additional 16 h, a saturated NH_4Cl solution (100 mL) was added. The mixture was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were washed with HCl (2 N, 50 mL), water (50 mL) and saturated NaCl solution (50 mL). After that the combined organic layers were dried ($MgSO_4$) and concentrated under vacuum. The residue was purified by flash chromatography (SiO_2, 200 g, PE/EtOAc, 90:10, R_f = 0.35) to give **113** (1.75 g, 6.48 mmol, 93 %) as a dark yellow solid.

M.p.: 119 °C.

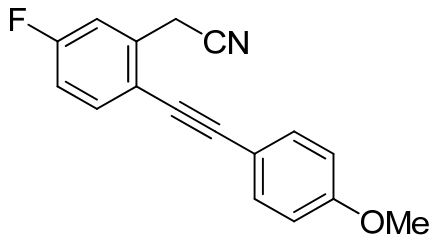
^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.94 (s, 2 H), 7.02-7.08 (m, 1 H), 7.23 (dd, *J* = 8.9, 2.4 Hz, 1 H), 7.34 (d, *J* = 8.5 Hz, 2 H), 7.46 (d, *J* = 8.5 Hz, 1 H), 7.54 (dd, *J* = 8.5, 5.6 Hz, 1 H) ppm.

^{13}C NMR (126 MHz, DEPT, $CDCl_3$): δ = 22.8 (CH_2), 85.8 (C), 94.2 (C), 115.6 (d, *J* = 22 Hz, CH), 115.8 (d, *J* = 24 Hz, CH), 116.7 (C), 118.6 (d, *J* = 3 Hz, C), 120.7 (C), 128.8 (CH), 132.7 (CH), 134.1 (d, *J* = 8 Hz, C), 134.2 (d, *J* = 9 Hz, CH), 135.0 (C), 162.5 (d, *J* = 252 Hz, CF) ppm.

IR (neat): $\tilde{\nu}$ = 2950, 2263, 2244, 1608, 1582, 1496, 1415, 1400, 1275, 1217, 1199, 1087, 1011, 966, 832 cm^{-1}.

MS (EI): *m/z* (%) = 271 (23) [M, ^{37}Cl]$^+$, 269 (63) [M, ^{35}Cl]$^+$, 234 (100), 232 (28), 207 (30), 116 (5).

HRMS: calcd. ($C_{16}H_9ClFN$) 269.0408; found 269.0411.



$C_{17}H_{12}FNO$
MW: 265.28

2-(5-Fluoro-2-((4-methoxyphenyl)ethynyl)phenyl)acetonitrile (**114**): $Pd(PPh_3)_2Cl_2$ (98 mg, 0.14 mmol, 2 mol-%), CuI (13 mg, 0.07 mmol, 1 mol-%), PPh_3 (73 mg, 0.28 mmol, 4 mol-%), *i*Pr_2NH (30 mL) and toluene (20 mL) were placed in an oven dried and argon-filled Schlenk flask. After addition of 2-(2-bromo-5-fluorophenyl)acetonitrile (**59**, 1.50 g, 7.00 mmol), the mixture was stirred at 25 °C for 30 minutes, and 1-ethynyl-4-methoxybenzene (**87**, 1.02 mg, 7.70 mmol) was added. After this mixture had been stirred at 80 °C for an additional 16 h, a saturated NH_4Cl solution (100 mL) was added. The mixture was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were washed with HCl (2 N, 50 mL), water (50 mL) and saturated NaCl solution (50 mL). After that the combined organic layers were dried ($MgSO_4$)

and concentrated under vacuum. The residue was purified by flash chromatography (SiO_2, 200 g, PE/EtOAc, 90:10, R_f = 0.28) to give **114** (1.49 g, 5.60 mmol, 80 %) as a orange solid.

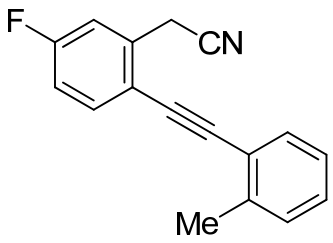
M.p.: 79 °C.
^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.82 (s, 3 H), 3.93 (s, 2 H), 6.86-6.90 (m, 2 H), 7.02 (dt, *J* = 8.3, 1.9 Hz, 1 H), 7.22 (d, *J* = 9.0 Hz, 1 H), 7.44-7.48 (m, 2 H), 7.51 (dd, *J* = 8.3, 5.8 Hz, 1 H) ppm.

^{13}C NMR (126 MHz, DEPT, $CDCl_3$): δ = 22.8 (CH_2), 55.3 (CH_3), 83.7 (C), 95.5 (C), 114.1 (CH), 114.3 (C), 115.4 (d, *J* = 21 Hz, CH), 115.6 (d, *J* = 23 Hz, CH), 116.8 (CN), 119.2 (d, *J* = 3 Hz, C), 133.0 (CH), 133.8 (d, *J* = 4 Hz, C), 133.9 (d, *J* = 5 Hz, C), 160.1 (C), 162.20 (d, *J* = 251 Hz, CF) ppm.

IR (neat): $\tilde{\nu}$ = 3009, 2971, 2940, 2907, 2841, 2240, 2216, 1611, 1509, 1427, 1278, 1251, 1278, 1251, 1153, 1031, 833, 821, 811 cm^{-1}.

MS (EI): *m/z* (%) = 265 (100) $[M]^+$, 250 (36), 222 (26), 195 (16), 175 (9), 168 (6).

HRMS: calcd. ($C_{17}H_{12}FNO$) 262.0903; found 262.0900.



$C_{17}H_{12}FN$
MW: 249.28

2-(5-Fluoro-2-(o-tolylethynyl)phenyl)acetonitrile (**115**): $Pd(PPh_3)_2Cl_2$ (98 mg, 0.14 mmol, 2 mol-%), CuI (13 mg, 0.07 mmol, 1 mol-%), PPh_3 (73 mg, 0.28 mmol, 4 mol-%), *i*Pr_2NH (30 mL) and toluene (20 mL) were placed in an oven dried and argon-filled Schlenk flask. After addition of 2-(2-bromo-5-fluorophenyl)acetonitrile (**59**, 1.50 g, 7.00 mmol), the mixture was stirred at 25 °C for 30 minutes, and 1-ethynyl-2-methylbenzene (**88**, 976 mg, 8.40 mmol) was added. After this mixture had been

stirred at 80 °C for an additional 16 h, a saturated NH_4Cl solution (100 mL) was added. The mixture was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were washed with HCl (2 N, 50 mL), water (50 mL) and saturated NaCl solution (50 mL). After that the combined organic layers were dried ($MgSO_4$) and concentrated under vacuum. The residue was purified by flash chromatography (SiO_2, 160 g, PE/EtOAc, 95:5, R_f = 0.20) to give **115** (1.66 g, 6.64 mmol, 95 %) as a yellow-orange solid.

M.p.: 79 °C.

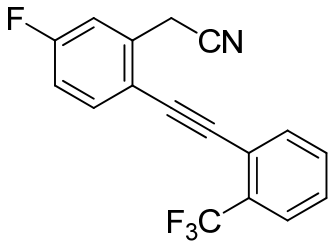
^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.50 (s, 3 H), 3.96 (s, 2 H), 7.05 (dt, *J* = 8.4, 2.6 Hz, 1 H), 7.19 (dt, *J* = 7.3, 1.4 Hz, 1 H), 7.23-7.29 (m, 1 H), 7.50 (d, *J* = 7.6 Hz, 1 H), 7.55 (dd, *J* = 8.6, 5.7 Hz, 1 H) ppm.

^{13}C NMR (126 MHz, DEPT, $CDCl_3$): δ = 20.9 (CH_3), 22.8 (CH_2), 88.8 (C), 94.3 (C), 115.5 (d, *J* = 15 Hz, CH), 115.7 (d, *J* = 17 Hz, CH), 116.8 (C), 119.1 (d, *J* = 3 Hz, C), 122.1 (C), 125.7 (CH), 128.9 (CH), 129.6 (CH), 132.0 (CH), 133.8 (d, *J* = 8 Hz, C), 134.2 (d, *J* = 9 Hz, CH), 139.9 (C), 162.38 (d, *J* = 252 Hz, CF) ppm.

IR (neat): $\tilde{\nu}$ = 2934, 1610, 1582, 1495, 1428, 1270, 1212, 1157, 1146, 852, 817 cm^{-1}.

MS (EI): *m/z* (%) = 249 (77) $[M]^+$, 248 (100), 221 (38), 110 (8).

HRMS: calcd. ($C_{17}H_{12}FN$) 249.0954; found 249.0950.



$C_{17}H_9F_4N$
MW: 303.25

2-(5-Fluoro-2-((2-(trifluoromethyl)phenyl)ethynyl)phenyl)acetonitrile (**116**): $Pd(PPh_3)_2Cl_2$ (98 mg, 0.14 mmol, 2 mol-%), CuI (13 mg, 0.07 mmol, 1 mol-%), PPh_3 (73 mg, 0.28 mmol, 4 mol-%), *i*Pr_2NH (20 mL) and toluene (15 mL) were placed in an oven dried and argon-filled Schlenk flask. After addition of 2-(2-bromo-5-fluorophenyl)acetonitrile (**59**, 1.50 g, 7.00 mmol), the mixture was stirred at 25 °C for 30 minutes, and 1-ethynyl-2-(trifluoromethyl)benzene (**89**, 1.43 g, 8.40 mmol) was added. After this mixture had been stirred at 80 °C for an additional 16 h, a saturated NH_4Cl solution (100 mL) was added. The mixture was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were washed with HCl (2 N, 50 mL), water (50 mL) and saturated NaCl solution (50 mL). After that the combined organic layers were dried ($MgSO_4$) and concentrated under vacuum. The residue was purified by flash chromatography (SiO_2, 190 g, PE/EtOAc, 90:10, R_f = 0.22) to give **116** (1.89 g, 6.64 mmol, 89 %) as a light yellow solid.

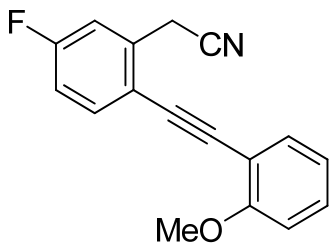
^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.99 (s, 2 H), 7.07 (dt, *J* = 8.3, 2.5 Hz, 1 H), 7.30 (dd, *J* = 9.0, 2.4 Hz, 1 H), 7.47 (t, *J* = 7.7 Hz, 1 H), 7.54-7.61 (m, 2 H), 7.70 (t, *J* = 8.5 Hz, 2 H) ppm.

^{13}C NMR (126 MHz, DEPT, $CDCl_3$): δ = 22.5 (CH_2), 90.4 (C), 90.9 (C), 115.6 (d, *J* = 22 Hz, CH), 115.8 (d, *J* = 24 Hz, CH), 116.8 (C), 118.2 (d, *J* = 4 Hz, C), 120.6 (C), 123.6 (q, *J* = 274 Hz, CF_3), 126.0 (q, *J* = 5 Hz, CH), 128.6 (CH), 131.2 (q, *J* = 31 Hz, C), 131.7 (CH), 133.9 (CH), 134.6 (d, *J* = 6 Hz, CH), 134.7 (d, *J* = 6 Hz, C), 162.9 (d, *J* = 253 Hz, CF) ppm.

IR (neat): $\tilde{\nu}$ = 3083, 1502, 1429, 1317, 1264, 1208, 1172, 1152, 1107, 1058, 1032, 956, 856 cm^{-1}.

MS (EI): *m/z* (%) = 303 (100) $[M]^+$, 282 (22), 263 (76), 256 (13), 234 (10), 207 (5), 151 (5), 128 (5).

HRMS: calcd. ($C_{17}H_9F_4N$) 303.0671; found 303.0668.



$C_{17}H_{12}FNO$
MW: 265.28

2-(5-Fluoro-2-((2-methoxyphenyl)ethynyl)phenyl)acetonitrile (**117**): $Pd(PPh_3)_2Cl_2$ (98 mg, 0.14 mmol, 2 mol-%), CuI (13 mg, 0.07 mmol, 1 mol-%), PPh_3 (73 mg, 0.28 mmol, 4 mol-%), *i*Pr_2NH (20 mL) and toluene (15 mL) were placed in an oven dried and argon-filled Schlenk flask. After addition of 2-(2-bromo-5-fluorophenyl)acetonitrile (**59**, 1.50 g, 7.00 mmol), the mixture was stirred at 25 °C for 30 minutes, and 1-ethynyl-2-methoxybenzene (**90**, 1.11 g, 8.40 mmol) was added. After this mixture had been stirred at 80 °C for an additional 16 h, a saturated NH_4Cl solution (100 mL) was added. The mixture was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were washed with HCl (2 N, 50 mL), water (50 mL) and saturated NaCl solution (50 mL). After that the combined organic layers were dried ($MgSO_4$) and concentrated under vacuum. The residue was purified by flash chromatography (SiO_2, 180 g, PE/EtOAc, 90:10, R_f = 0.24) to give **117** (1.69 g, 6.35 mmol, 91 %) as a light yellow solid.

M.p.: 74 °C.

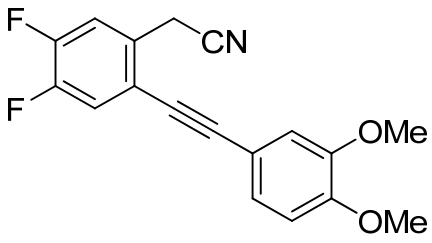
^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.99 (s, 2 H), 7.07 (dt, *J* = 8.3, 2.5 Hz, 1 H), 7.30 (dd, *J* = 9.0, 2.4 Hz, 1 H), 7.47 (t, *J* = 7.7 Hz, 1 H), 7.54-7.61 (m, 2 H), 7.70 (t, *J* = 8.5 Hz, 2 H) ppm.

^{13}C NMR (126 MHz, DEPT, $CDCl_3$): δ = 22.5 (CH_2), 90.4 (C), 90.9 (C), 115.6 (d, *J* = 22 Hz, CH), 115.8 (d, *J* = 24 Hz, CH), 116.8 (C), 118.2 (d, *J* = 4 Hz, C), 120.6 (C), 123.6 (q, *J* = 274 Hz, CF_3), 126.0 (q, *J* = 5 Hz, CH), 128.6 (CH), 131.2 (q, *J* = 31 Hz, C), 131.7 (CH), 133.9 (CH), 134.6 (d, *J* = 6 Hz, CH), 134.7 (d, *J* = 6 Hz, C), 162.9 (d, *J* = 253 Hz, CF) ppm.

IR (neat): $\tilde{\nu}$ = 3083, 1502, 1429, 1317, 1264, 1208, 1172, 1152, 1107, 1058, 1032, 956, 856 cm^{-1}.

MS (EI): *m/z* (%) = 303 (100) $[M]^+$, 282 (22), 263 (76), 256 (13), 234 (10), 207 (5), 151 (5), 128 (5).

HRMS: calcd. ($C_{17}H_9F_4N$) 303.0671; found 303.0668.



$C_{18}H_{13}F_2NO_2$
MW: 313.30

2-(2-((3,4-Dimethoxyphenyl)ethynyl)-4,5-difluorophenyl)acetonitrile (**118**): $Pd(PPh_3)_2Cl_2$ (155 mg, 0.22 mmol, 4 mol-%), CuI (84 mg, 0.44 mmol, 8 mol-%), PPh_3 (115 mg, 0.44 mmol, 8 mol-%), *i*Pr_2NH (6 mL) and DMF (6 mL) were placed in an oven dried and argon-filled Schlenk flask. After addition of 2-(2-bromo-4,5-difluorophenyl)acetonitrile (**60**, 1.28 g, 5.52 mmol), the mixture was stirred at 25 °C for 30 minutes, and 4-ethynyl-1,2-dimethoxybenzene (**66**, 900 mg, 5.55 mmol) was added. After this mixture had been stirred at 80 °C for an additional 16 h, a saturated NH_4Cl solution (200 mL) was added. The mixture was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic layers were dried ($MgSO_4$) and concentrated under vacuum. The residue was purified by flash chromatography (SiO_2, 180 g, PE/EtOAc, 80:20, R_f = 0.19) to give **118** (1.36 g, 4.34 mmol, 79 %) as a colorless solid.

M.p.: 114 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.92 (s, 8 H), 6.86 (d, *J* = 8.5 Hz, 1 H), 7.03 (d, *J* = 1.9 Hz, 1 H), 7.15 (dd, *J* = 8.2, 1.8 Hz, 1 H), 7.33 (dd, *J* = 10.5, 7.7 Hz, 1 H), 7.37 (dd, *J* = 10.6, 7.7 Hz, 1 H) ppm.

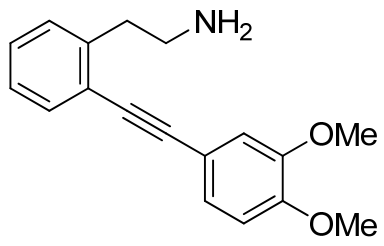
^{13}C NMR (75 MHz, DEPT, $CDCl_3$): δ = 22.3 (CH_2), 55.9 (CH_3), 56.0 (CH_3), 82.7 (C), 96.6 (C), 111.1 (CH), 113.9 (C), 114.1 (CH), 116.7 (C), 117.6 (d, *J* = 20 Hz, CH), 119.9 (dd, *J* = 8, 4 Hz, C), 120.9 (d, *J* = 19 Hz, CH), 125.2 (CH), 128.6 (dd, *J* = 6, 4

Hz, C), 149.7 (dd, *J* = 251, 13 Hz, CF), 148.9 (C), 150.3 (C), 150.1 (dd, *J* = 254, 13 Hz, CF) ppm.

IR (KBr): $\tilde{\nu}$ = 3000, 2966, 2939, 2839, 2257, 2214, 1600, 1578, 1517, 1466, 1445, 1424, 1413, 1346, 1320, 1251, 1224, 1173, 1137, 1023, 882, 869, 815, 754 cm^{-1}.

MS (EI): *m/z* (%) = 313 (100) $[M]^+$, 298 (10), 270 (10), 243 (12), 226 (12), 212 (5), 200 (5), 162 (11), 151 (10), 113 (6), 91 (6).

HRMS: calcd. ($C_{18}H_{13}NO_2F_2$) 313.0914; found 313.0930.



$C_{18}H_{19}NO_2$
MW: 281.35

2-(2-((3,4-Dimethoxyphenyl)ethynyl)phenyl)ethanamine (**119**): A solution of $AlCl_3$ (2.00 g, 15.0 mmol) in Et_2O (15 mL) was rapidly added to a suspension of $LiAlH_4$ (569 mg, 15.0 mmol) in Et_2O (10 mL) and the mixture was stirred at 25 °C for 30 minutes. Then, a solution of nitrile **91** (4.16 g, 15.0 mmol) in Et_2O (15 mL) was slowly added. After the mixture had been stirred at 25 °C for additional 2 h, water was added dropwise to decompose the excess of $LiAlH_4$ and aqueous KOH (5 N, 10 mL) was then added. The colloidal mixture was extracted with Et_2O (10 × 30 mL) and the combined organic layers were dried ($MgSO_4$). After concentration under vacuum and purification by flash chromatography (SiO_2, 450 g, MTBE/7 N NH_3 in MeOH 90:10, R_f = 0.31), **119** (4.03 g, 14.3 mmol, 95 %) was isolated as a colorless oil.

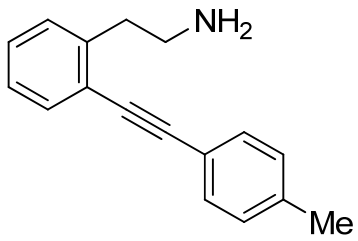
^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.42 (br. s, 2 H), 3.01 (t, *J* = 6.5 Hz, 2 H), 3.07 (t, *J* = 6.4 Hz, 2 H), 3.91 (s, 3 H), 3.92 (s, 3 H), 6.85 (d, *J* = 8.3 Hz, 1 H), 7.02 (d, *J* = 1.8 Hz, 1 H), 7.13 (dd, *J* = 8.3, 1.8 Hz, 1 H), 7.18-7.29 (m, 3 H), 7.52 (d, *J* = 7.6 Hz, 1 H) ppm.

^{13}C NMR (126 MHz, DEPT, $CDCl_3$) δ = 39.1 (CH_2), 42.8 (CH_2), 55.9 (CH_3), 55.9 (CH_3), 86.6 (C), 93.1 (C), 111.0 (CH), 114.1 (CH), 115.5 (C), 123.2 (C), 124.8 (CH), 126.2 (CH), 128.2 (CH), 129.3 (CH), 132.3 (CH), 141.6 (C), 148.7 (C), 149.5 (C) ppm.

IR (neat): $\tilde{\nu}$ = 2935, 2838, 1512, 1464, 1328, 1248, 1133, 1023, 758 cm^{-1}.

MS (EI): *m/z* (%) = 281 (44) [M]$^+$, 280 (37), 252 (24), 178 (24), 165 (57), 151 (100), 144 (35), 130 (35).

HRMS: calcd. ($C_{18}H_{19}NO_2$) 281.1416; found 281.1422.



$C_{17}H_{17}N$
MW: 235.32

2-(2-(p-Tolylethynyl)phenyl)ethanamine (**120**): A solution of $AlCl_3$ (520 mg, 3.90 mmol) in Et_2O (5 mL) was rapidly added to a suspension of $LiAlH_4$ (133 mg, 3.90 mmol) in Et_2O (5 mL) and the mixture was stirred at 25 °C for 30 minutes. Then, a solution of nitrile **92** (902 mg, 3.90 mmol) in Et_2O (10 mL) was slowly added. After the mixture had been stirred at 25 °C for additional 2 h, aqueous KOH (5 N, 5 mL) and saturated K_2SO_4 solution (5 mL) was added dropwise to decompose the excess of $LiAlH_4$. The mixture was filtrated and the precipitate was washed with CH_2Cl_2 (2 × 50 mL). The filtrate was extracted with CH_2Cl_2 (5 × 30 mL) and the combined organic layers were dried ($MgSO_4$). After concentration under vacuum and purification by flash chromatography (SiO_2, 80 g, MTBE/7 N NH_3 in MeOH 95:5, R_f = 0.16), **120** (799 mg, 3.40 mmol, 87 %) was isolated as a yellow oil.

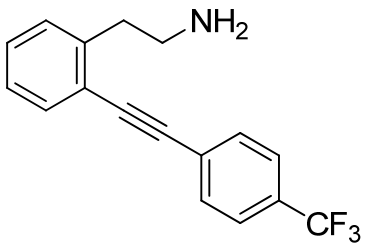
^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.23 (br. s, 2 H), 2.36 (s, 3 H), 2.99 (t, *J* = 6.5 Hz, 2 H), 3.06 (t, *J* = 6.3 Hz, 2 H), 7.15 (d, *J* = 8.0 Hz, 2 H), 7.17-7.27 (m, 3 H), 7.41 (d, *J* = 8.0 Hz, 2 H), 7.51 (d, *J* = 7.3 Hz, 1 H) ppm.

^{13}C NMR (126 MHz, DEPT, $CDCl_3$) δ = 21.4 (CH_3), 39.1 (CH_2), 42.8 (CH_2), 87.4 (C), 93.1 (C), 120.2 (C), 123.1 (C), 126.1 (CH), 128.2 (CH), 129.1 (CH), 129.3 (CH), 131.3 (CH), 132.2 (CH), 138.4 (C), 141.6 (C) ppm.

IR (neat): $\tilde{\nu}$ = 2921, 1509, 1481, 1446, 1041, 1019, 814, 754 cm^{-1}.

MS (EI): *m/z* (%) = 235 (56) [M]$^+$, 206 (53), 205 (94), 189 (100), 177 (94), 164 (64), 143 (37), 130 (43).

HRMS: calcd. ($C_{17}H_{17}N$) 235.1361; found 235.1365.



$C_{17}H_{14}F_3N$
MW: 289.29

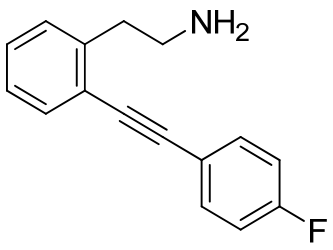
2-(2-((4-(Trifluoromethyl)phenyl)ethynyl)phenyl)ethanamine (**121**): A solution of $AlCl_3$ (95 mg, 2.50 mmol) in Et_2O (4 mL) was rapidly added to a suspension of $LiAlH_4$ (333 mg, 2.50 mmol) in Et_2O (4 mL) and the mixture was stirred at 25 °C for 30 minutes. Then, a solution of nitrile **93** (713 mg, 2.50 mmol) in Et_2O (5 mL) was slowly added. After the mixture had been stirred at 25 °C for additional 2 h, aqueous KOH (5 N, 2 mL) and saturated K_2SO_4 solution (2 mL) was added dropwise to decompose the excess of $LiAlH_4$. The mixture was filtrated and the precipitate was washed with CH_2Cl_2 (2 × 50 mL). The filtrate was extracted with CH_2Cl_2 (5 × 30 mL) and the combined organic layers were dried ($MgSO_4$). After concentration under vacuum and purification by flash chromatography (SiO_2, 70 g, MTBE/7 N NH_3 in MeOH 98:2, R_f = 0.14), **121** (582 mg, 2.01 mmol, 80 %) was isolated as a light yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.21 (br. s, 2 H), 3.00 (t, *J* = 6.5 Hz, 2 H), 3.06 (t, *J* = 6.5 Hz, 2 H), 7.19-7.26 (m, 2 H), 7.28-7.32 (m, 1 H), 7.51-7.56 (m, 1 H), 7.57-7.63 (m, 4 H) ppm.

^{13}C NMR (126 MHz, DEPT, $CDCl_3$): δ = 39.0 (CH_2), 42.7 (CH_2), 90.4 (C), 91.4 (C), 122.2 (C), 123.8 (q, J = 272 Hz, CF_3), 125.2 (q, J = 4 Hz, CH), 126.2 (CH), 127.1 (C), 128.9 (CH), 129.4 (CH), 129.8 (q, J = 33 Hz, C), 131.6 (CH), 132.5 (CH), 142.0 (C) ppm.

IR (neat): $\tilde{\nu}$ = 2928, 2856, 1611, 1405, 1317, 1178, 1131, 1105, 1064, 996, 895, 840, 762 cm^{-1}.
MS (CI): *m/z* (%) = 290 (100) $[M + H]^+$, 289 (30), 189 (3), 144 (4).

HRMS: (CI) calcd. ($C_{17}H_{15}F_3N$) 290.1157; found 290.1153.



$C_{16}H_{14}FN$
MW: 239.29

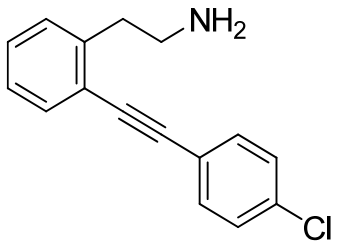
2-(2-((4-Fluorophenyl)ethynyl)phenyl)ethanamine (**122**): A solution of $AlCl_3$ (667 mg, 5.00 mmol) in Et_2O (7 mL) was rapidly added to a suspension of $LiAlH_4$ (190 mg, 5.00 mmol) in Et_2O (7 mL) and the mixture was stirred at 25 °C for 30 minutes. Then, a solution of nitrile **94** (1.18 g, 5.00 mmol) in Et_2O (15 mL) was slowly added. After the mixture had been stirred at 25 °C for additional 2 h, aqueous KOH (5 N, 5 mL) and saturated K_2SO_4 solution (5 mL) was added dropwise to decompose the excess of $LiAlH_4$. The mixture was filtrated and the precipitate was washed with CH_2Cl_2 (2 × 50 mL). The filtrate was extracted with CH_2Cl_2 (5 × 30 mL) and the combined organic layers were dried ($MgSO_4$). After concentration under vacuum and purification by flash chromatography (SiO_2, 80 g, MTBE/7 N NH_3 in MeOH 95:5, R_f = 0.14), **122** (979 mg, 4.09 mmol, 82 %) was isolated as a yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.29 (br. s, 2 H), 2.99 (t, J = 6.7 Hz, 2 H), 3.06 (t, J = 6.8 Hz, 2 H), 7.05 (t, J = 8.5 Hz, 2 H), 7.18-7.32 (m, 3 H), 7.46-7.54 (m, 3 H) ppm.

^{13}C NMR (126 MHz, DEPT, $CDCl_3$): δ = 39.1 (CH_2), 42.8 (CH_2), 87.7 (C), 91.8 (C), 115.7 (d, *J* = 22 Hz, CH), 119.4 (d, *J* = 3 Hz, C), 122.8 (C), 126.2 (CH), 128.5 (CH), 129.4 (CH), 132.3 (CH), 133.3 (d, *J* = 8 Hz, CH), 141.7 (C), 162.5 (d, *J* = 250 Hz, CF) ppm.

IR (neat): $\tilde{\nu}$ = 2928, 2863, 1597, 1505, 1222, 1156, 1093, 833, 755 cm^{-1}.

MS (EI): *m/z* (%) = 239 (70) [M]$^+$, 238 (100), 222 (20), 207 (70), 183 (37), 144 (48), 130 (19), 115 (8).
HRMS: calcd. ($C_{16}H_{14}FN$) 239.1110; found 239.1106.



$C_{16}H_{14}ClN$
MW: 255.74

2-(2-((4-Chlorophenyl)ethynyl)phenyl)ethanamine (**123**): A solution of $AlCl_3$ (543 mg, 4.07 mmol) in Et_2O (6 mL) was rapidly added to a suspension of $LiAlH_4$ (154 mg, 4.07 mmol) in Et_2O (6 mL) and the mixture was stirred at 25 °C for 30 minutes. Then, a solution of nitrile **95** (1.02 mg, 4.07 mmol) in Et_2O (10 mL) was slowly added. After the mixture had been stirred at 25 °C for additional 2 h, aqueous KOH (5 N, 5 mL) and saturated K_2SO_4 solution (5 mL) was added dropwise to decompose the excess of $LiAlH_4$. The mixture was filtrated and the precipitate was washed with CH_2Cl_2 (2 × 50 mL). The filtrate was extracted with CH_2Cl_2 (5 × 30 mL) and the combined organic layers were dried ($MgSO_4$). After concentration under vacuum and purification by flash chromatography (SiO_2, 80 g, MTBE/7 N NH_3 in MeOH 95:5, R_f = 0.48), **123** (1.01 g, 3.93 mmol, 96 %) was isolated as a yellow oil.

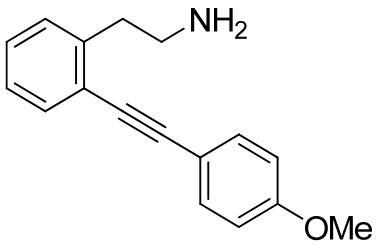
^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.33 (br. s, 2 H), 2.98 (t, *J* = 6.6 Hz, 2 H), 3.05 (t, *J* = 6.5 Hz, 2 H), 7.18-7.34 (m, 5 H), 7.43 (d, *J* = 8.5 Hz, 2 H), 7.51 (d, *J* = 7.5 Hz, 1 H) ppm.

^{13}C NMR (126 MHz, DEPT, $CDCl_3$) δ = 38.9 (CH_2), 42.7 (CH_2), 88.9 (C), 91.7 (C), 121.7 (C), 122.5 (C), 126.2 (CH), 128.6 (CH), 128.6 (CH), 129.3 (CH), 132.3 (CH), 132.6 (CH), 134.2 (C), 141.7 (C) ppm.

IR (neat): $\tilde{\nu}$ = 2924, 2860, 1590, 1490, 1446, 1397, 1088, 1013, 824, 754 cm^{-1}.

MS (EI): *m/z* (%) = 257 (11) [M, ^{37}Cl]$^+$, 255 (38) [M, ^{35}Cl]$^+$, 254 (50), 191 (47), 189 (100), 144 (71), 130 (26).

HRMS: calcd. ($C_{16}H_{14}ClN$) 255.0815; found 255.0812.



$C_{17}H_{17}NO$
MW: 251.32

2-(2-((4-Methoxyphenyl)ethynyl)phenyl)ethanamine (**124**): A solution of $AlCl_3$ (533 mg, 4.00 mmol) in Et_2O (6 mL) was rapidly added to a suspension of $LiAlH_4$ (152 mg, 4.00 mmol) in Et_2O (6 mL) and the mixture was stirred at 25 °C for 30 minutes. Then, a solution of nitrile **96** (989 mg, 4.00 mmol) in Et_2O (10 mL) was slowly added. After the mixture had been stirred at 25 °C for additional 2 h, aqueous KOH (5 N, 4 mL) and saturated K_2SO_4 solution (4 mL) was added dropwise to decompose the excess of $LiAlH_4$. The mixture was filtrated and the precipitate was washed with CH_2Cl_2 (2 × 50 mL). The filtrate was extracted with CH_2Cl_2 (5 × 30 mL) and the combined organic layers were dried ($MgSO_4$). After concentration under vacuum and purification by flash chromatography (SiO_2, 80 g, MTBE/7 N NH_3 in MeOH 95:5, R_f = 0.30), **124** (780 mg, 3.10 mmol, 78 %) was isolated as a light yellow solid.

M.p.: 52 °C.

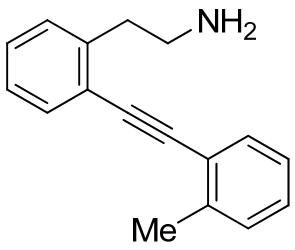
^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.22 (br. s, 2 H), 2.99 (t, *J* = 6.7 Hz, 2 H), 3.05 (t, *J* = 6.8 Hz, 2 H), 3.81 (s, 3 H), 6.87 (d, *J* = 8.6 Hz, 2 H), 7.16-7.27 (m, 3 H), 7.45 (d, *J* = 8.6 Hz, 2 H), 7.50 (d, *J* = 7.6 Hz, 1 H) ppm.

^{13}C NMR (126 MHz, DEPT, $CDCl_3$) δ = 39.1 (CH_2), 42.7 (CH_2), 55.2 (CH_3), 86.7 (C), 92.9 (C), 114.0 (CH), 115.4 (C), 123.2 (C), 126.1 (CH), 128.0 (CH), 129.3 (CH), 132.1 (CH), 132.8 (CH), 141.5 (C), 159.6 (C) ppm.

IR (neat): $\tilde{\nu}$ = 3360, 3015, 2930, 1606, 1597, 1509, 1442, 1288, 1247, 1177, 1026, 833 cm^{-1}.

MS (EI): *m/z* (%) = 251 (59) $[M]^+$, 250 (71), 222 (50), 207 (37), 178 (100), 151 (35), 144 (50), 121 (47).

HRMS: calcd. ($C_{17}H_{17}NO$) 251.1310; found 251.1313.



$C_{17}H_{17}N$
MW: 235.32

2-(2-(o-Tolylethynyl)phenyl)ethanamine (**125**): A solution of $AlCl_3$ (667 mg, 5.00 mmol) in Et_2O (7 mL) was rapidly added to a suspension of $LiAlH_4$ (190 mg, 5.00 mmol) in Et_2O (7 mL) and the mixture was stirred at 25 °C for 30 minutes. Then, a solution of nitrile **97** (1.16 mg, 5.00 mmol) in Et_2O (15 mL) was slowly added. After the mixture had been stirred at 25 °C for additional 2 h, aqueous KOH (5 N, 5 mL) and saturated K_2SO_4 solution (5 mL) was added dropwise to decompose the excess of $LiAlH_4$. The mixture was filtrated and the precipitate was washed with CH_2Cl_2 (2 × 50 mL). The filtrate was extracted with CH_2Cl_2 (5 × 30 mL) and the combined organic layers were dried ($MgSO_4$). After concentration under vacuum and purification by flash chromatography (SiO_2, 110 g, MTBE/7 N NH_3 in MeOH 95:5, R_f = 0.15), **125** (993 mg, 4.22 mmol, 84 %) was isolated as a light yellow oil.

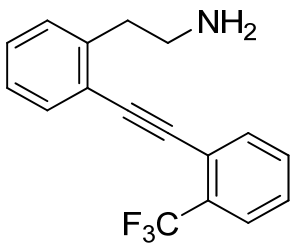
^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.21 (br. s, 2 H), 2.52 (s, 3 H), 3.00-3.04 (m, 2 H), 3.04-3.08 (m, 2 H), 7.15-7.30 (m, 6 H), 7.50 (d, *J* = 7.4 Hz, 1 H), 7.54 (d, *J* = 7.4 Hz, 1 H) ppm.

^{13}C NMR (126 MHz, DEPT, $CDCl_3$) δ = 20.9 (CH_3), 39.2 (CH_2), 42.8 (CH_2), 91.9 (C), 91.9 (C), 123.1 (C), 123.2 (C), 125.6 (CH), 126.2 (CH), 128.3 (CH), 128.3 (CH), 129.4 (CH), 129.5 (CH), 131.9 (CH), 132.4 (CH), 139.8 (C), 141.5 (C) ppm.

IR (neat): $\tilde{\nu}$ = 3060, 3021, 2922, 2860, 1490, 1455, 1109, 1042, 832, 752 cm^{-1}.

MS (EI): *m/z* (%) = 235 (93) [M]$^+$, 234 (67), 218 (72), 205 (100), 202 (99), 189 (45), 144 (96), 130 (31), 115 (25).

HRMS: calcd. ($C_{17}H_{17}N$) 235.1361; found 235.1365.



$C_{17}H_{14}F_3N$
MW: 289.29

2-(2-((2-(Trifluoromethyl)phenyl)ethynyl)phenyl)ethanamine (**126**): A solution of $AlCl_3$ (667 mg, 5.00 mmol) in Et_2O (7 mL) was rapidly added to a suspension of $LiAlH_4$ (190 mg, 5.00 mmol) in Et_2O (7 mL) and the mixture was stirred at 25 °C for 30 minutes. Then, a solution of nitrile **98** (1.43 g, 5.00 mmol) in Et_2O (15 mL) was slowly added. After the mixture had been stirred at 25 °C for additional 2 h, aqueous KOH (5 N, 5 mL) and saturated K_2SO_4 solution (5 mL) was added dropwise to decompose the excess of $LiAlH_4$. The mixture was filtrated and the precipitate was washed with CH_2Cl_2 (2 × 50 mL). The filtrate was extracted with CH_2Cl_2 (5 × 30 mL) and the combined organic layers were dried ($MgSO_4$). After concentration under vacuum and purification by flash chromatography (SiO_2, 120 g, MTBE/7 N NH_3 in MeOH 95:5, R_f = 0.31), **126** (1.10 g, 3.79 mmol, 76 %) was isolated as a yellow oil.

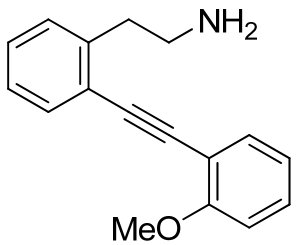
^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.42 (br. s, 2 H), 2.98-3.06 (m, 4 H), 7.20-7.27 (m, 2 H), 7.30 (t, *J* = 7.5 Hz, 1 H), 7.40 (t, *J* = 7.8 Hz, 1 H), 7.51 (t, *J* = 7.6 Hz, 1 H), 7.56 (d, *J* = 7.6 Hz, 1 H), 7.68 (dd, *J* = 7.7, 3.0 Hz, 2 H) ppm.

^{13}C NMR (126 MHz, DEPT, $CDCl_3$): δ = 38. 9 (CH_2), 43.1 (CH_2), 88.6 (C), 93.7 (C), 121.6 (C), 122.4 (C), 123.6 (q, *J* = 273 Hz, CF_3), 125.8 (q, *J* = 5 Hz, CH), 126.2 (CH), 127.9 (CH), 129.0 (CH), 129.4 (CH), 130.9 (q, *J* = 30 Hz, C), 131.4 (CH), 132.8 (CH), 134.0 (CH), 142.1 (C) ppm.

IR (neat): $\tilde{\nu}$ = 2929, 2867, 2217, 1603, 1573, 1494, 1450, 1318, 1261, 1124, 1108, 1055, 1032, 755 cm^{-1}.

MS (EI): *m/z* (%) = 289 (39) $[M]^+$, 288 (43), 260 (34), 238 (57), 220 (44), 189 (21), 144 (100).

HRMS: calcd. ($C_{17}H_{14}F_3N$) 289.1078; found 289.1081.



$C_{17}H_{17}NO$
MW: 251.32

2-(2-((2-Methoxyphenyl)ethynyl)phenyl)ethanamine (**127**): A solution of $AlCl_3$ (667 mg, 5.00 mmol) in Et_2O (7 mL) was rapidly added to a suspension of $LiAlH_4$ (190 mg, 5.00 mmol) in Et_2O (7 mL) and the mixture was stirred at 25 °C for 30 minutes. Then, a solution of nitrile **99** (1.24 g, 5.00 mmol) in Et_2O (15 mL) was slowly added. After the mixture had been stirred at 25 °C for additional 2 h, aqueous KOH (5 N, 5 mL) and saturated K_2SO_4 solution (5 mL) was added dropwise to decompose the excess of $LiAlH_4$. The mixture was filtrated and the precipitate was washed with CH_2Cl_2 (2 × 50 mL). The filtrate was extracted with CH_2Cl_2 (5 × 30 mL) and the combined organic layers were dried ($MgSO_4$). After concentration under vacuum and purification by

flash chromatography (SiO_2, 110 g, MTBE/7 N NH_3 in MeOH 95:5, R_f = 0.12), **127** (1.11 g, 4.42 mmol, 89 %) was isolated as a light yellow oil.

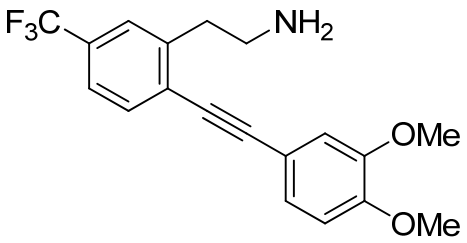
^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.21 (br. s, 2 H), 3.00-3.09 (m, 4 H), 3.90 (s, 3 H), 6.90 (d, *J* = 8.3 Hz, 1 H), 6.94 (t, *J* = 7.6 Hz, 1 H), 7.19 (td, *J* = 7.1, 1.4 Hz, 1 H), 7.22-7.26 (m, 2 H), 7.30 (dt, *J* = 7.8, 1.3 Hz, 1 H), 7.48 (dd, *J* = 7.5, 1.4 Hz, 1 H), 7.54 (d, *J* = 7.5 Hz, 1 H) ppm.

^{13}C NMR (126 MHz, DEPT, $CDCl_3$) δ = 39.2 (CH_2), 43.2 (CH_2), 55.7 (CH_3), 89.3 (C), 92.3 (C), 110.5 (CH), 112.5 (C), 120.4 (CH), 123.4 (C), 126.0 (CH), 128.2 (CH), 129.3 (CH), 129.6 (CH), 132.0 (CH), 133.1 (CH), 141.9 (C), 159.9 (C) ppm.

IR (neat): $\tilde{\nu}$ = 3059, 2938, 2836, 1594, 1573, 1494, 1479, 1461, 1433, 1275, 1244, 1022, 748 cm^{-1}.

MS (EI): *m/z* (%) = 251 (75) $[M]^+$, 250 (95), 222 (37), 207 (71), 178 (100), 152 (37), 144 (90), 130 (47), 115 (31).

HRMS: calcd. ($C_{17}H_{17}NO$) 251.1310; found 251.1316.



$C_{19}H_{18}F_3NO_2$
MW: 349.35

2-(2-((3,4-Dimethoxyphenyl)ethynyl)-5-(trifluoromethyl)phenyl)ethanamine (**128**): A solution of $AlCl_3$ (339 mg, 3.00 mmol) in Et_2O (5 mL) was rapidly added to a suspension of $LiAlH_4$ (114 mg, 3.00 mmol) in Et_2O (3 mL) and the mixture was stirred at 25 °C for 30 minutes. Then, a solution of nitrile **100** (1.04 g, 3.00 mmol) in Et_2O (6 mL) was slowly added. After the mixture had been stirred at 25 °C for additional 2 h, water was added dropwise to decompose the excess of $LiAlH_4$ and aqueous KOH (5 N, 10 mL) was then added. The colloidal mixture was extracted with Et_2O (10 × 30

mL) and the combined organic layers were dried ($MgSO_4$). After concentration under vacuum and purification by flash chromatography (SiO_2, 120 g, MTBE/7 N NH_3 in MeOH 90:10, R_f = 0.33), **128** (980 g, 2.81 mmol, 93 %) was isolated as a yellow solid.

M.p.: 83 °C.

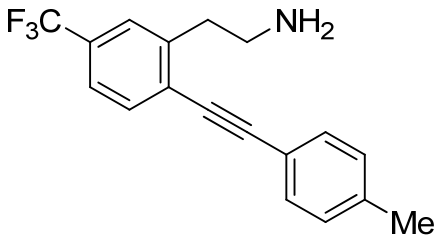
^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.24 (br. s, 2 H), 3.07-3.11 (m, 4 H), 3.90 (s, 3 H), 3.91 (s, 3 H), 6.84 (d, *J* = 8.3 Hz, 1 H), 7.02 (d, *J* = 1.7 Hz, 1 H), 7.15 (dd , *J* = 8.3, 1.9 Hz, 1H), 7.40-7.50 (m, 2 H), 7.60 (d, *J* = 7.9 Hz, 1 H) ppm.

^{13}C NMR (75 MHz, DEPT, $CDCl_3$): δ = 38.3 (CH_2), 42.2 (CH_2), 55.9 (CH_3), 56.0 (CH_3), 85.3 (C), 95.6 (C), 111.1 (CH), 114.2 (CH), 114.7 (C), 123.1 (q, *J* = 4 Hz, CH), 123.9 (q, *J* = 272 Hz, CF_3), 125.1 (CH), 126.0 (q, *J* = 4 Hz, CH), 127.1 (C), 129.7 (q, *J* = 33 Hz, C), 132.5 (CH), 141.8 (C), 148.8 (C), 150.0 (C) ppm.

IR (KBr): $\tilde{\nu}$ = 3386, 2999, 2946, 2838, 2206, 1615, 1598, 1577, 1518, 1471, 1456, 1441, 1412, 1327, 1256, 1229, 1173, 1125, 1020, 860, 844, 833, 815, 807 cm^{-1}.

MS (EI): *m/z* (%) = 349 (100) $[M]^+$, 334 (16), 330 (21), 318 (26), 273 (8), 233 (16), 212 (27), 198 (22), 166 (20), 162 (16), 151 (54), 113 (12), 86 (17).

HRMS: calcd. ($C_{19}H_{18}NO_2F_3$) 349.1290; found 349.1270.



$C_{18}H_{16}F_3N$
MW: 303.32

2-(2-(p-Tolylethynyl)-5-(trifluoromethyl)phenyl)ethanamine (**129**): A solution of $AlCl_3$ (667 mg, 5.00 mmol) in Et_2O (7 mL) was rapidly added to a suspension of $LiAlH_4$ (190 mg, 5.00 mmol) in Et_2O (7 mL) and the mixture was stirred at 25 °C for

30 minutes. Then, a solution of nitrile **101** (1.50 g, 5.00 mmol) in Et_2O (10 mL) was slowly added. After the mixture had been stirred at 25 °C for additional 2 h, aqueous KOH (5 N, 5 mL) and saturated K_2SO_4 solution (5 mL) was added dropwise to decompose the excess of $LiAlH_4$. The mixture was filtrated and the precipitate was washed with CH_2Cl_2 (2 × 50 mL). The filtrate was extracted with CH_2Cl_2 (5 × 30 mL) and the combined organic layers were dried ($MgSO_4$). After concentration under vacuum and purification by flash chromatography (SiO_2, 110 g, MTBE/7 N NH_3 in MeOH 95:5, R_f = 0.31), **129** (1.38 g, 4.55 mmol, 91 %) was isolated as a colorless oil.

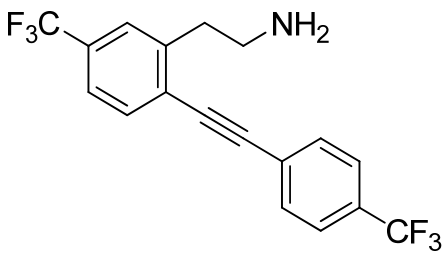
^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.34 (br. s, 2 H), 2.37 (s, 3 H), 3.01-3.11 (m, 4 H), 7.17 (d, *J* = 8.0 Hz, 2 H), 7.44 (t, *J* = 9.0 Hz, 3 H), 7.49 (s, 1 H), 7.60 (d, *J* = 8.0 Hz, 1 H) ppm.

^{13}C NMR (126 MHz, DEPT, $CDCl_3$): δ = 21.5 (CH_3), 39.0 (CH_2), 42.5 (CH_2), 86.1 (C), 95.5 (C), 119.5 (C), 123.0 (q, *J* = 4 Hz, CH), 123.9 (q, *J* = 272 Hz, CF_3), 125.9 (d, *J* = 3 Hz, CH), 127.0 (C), 129.2 (CH), 129.7 (q, *J* = 32 Hz, C), 131.5 (CH), 132.5 (CH), 139.1 (C), 142.4 (C) ppm.

IR (neat): $\tilde{\nu}$ = 3174, 2927, 2847, 2215, 1607, 1517, 1319, 1276, 1176, 1105, 1073, 907, 836, 818 cm^{-1}.

MS (EI): *m/z* (%) = 303 (43) $[M]^+$, 286 (23), 272 (35), 220 (25), 213 (31), 204 (44), 202 (100), 188 (30), 176 (23), 152 (47), 120 (24).

HRMS: calcd. ($C_{18}H_{16}F_3N$) 303.1235; found 303.1230.



$C_{18}H_{13}F_6N$
MW: 357.29

2-(5-(Trifluoromethyl)-2-((4-(trifluoromethyl)phenyl)ethynyl)phenyl)ethanamine (**130**): A solution of $AlCl_3$ (507 mg, 3.80 mmol) in Et_2O (8 mL) was rapidly added to a suspension of $LiAlH_4$ (144 mg, 3.80 mmol) in Et_2O (8 mL) and the mixture was stirred at 25 °C for 30 minutes. Then, a solution of nitrile **102** (1.34 g, 3.80 mmol) in Et_2O (15 mL) was slowly added. After the mixture had been stirred at 25 °C for additional 2 h, aqueous KOH (5 N, 5 mL) and saturated K_2SO_4 solution (5 mL) was added dropwise to decompose the excess of $LiAlH_4$. The mixture was filtrated and the precipitate was washed with CH_2Cl_2 (2 × 50 mL). The filtrate was extracted with CH_2Cl_2 (5 × 30 mL) and the combined organic layers were dried ($MgSO_4$). After concentration under vacuum and purification by flash chromatography (SiO_2, 130 g, MTBE/7 N NH_3 in MeOH 95:5, R_f = 0.28), **130** (1.31 g, 3.65 mmol, 96 %) was isolated as a yellow oil.

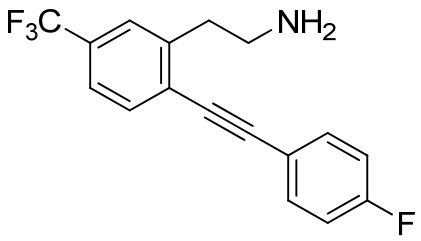
^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.28 (br. s, 2 H), 3.03-3.14 (m, 4 H), 7.46-7.55 (m, 2 H), 7.61-7.68 (m, 5 H) ppm.

^{13}C NMR (126 MHz, DEPT, $CDCl_3$): δ = 38.9 (CH_2), 42.5 (CH_2), 88.9 (C), 93.5 (C), 123.1 (q, *J* = 3 Hz, CH), 123.8 (q, *J* = 273 Hz, CF_3), 123.8 (q, *J* = 273 Hz, CF_3), 125.4 (q, *J* = 4 Hz, CH), 126.0 (CH), 126.4 (C), 128.5 (C), 130.5 (q, *J* = 33 Hz, C), 130.5 (q, *J* = 32 Hz, C), 131.8 (CH), 132.8 (CH), 142.8 (C) ppm.

IR (neat): $\tilde{\nu}$ = 3378, 2932, 2869, 1613, 1407, 1321, 1169, 1120, 1102, 1064, 832 cm^{-1}.

MS (EI): *m/z* (%) = 357 (100) $[M]^+$, 338 (32), 327 (26), 221 (21), 301 (19), 288 (25), 256 (24), 238 (47), 212 (22), 198 (22), 189 (51), 133 (7).

HRMS: calcd. ($C_{18}H_{13}F_6N$) 357.0952; found 357.0949.



$C_{17}H_{13}F_4N$
MW: 307.29

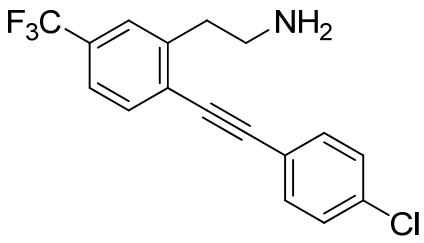
2-(2-((4-Fluorophenyl)ethynyl)-5-(trifluoromethyl)phenyl)ethanamine (**131**): A solution of $AlCl_3$ (667 mg, 5.00 mmol) in Et_2O (7 mL) was rapidly added to a suspension of $LiAlH_4$ (190 mg, 5.00 mmol) in Et_2O (7 mL) and the mixture was stirred at 25 °C for 30 minutes. Then, a solution of nitrile **103** (1.52 g, 5.00 mmol) in Et_2O (10 mL) was slowly added. After the mixture had been stirred at 25 °C for additional 2 h, aqueous KOH (5 N, 5 mL) and saturated K_2SO_4 solution (5 mL) was added dropwise to decompose the excess of $LiAlH_4$. The mixture was filtrated and the precipitate was washed with CH_2Cl_2 (2 × 50 mL). The filtrate was extracted with CH_2Cl_2 (5 × 30 mL) and the combined organic layers were dried ($MgSO_4$). After concentration under vacuum and purification by flash chromatography (SiO_2, 140 g, MTBE/7 N NH_3 in MeOH 95:5, R_f = 0.27), **131** (1.32 g, 4.28 mmol, 86 %) was isolated as a yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.31 (br. s, 2 H), 3.02-3.06 (m, 2 H), 3.06-3.10 (m, 2 H), 7.07 (t, *J* = 8.5 Hz, 2 H), 7.46 (d, *J* = 8.1 Hz, 1 H), 7.49-7.54 (m, 3 H), 7.61 (d, *J* = 8.0 Hz, 1 H) ppm.

^{13}C NMR (126 MHz, DEPT, $CDCl_3$): δ = 38.9 (CH_2), 42.5 (CH_2), 86.4 (C), 94.1 (C), 115.8 (d, *J* = 22 Hz, CH), 118.7 (d, *J* = 3 Hz, C), 123.0 (q, *J* = 4 Hz, CH), 123.9 (q, *J* = 272 Hz, CF_3), 126.0 (q, *J* = 4 Hz, CH), 126.6 (C), 130.0 (q, *J* = 32 Hz, C), 132.6 (CH), 133.5 (d, *J* = 8 Hz, CH), 142.5 (C), 162.8 (d, *J* = 251 Hz, CF) ppm.

IR (neat): $\tilde{\nu}$ = 2934, 2866, 1600, 1513, 1419, 1329, 1231 1167, 1155, 1120, 1076, 832 cm^{-1}.
MS (EI): *m/z* (%) = 307 (100) $[M]^+$, 288 (23), 277 (25), 256 (33), 251 (27), 212 (50), 207 (90), 124 (9).

HRMS: (CI) calcd. ($C_{17}H_{13}F_4N$) 307.0984; found 307.0992.



$C_{17}H_{13}ClF_3N$
MW: 323.74

2-(2-((4-Chlorophenyl)ethynyl)-5-(trifluoromethyl)phenyl)ethanamine (**132**): A solution of $AlCl_3$ (667 mg, 5.00 mmol) in Et_2O (7 mL) was rapidly added to a suspension of $LiAlH_4$ (190 mg, 5.00 mmol) in Et_2O (7 mL) and the mixture was stirred at 25 °C for 30 minutes. Then, a solution of nitrile **104** (1.60 g, 5.00 mmol) in Et_2O (10 mL) was slowly added. After the mixture had been stirred at 25 °C for additional 2 h, aqueous KOH (5 N, 5 mL) and saturated K_2SO_4 solution (5 mL) was added dropwise to decompose the excess of $LiAlH_4$. The mixture was filtrated and the precipitate was washed with CH_2Cl_2 (2 × 50 mL). The filtrate was extracted with CH_2Cl_2 (5 × 30 mL) and the combined organic layers were dried ($MgSO_4$). After concentration under vacuum and purification by flash chromatography (SiO_2, 100 g, MTBE/7 N NH_3 in MeOH 95:5, R_f = 0.67), **132** (1.39 g, 4.29 mmol, 86 %) was isolated as a yellow oil.

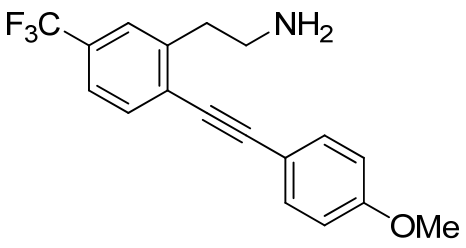
^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.36 (br. s, 2 H), 3.01-3.05 (m, 2 H), 3.05-3.10 (m, 2 H), 7.34 (d, *J* = 8.4 Hz, 2 H), 7.46 (d, *J* = 8.4 Hz, 3 H), 7.50 (s, 1 H), 7.60 (d, *J* = 8.0 Hz, 1 H) ppm.

^{13}C NMR (126 MHz, DEPT, $CDCl_3$): δ = 38.9 (CH_2), 42.4 (CH_2), 87.6 (C), 93.9 (C), 121.0 (C), 123.0 (q, *J* = 4 Hz, CH), 123.8 (q, *J* = 273 Hz, CF_3), 125.9 (q, *J* = 3 Hz, CH), 126.4 (C), 128.8 (CH), 130.1 (q, *J* = 33 Hz, C), 132.6 (CH), 132.7 (CH), 134.9 (C), 142.5 (C) ppm.

IR (neat): $\tilde{\nu}$ = 2933, 2868, 1591, 1504, 1485, 1327, 1274, 1167, 1111, 1089, 1014, 828 cm^{-1}.

MS (EI): *m/z* (%) = 325 (18) [M, ^{37}Cl]$^+$, 323 (60) [M, ^{35}Cl]$^+$, 257 (28), 238 (27), 212 (83), 189 (100), 140 (12), 125 (15).

HRMS: (CI) calcd. ($C_{17}H_{13}ClF_3N$) 323.0689; found 323.0684.



$C_{18}H_{16}F_3NO$
MW: 319.32

2-(2-((4-Methoxyphenyl)ethynyl)-5-(trifluoromethyl)phenyl)ethanamine (**133**): A solution of $AlCl_3$ (573 mg, 4.30 mmol) in Et_2O (6 mL) was rapidly added to a suspension of $LiAlH_4$ (163 mg, 4.30 mmol) in Et_2O (6 mL) and the mixture was stirred at 25 °C for 30 minutes. Then, a solution of nitrile **105** (1.36 g, 4.30 mmol) in Et_2O (10 mL) was slowly added. After the mixture had been stirred at 25 °C for additional 2 h, aqueous KOH (5 N, 5 mL) and saturated K_2SO_4 solution (5 mL) was added dropwise to decompose the excess of $LiAlH_4$. The mixture was filtrated and the precipitate was washed with CH_2Cl_2 (2 × 50 mL). The filtrate was extracted with CH_2Cl_2 (5 × 30 mL) and the combined organic layers were dried ($MgSO_4$). After concentration under vacuum and purification by flash chromatography (SiO_2, 110 g, MTBE/7 N NH_3 in MeOH 95:5, R_f = 0.35), **133** (1.17 g, 3.66 mmol, 85 %) was isolated as a colorless solid.

M.p.: 91 °C.

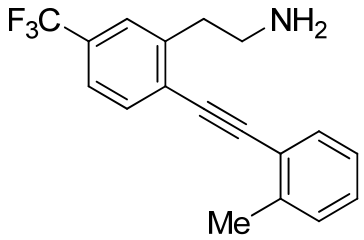
^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.29 (br. s, 2 H), 3.02-3.10 (m, 4 H), 3.82 (s, 3 H), 6.89 (d, J = 8.6 Hz, 2 H), 7.42-7.49 (m, 4 H), 7.59 (d, J = 8.0 Hz, 1 H) ppm.

^{13}C NMR (126 MHz, DEPT, $CDCl_3$): δ = 39.0 (CH_2), 42.5 (CH_2), 55.2 (CH_3), 85.5 (C), 95.4 (C), 114.1 (CH), 114.6 (C), 122.9 (q, J = 3 Hz, CH), 123.9 (q, J = 272 Hz, CF_3), 125.9 (q, J = 4 Hz, CH), 127.1 (C), 129.5 (q, J = 32 Hz, C), 132.3 (CH), 133.1 (CH), 142.2 (C), 160.0 (C) ppm.

IR (neat): $\tilde{\nu}$ = 2938, 2840, 2215, 1601, 1514, 1441, 1319, 1245, 1169, 1106, 1023, 909, 829 cm^{-1}.

MS (EI): *m/z* (%) = 319 (86) $[M]^+$, 318 (100), 300 (18), 288 (26), 246 (26), 227 (15), 212 (26), 198 (18), 176 (23), 136 (35), 121 (41), 108 (18).

HRMS: calcd. ($C_{18}H_{16}F_3NO$) 319.1184; found 319.1182.



$C_{18}H_{16}F_3N$
MW: 303.32

2-(2-(o-Tolylethynyl)-5-(trifluoromethyl)phenyl)ethanamine (**134**): A solution of $AlCl_3$ (667 mg, 5.00 mmol) in Et_2O (7 mL) was rapidly added to a suspension of $LiAlH_4$ (190 mg, 5.00 mmol) in Et_2O (7 mL) and the mixture was stirred at 25 °C for 30 minutes. Then, a solution of nitrile **106** (1.50 g, 5.00 mmol) in Et_2O (15 mL) was slowly added. After the mixture had been stirred at 25 °C for additional 2 h, aqueous KOH (5 N, 5 mL) and saturated K_2SO_4 solution (5 mL) was added dropwise to decompose the excess of $LiAlH_4$. The mixture was filtrated and the precipitate was washed with CH_2Cl_2 (2 × 50 mL). The filtrate was extracted with CH_2Cl_2 (5 × 30 mL) and the combined organic layers were dried ($MgSO_4$). After concentration under vacuum and purification by flash chromatography (SiO_2, 80 g, MTBE/7 N NH_3 in MeOH 95:5, R_f = 0.28), **134** (1.30 g, 4.30 mmol, 86 %) was isolated as a light yellow oil.

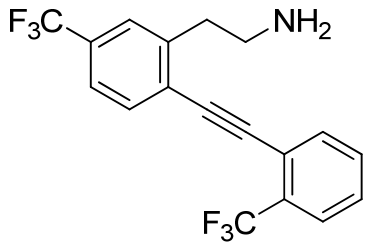
^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.20 (br. s, 2 H), 2.53 (s, 3 H), 3.03-3.11 (m, 4 H), 7.19 (dt, *J* = 7.3, 1.8 Hz, 1 H), 7.23-7.30 (m, 2 H), 7.46 (d, *J* = 8.1 Hz, 1 H), 7.50-7.52 (m, 2 H), 7.63 (d, *J* = 8.0 Hz, 1 H) ppm.

^{13}C NMR (126 MHz, DEPT, $CDCl_3$): δ = 20.8 (CH_3), 39.1 (CH_2), 42.6 (CH_2), 90.6 (C), 94.2 (C), 122.4 (C), 123.0 (q, *J* = 4 Hz, CH), 123.9 (q, *J* = 272 Hz, CF_3), 125.7 (CH), 126.0 (q, *J* = 3 Hz, CH), 127.0 (C), 128.9 (CH), 129.6 (CH), 129.9 (q, *J* = 32 Hz, C), 132.1 (CH), 132.7 (CH), 140.1 (C), 142.2 (C) ppm.

IR (neat): $\tilde{\nu}$ = 2926, 2863, 1614, 1418, 1328, 1167, 1155, 1117, 1097, 832, 755 cm^{-1}.

MS (EI): *m/z* (%) = 303 (99) $[M]^+$, 286 (51), 233 (22), 212 (64), 202 (100), 189 (22), 131 (32), 115 (19).

HRMS: calcd. ($C_{18}H_{16}F_3N$) 303.1235; found 303.1239.



$C_{18}H_{13}F_6N$
MW: 357.29

2-(5-(Trifluoromethyl)-2-((2-(trifluoromethyl)phenyl)ethynyl)phenyl)ethanamine (**135**): A solution of $AlCl_3$ (589 mg, 4.42 mmol) in Et_2O (7 mL) was rapidly added to a suspension of $LiAlH_4$ (168 mg, 4.42 mmol) in Et_2O (6 mL) and the mixture was stirred at 25 °C for 30 minutes. Then, a solution of nitrile **107** (1.56 mg, 4.42 mmol) in Et_2O (15 mL) was slowly added. After the mixture had been stirred at 25 °C for additional 2 h, aqueous KOH (5 N, 5 mL) and saturated K_2SO_4 solution (5 mL) was added dropwise to decompose the excess of $LiAlH_4$. The mixture was filtrated and the precipitate was washed with CH_2Cl_2 (2 × 50 mL). The filtrate was extracted with CH_2Cl_2 (5 × 30 mL) and the combined organic layers were dried ($MgSO_4$). After concentration under vacuum and purification by flash chromatography (SiO_2, 120 g, MTBE/7 N NH_3 in MeOH 95:5, R_f = 0.48), **135** (1.48 g, 4.13 mmol, 93 %) was isolated as a yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.40 (br. s, 2 H), 3.01-3.10 (m, 4 H), 7.44-7.49 (m, 2 H), 7.52 (s, 1 H), 7.55 (t, *J* = 7.6 Hz, 1 H), 7.65 (d, *J* = 8.0 Hz, 1 H), 7.70 (d, *J* = 4.2 Hz, 1 H), 7.71 (d, *J* = 4.5 Hz, 1 H) ppm.

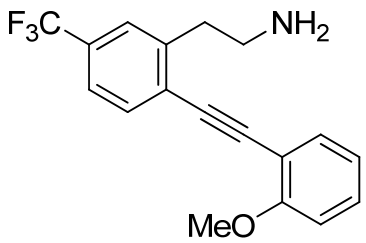
^{13}C NMR (126 MHz, DEPT, $CDCl_3$): δ = 38.9 (CH_2), 42.9 (CH_2), 90.6 (C), 92.1 (C), 120.9 (C), 123.0 (q, *J* = 4 Hz, CH), 123.6 (q, *J* = 273 Hz, CF_3), 123.8 (q, *J* = 272 Hz,

CF_3), 126.0 (q, *J* = 5 Hz, CH), 126.1 (q, *J* = 4 Hz, CH), 126.2 (C), 128.5 (CH), 130.6 (q, *J* = 33 Hz, C), 131.2 (q, *J* = 30 Hz, C), 131.6 (CH), 133.1 (CH), 134.2 (CH), 142.6 (C) ppm.

IR (neat): $\tilde{\nu}$ = 2935, 2868, 1615, 1602, 1574, 1451, 1419, 1319, 1170, 1109, 1055, 1032, 833, 763 cm^{-1}.

MS (EI): *m/z* (%) = 357 (46) $[M]^+$, 356 (23), 278 (21), 256 (24), 238 (100), 212 (99), 189 (17).

HRMS: calcd. ($C_{18}H_{13}F_6N$) 357.0952; found 357.0945.



$C_{18}H_{16}F_3NO$
MW: 319.32

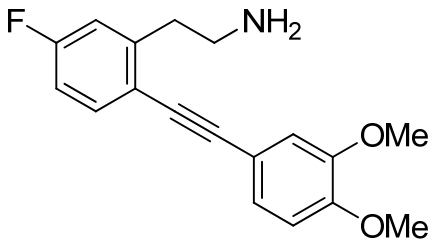
2-(2-((2-Methoxyphenyl)ethynyl)-5-(trifluoromethyl)phenyl)ethanamine (**136**): A solution of $AlCl_3$ (667 mg, 5.00 mmol) in Et_2O (7 mL) was rapidly added to a suspension of $LiAlH_4$ (190 mg, 5.00 mmol) in Et_2O (7 mL) and the mixture was stirred at 25 °C for 30 minutes. Then, a solution of nitrile **108** (1.58 g, 5.00 mmol) in Et_2O (10 mL) was slowly added. After the mixture had been stirred at 25 °C for additional 2 h, aqueous KOH (5 N, 5 mL) and saturated K_2SO_4 solution (5 mL) was added dropwise to decompose the excess of $LiAlH_4$. The mixture was filtrated and the precipitate was washed with CH_2Cl_2 (2 × 50 mL). The filtrate was extracted with CH_2Cl_2 (5 × 30 mL) and the combined organic layers were dried ($MgSO_4$). After concentration under vacuum and purification by flash chromatography (SiO_2, 110 g, MTBE/7 N NH_3 in MeOH 95:5, R_f = 0.30), **136** (1.29 g, 4.05 mmol, 81 %) was isolated as a light yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.22 (br. s, 2 H), 3.09 (s, 4 H), 3.92 (s, 3 H), 6.92 (d, *J* = 8.4 Hz, 1 H), 6.96 (t, *J* = 7.4 Hz, 1 H), 7.34 (t, *J* = 7.9 Hz, 1 H), 7.45 (d, *J* = 8.0 Hz, 1 H), 7.47-7.51 (m, 2 H), 7.63 (d, *J* = 8.0 Hz, 1 H) ppm.
^{13}C NMR (126 MHz, DEPT, $CDCl_3$): δ = 39.1 (CH_2), 43.0 (CH_2), 55.7 (CH_3), 91.0 (C), 91.7 (C), 110.6 (CH), 111.9 (C), 120.5 (CH), 122. 9 (q, *J* = 4 Hz, CH), 124.0 (q, *J* = 276 Hz, CF_3), 125.9 (q, *J* = 4 Hz, CH), 127.3 (C), 129.7 (q, *J* = 32 Hz, C), 130.3 (CH), 132.3 (CH), 133.2 (CH), 142.7 (C), 160.2 (C) ppm.

IR (neat): $\tilde{\nu}$ = 2942, 2839, 2214, 1596, 1328, 1275, 1165, 1155, 1116, 1023, 832, 749 cm^{-1}.

MS (EI): *m/z* (%) = 319 (100) $[M]^+$, 318 (77), 288 (47), 212 (96), 205 (45), 200 (55), 189 (55), 176 (45), 147 (30), 121 (46).

HRMS: calcd. ($C_{18}H_{16}F_3NO$) 319.1184; found 319.1177.



$C_{18}H_{18}FNO_2$
MW: 299.34

2-(2-((3,4-Dimethoxyphenyl)ethynyl)-5-fluorophenyl)ethanamine (**137**): A solution of $AlCl_3$ (467 mg, 3.50 mmol) in Et_2O (5 mL) was rapidly added to a suspension of $LiAlH_4$ (133 mg, 3.50 mmol) in Et_2O (4 mL) and the mixture was stirred at 25 °C for 30 minutes. Then, a solution of nitrile **109** (1.03 g, 3.50 mmol) in Et_2O (7 mL) was slowly added. After the mixture had been stirred at 25 °C for additional 2 h, water was added dropwise to decompose the excess of $LiAlH_4$ and aqueous KOH (5 N, 10 mL) was then added. The colloidal mixture was extracted with Et_2O (10 × 30 mL) and the combined organic layers were dried ($MgSO_4$). After concentration under vacuum and purification by flash chromatography (SiO_2, 220 g, MTBE/7 N NH_3 in MeOH 90:10, R_f = 0.33), **137** (1.94 g, 3.15 mmol, 90 %) was isolated as a yellow oil.

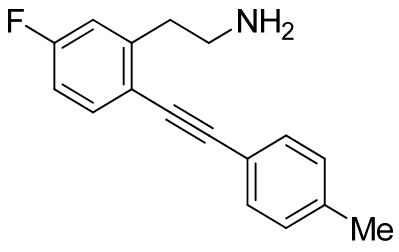
^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.35 (br. s, 2H), 2.99 (t, *J* = 6.7 Hz, 2 H), 3.07 (t, *J* = 6.4 Hz, 2 H), 3.91 (s, 6 H), 6.84 (d, *J* = 8.2 Hz, 1 H), 6.91 (dt, *J* = 8.4, 2.5 Hz, 1 H), 6.96 (dd, *J* = 9.5, 2.4 Hz, 1 H), 7.01 (d, *J* = 1.5 Hz, 1 H), 7.11 (dd, *J* = 8.1, 1.6 Hz, 1 H), 7.49 (dd, *J* = 8.4, 5.9 Hz, 1 H) ppm.

^{13}C NMR (126 MHz, DEPT, $CDCl_3$): δ = 39.0 (CH_2), 42.5 (CH_2), 55.9 (CH_3), 55.9 (CH_3), 85.6 (C), 92.7 (C), 111.1 (CH), 113.4 (d, *J* = 22 Hz, CH), 114.1 (CH), 115.4 (C), 116.2 (d, *J* = 22 Hz, CH), 119.3 (d, *J* = 3 Hz, C), 124.8 (CH), 133.9 (d, *J* = 9 Hz, CH), 144.3 (d, *J* = 7 Hz, CH), 148.7 (C), 149.6 (C), 162.2 (d, *J* = 250 Hz, CF) ppm.

IR (neat): $\tilde{\nu}$ = 3056, 3933, 2838, 2773, 2364, 1602, 1580, 1516, 1444, 1367, 1328, 1253, 1235, 1131, 1069, 1027, 817, 763, 735, 701 cm^{-1}.

MS (EI): *m/z* (%) = 299 (96) $[M]^+$, 298 (47), 283 (11), 270 (22), 269 (10), 268 (24), 255 (12), 223 (13), 207 (11), 196 (16), 183 (37), 166 (31), 162 (34), 161 (11), 151 (100), 148 (35), 138 (16).

HRMS: calcd. ($C_{18}H_{18}NO_2F$) 299.1322; found 299.1322.



$C_{17}H_{16}FN$
MW:253,31

2-(5-Fluoro-2-(p-tolylethynyl)phenyl)ethanamine (**138**): A solution of $AlCl_3$ (533 mg, 4.00 mmol) in Et_2O (6 mL) was rapidly added to a suspension of $LiAlH_4$ (152 mg, 4.00 mmol) in Et_2O (6 mL) and the mixture was stirred at 25 °C for 30 minutes. Then, a solution of nitrile **110** (997 mg, 4.00 mmol) in Et_2O (10 mL) was slowly added. After the mixture had been stirred at 25 °C for additional 2 h, aqueous KOH (5 N, 5 mL) and saturated K_2SO_4 solution (5 mL) was added dropwise to decompose the excess of $LiAlH_4$. The mixture was filtrated and the precipitate was washed with CH_2Cl_2 (2 × 50 mL). The filtrate was extracted with CH_2Cl_2 (5 × 30 mL) and the combined organic

layers were dried ($MgSO_4$). After concentration under vacuum and purification by flash chromatography (SiO_2, 110 g, MTBE/7 N NH_3 in MeOH 95:5, R_f = 0.24), **138** (887 mg, 3.50 mmol, 88 %) was isolated as a yellow oil.

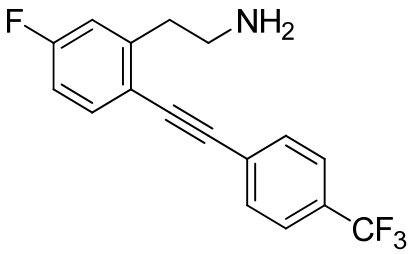
^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.26 (br. s, 2 H), 2.36 (s, 3 H), 2.98 (t, *J* = 6.8 Hz, 2 H), 3.06 (t, *J* = 6.8 Hz, 2 H), 6.90 (dt, *J* = 8.4, 2.6 Hz, 1 H), 6.95 (dd, *J* = 9.5, 2.6 Hz, 1 H), 7.15 (d, *J* = 7.9 Hz, 2 H), 7.40 (d, *J* = 8.1 Hz, 2 H), 7.48 (dd, *J* = 8.5, 5.9 Hz, 1 H) ppm.

^{13}C NMR (126 MHz, DEPT, $CDCl_3$): δ = 21.4 (CH_3), 39.0 (CH_2), 42.5 (CH_2), 86.4 (C), 92.7 (C), 113.4 (d, *J* = 22 Hz, CH), 116.2 (d, *J* = 22 Hz, CH), 119.2 (d, *J* = 3 Hz, C), 120.0 (C), 129.1 (CH), 131.3 (CH), 133.9 (d, *J* = 9 Hz, CH), 138.5 (C), 144.4 (d, *J* = 8 Hz, C), 162.2 (d, *J* = 250 Hz, CF) ppm.

IR (neat): $\tilde{\nu}$ = 2923, 1604, 1578, 1510, 1486, 1418, 1272, 1223, 1153, 1020, 957, 813 cm^{-1}.

MS (EI): *m/z* (%) = 253 (42) $[M]^+$, 252 (58), 238 (46), 223 (90), 207 (98), 162 (100), 133 (59).

HRMS: calcd. ($C_{17}H_{16}FN$) 253.1267; found 253.1271.



$C_{17}H_{13}F_4N$
MW: 307.29

2-(5-Fluoro-2-((4-(trifluoromethyl)phenyl)ethynyl)phenyl)ethanamine (**139**): A solution of $AlCl_3$ (467 mg, 3.50 mmol) in Et_2O (5 mL) was rapidly added to a suspension of $LiAlH_4$ (133 mg, 3.50 mmol) in Et_2O (4 mL) and the mixture was stirred at 25 °C for 30 minutes. Then, a solution of nitrile **111** (1.06 g, 3.50 mmol) in Et_2O (10 mL) was slowly added. After the mixture had been stirred at 25 °C for additional 2 h,

aqueous KOH (5 N, 4 mL) and saturated K_2SO_4 solution (4 mL) was added dropwise to decompose the excess of $LiAlH_4$. The mixture was filtrated and the precipitate was washed with CH_2Cl_2 (2 × 50 mL). The filtrate was extracted with CH_2Cl_2 (5 × 30 mL) and the combined organic layers were dried ($MgSO_4$). After concentration under vacuum and purification by flash chromatography (SiO_2, 110 g, MTBE/7 N NH_3 in MeOH 95:5, R_f = 0.38), **139** (891 mg, 2.90 mmol, 83 %) was isolated as a colorless oil.

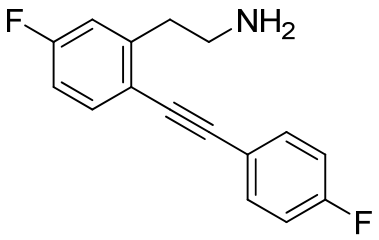
^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.19 (br. s, 2 H), 2.99 (t, *J* = 6.8 Hz, 2 H), 3.07 (t, *J* = 6.5 Hz, 2 H), 6.93 (dd, *J* = 11.7, 4.7 Hz, 1 H), 6.99 (d, *J* = 9.3 Hz, 1 H), 7.49-7.54 (m, 1 H), 7.60 (s, 4 H) ppm.

^{13}C NMR (126 MHz, DEPT, $CDCl_3$): δ = 39.0 (CH_2), 42.5 (CH_2), 89.4 (C), 91.2 (C), 113.6 (d, *J* = 22 Hz, CH), 116.4 (d, *J* = 22 Hz, CH), 118.3 (d, *J* = 3 Hz, C), 123.9 (q, *J* = 272 Hz, CF_3), 125.3 (q, *J* = 3 Hz, CH), 127.0 (C), 130.0 (q, *J* = 33 Hz, C), 131.6 (CH), 134.3 (d, *J* = 9 Hz, CH), 144.9 (d, *J* = 8 Hz, C), 162.7 (d, *J* = 251 Hz, CF) ppm.

IR (neat): $\tilde{\nu}$ = 2931, 2864, 2217, 1605, 1488, 1321, 1227, 1165, 1122, 1104, 1016, 839, 817 cm^{-1}.

MS (EI): *m/z* (%) = 307 (94) [M]$^+$, 306 (100), 290 (17), 277 (40), 256 (28), 251 (14), 238 (13), 207 (60), 180 (12), 162 (55), 148 (15), 132 (16).

HRMS: calcd. ($C_{17}H_{13}F_4N$) 307.0984; found 307.0980.



$C_{16}H_{13}F_2N$
MW: 257.28

2-(5-Fluoro-2-((4-fluorophenyl)ethynyl)phenyl)ethanamine (**140**): A solution of $AlCl_3$ (667 mg, 5.00 mmol) in Et_2O (7 mL) was rapidly added to a suspension of

$LiAlH_4$ (190 mg, 5.00 mmol) in Et_2O (7 mL) and the mixture was stirred at 25 °C for 30 minutes. Then, a solution of nitrile **110** (1.27 g, 5.00 mmol) in Et_2O (10 mL) was slowly added. After the mixture had been stirred at 25 °C for additional 2 h, aqueous KOH (5 N, 5 mL) and saturated K_2SO_4 solution (5 mL) was added dropwise to decompose the excess of $LiAlH_4$. The mixture was filtrated and the precipitate was washed with CH_2Cl_2 (2 × 50 mL). The filtrate was extracted with CH_2Cl_2 (5 × 30 mL) and the combined organic layers were dried ($MgSO_4$). After concentration under vacuum and purification by flash chromatography (SiO_2, 120 g, MTBE/7 N NH_3 in MeOH 95:5, R_f = 0.20), **140** (1.01 g, 3.91 mmol, 78 %) was isolated as a orange-yellow oil.

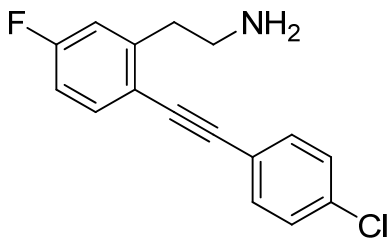
^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.47 (br. s, 2 H), 2.97 (t, *J* = 6.8 Hz, 2 H), 3.06 (t, *J* = 6.8 Hz, 2 H), 6.89-6.94 (m, 1 H), 6.96 (d, *J* = 9.4 Hz, 1 H), 7.04 (dt, *J* = 8.7, 1.6 Hz, 2 H), 7.45-7.51 (m, 3 H) ppm.

^{13}C NMR (126 MHz, DEPT, $CDCl_3$): δ = 38.9 (CH_2), 42.4 (CH_2), 86.7 (C), 91.5 (C), 113.5 (d, *J* = 22 Hz, CH), 115.7 (d, *J* = 22 Hz, CH), 116.3 (d, *J* = 22 Hz, CH), 118.8 (d, *J* = 3 Hz, CH), 119.2 (d, *J* = 4 Hz, C), 133.2 (d, *J* = 8 Hz, CH), 134.0 (d, *J* = 9 Hz, CH), 144.4 (d, *J* = 8 Hz, C), 162.4 (d, *J* = 250 Hz, CF), 162.5 (d, *J* = 250 Hz, CF) ppm.

IR (neat): $\tilde{\nu}$ = 2930, 2862, 1602, 1579, 1506, 1487, 1218, 1154, 833 cm^{-1}.

MS (EI): *m/z* (%) = 257 (80) $[M]^+$, 256 (100), 240 (21), 227 (52), 225 (57), 200 (39), 162 (52), 148 (9), 133 (14).

HRMS: calcd. ($C_{16}H_{13}F_2N$) 257.1016; found 257.1011.



$C_{16}H_{13}ClFN$
MW: 273.73

2-(2-((4-Chlorophenyl)ethynyl)-5-fluorophenyl)ethanamine (**141**): A solution of $AlCl_3$ (667 mg, 5.00 mmol) in Et_2O (7 mL) was rapidly added to a suspension of $LiAlH_4$ (190 mg, 5.00 mmol) in Et_2O (7 mL) and the mixture was stirred at 25 °C for 30 minutes. Then, a solution of nitrile **113** (1.35 mg, 5.00 mmol) in Et_2O (10 mL) was slowly added. After the mixture had been stirred at 25 °C for additional 2 h, aqueous KOH (5 N, 5 mL) and saturated K_2SO_4 solution (5 mL) was added dropwise to decompose the excess of $LiAlH_4$. The mixture was filtrated and the precipitate was washed with CH_2Cl_2 (2 × 50 mL). The filtrate was extracted with CH_2Cl_2 (5 × 30 mL) and the combined organic layers were dried ($MgSO_4$). After concentration under vacuum and purification by flash chromatography (SiO_2, 80 g, MTBE/7 N NH_3 in MeOH 95:5, R_f = 0.40), **141** (887 mg, 3.24 mmol, 65 %) was isolated as a yellow oil.

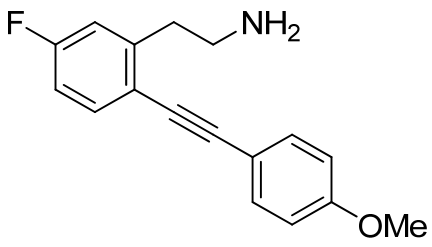
^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.29 (br. s, 2 H), 2.97 (t, *J* = 6.9 Hz, 2 H), 3.05 (t, *J* = 6.8 Hz, 2 H), 6.92 (dt, *J* = 8.3, 2.5 Hz, 1 H), 6.96 (dd, *J* = 9.5, 2.5 Hz, 1 H), 7.32 (d, *J* = 8.5 Hz, 2 H), 7.43 (d, *J* = 8.3 Hz, 2 H), 7.48 (dd, *J* = 8.5, 5.9 Hz, 1 H) ppm.

^{13}C NMR (126 MHz, DEPT, $CDCl_3$): δ = 38.9 (CH_2), 42.4 (CH_2), 88.0 (C), 91.4 (C), 113.5 (d, *J* = 22 Hz, CH), 116.3 (d, *J* = 22 Hz, CH), 118.7 (d, *J* = 3 Hz, C), 121.6 (C), 128.7 (CH), 132.5 (CH), 134.0 (d, *J* = 9 Hz, CH), 134.3 (C), 144.5 (d, *J* = 8 Hz, C), 162.4 (d, *J* = 250 Hz, C) ppm.

IR (neat): $\tilde{\nu}$ = 2928, 2863, 1605, 1578, 1493, 1224, 1087, 1014, 821 cm^{-1}.

MS (EI): *m/z* (%) = 275 (13) [M, ^{37}Cl]$^+$, 273 (42) [M, ^{35}Cl]$^+$, 272 (45), 207 (100), 181 (16), 162 (78), 148 (31), 133 (13).

HRMS: (CI) calcd. ($C_{16}H_{13}ClFN$) 273.0721; found 273.0724.



$C_{17}H_{16}FNO$
MW: 269.31

2-(5-Fluoro-2-((4-methoxyphenyl)ethynyl)phenyl)ethanamine (**142**): A solution of $AlCl_3$ (627 mg, 4.70 mmol) in Et_2O (7 mL) was rapidly added to a suspension of $LiAlH_4$ (178 mg, 4.70 mmol) in Et_2O (7 mL) and the mixture was stirred at 25 °C for 30 minutes. Then, a solution of nitrile **114** (1.25 g, 4.70 mmol) in Et_2O (10 mL) was slowly added. After the mixture had been stirred at 25 °C for additional 2 h, aqueous KOH (5 N, 5 mL) and saturated K_2SO_4 solution (5 mL) was added dropwise to decompose the excess of $LiAlH_4$. The mixture was filtrated and the precipitate was washed with CH_2Cl_2 (2 × 50 mL). The filtrate was extracted with CH_2Cl_2 (5 × 30 mL) and the combined organic layers were dried ($MgSO_4$). After concentration under vacuum and purification by flash chromatography (SiO_2, 80 g, MTBE/7 N NH_3 in MeOH 95:5, R_f = 0.34), **142** (896 mg, 3.33 mmol, 71 %) was isolated as a light yellow oil.

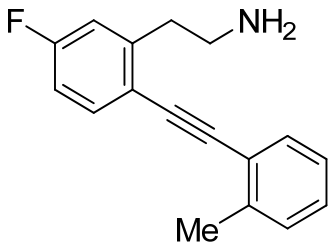
^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.22 (br. s, 2 H), 2.97 (t, *J* = 6.7 Hz, 2 H), 3.06 (t, *J* = 6.6 Hz, 2 H), 3.82 (s, 3 H), 6.86-6.93 (m, 3 H), 6.95 (d, *J* = 9.2 Hz, 1 H), 7.42-7.50 (m, 3 H) ppm.

^{13}C NMR (126 MHz, DEPT, $CDCl_3$): δ = 39.0 (CH_2), 42.5 (CH_2), 55.3 (CH_3), 85.7 (C), 92. 6 (C), 113.4 (d, *J* = 22 Hz, CH), 114.0 (CH), 115.2 (C), 116.2 (d, *J* = 22 Hz, CH), 119.3 (d, *J* = 3 Hz, C), 132.8 (CH), 133.8 (d, *J* = 9 Hz, CH), 144.2 (d, *J* = 8 Hz, C), 159.6 (C), 162.2 (d, *J* = 249 Hz, CF) ppm.

IR (neat): $\tilde{\nu}$ = 2934, 2838, 2212, 1887, 1605, 1509, 1286, 1246, 1174, 1152, 1028, 828 cm^{-1}.

MS (EI): *m/z* (%) = 269 (78) $[M]^+$, 268 (100), 252 (18), 240 (32), 225 (29), 195 (63), 162 (40), 148 (25), 136 (28), 121 (57).

HRMS: calcd. ($C_{17}H_{16}FNO$) 269.1216; found 269.1212.



$C_{17}H_{16}FN$
MW: 253.31

2-(5-Fluoro-2-(o-tolylethynyl)phenyl)ethanamine (**143**): A solution of $AlCl_3$ (667 mg, 5.00 mmol) in Et_2O (7 mL) was rapidly added to a suspension of $LiAlH_4$ (190 mg, 5.00 mmol) in Et_2O (7 mL) and the mixture was stirred at 25 °C for 30 minutes. Then, a solution of nitrile **115** (1.25 g, 5.00 mmol) in Et_2O (15 mL) was slowly added. After the mixture had been stirred at 25 °C for additional 2 h, aqueous KOH (5 N, 5 mL) and saturated K_2SO_4 solution (5 mL) was added dropwise to decompose the excess of $LiAlH_4$. The mixture was filtrated and the precipitate was washed with CH_2Cl_2 (2 × 50 mL). The filtrate was extracted with CH_2Cl_2 (5 × 30 mL) and the combined organic layers were dried ($MgSO_4$). After concentration under vacuum and purification by flash chromatography (SiO_2, 80 g, MTBE/7 N NH_3 in MeOH 95:5, R_f = 0.23), **143** (1.11 g, 4.39 mmol, 88 %) was isolated as a light yellow oil.

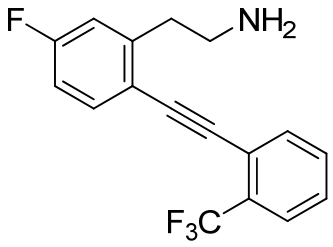
^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.16 (br. s, 2 H), 2.51 (s, 3 H), 2.99 (t, J = 6.6 Hz, 2 H), 3.06 (t, J = 6.5 Hz, 2 H), 6.91 (dt, J = 8.4, 2.6 Hz, 1 H), 6.96 (dd, J = 9.5, 2.6 Hz, 1 H), 7.15-7.20 (m, 1 H), 7.22-7.26 (m, 2 H), 7.47-7.53 (m, 2 H) ppm.

^{13}C NMR (126 MHz, DEPT, $CDCl_3$): δ = 20.8 (CH_3), 39.1 (CH_2), 42.5 (s, 1 H_2), 90.9 (C), 91.5 (C), 113.4 (d, J = 22 Hz, CH), 116.3 (d, J = 22 Hz, CH), 119.3 (d, J = 3 Hz, C), 122.9 (C), 125.6 (CH), 128.3 (CH), 129.5 (CH), 131.8 (CH), 134.1 (d, J = 9 Hz, CH), 139.7 (C), 144.2 (d, J = 8 Hz, C), 162.3 (d, J = 250 Hz, CF) ppm.

IR (neat): $\tilde{\nu}$ = 3060, 2925, 2861, 1600, 1578, 1493, 1272, 1225, 1154, 816, 754 cm^{-1}.

MS (EI): *m/z* (%) = 253 (99) $[M]^+$, 252 (63), 236 (81), 220 (85), 202 (38), 196 (30), 183 (20), 162 (100), 131 (32).

HRMS: calcd. ($C_{17}H_{16}FN$) 253.1267; found 253.1262.



$C_{17}H_{13}F_4N$
MW: 307.29

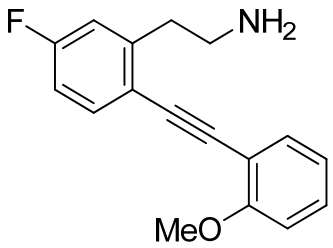
2-(5-Fluoro-2-((2-(trifluoromethyl)phenyl)ethynyl)phenyl)ethanamine (**144**): A solution of $AlCl_3$ (667 mg, 5.00 mmol) in Et_2O (7 mL) was rapidly added to a suspension of $LiAlH_4$ (190 mg, 5.00 mmol) in Et_2O (7 mL) and the mixture was stirred at 25 °C for 30 minutes. Then, a solution of nitrile **116** (1.52 g, 5.00 mmol) in Et_2O (10 mL) was slowly added. After the mixture had been stirred at 25 °C for additional 2 h, aqueous KOH (5 N, 5 mL) and saturated K_2SO_4 solution (5 mL) was added dropwise to decompose the excess of $LiAlH_4$. The mixture was filtrated and the precipitate was washed with CH_2Cl_2 (2 × 50 mL). The filtrate was extracted with CH_2Cl_2 (5 × 30 mL) and the combined organic layers were dried ($MgSO_4$). After concentration under vacuum and purification by flash chromatography (SiO_2, 120 g, MTBE/7 N NH_3 in MeOH 95:5, R_f = 0.41), **144** (1.26 g, 3.50 mmol, 82 %) was isolated as a yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.37 (br. s, 2 H), 2.96-3.06 (m, 4 H), 6.93 (dt, *J* = 8.3, 2.6 Hz, 1 H), 6.98 (dd, *J* = 9.4, 2.6 Hz, 1 H), 7.42 (t, *J* = 7.6 Hz, 1 H), 7.50-7.56 (m, 2 H), 7.66 (d, *J* = 7.7 Hz, 1 H), 7.69 (d, *J* = 7.9 Hz, 1 H) ppm.

^{13}C NMR (126 MHz, DEPT, $CDCl_3$): δ = 38.9 (CH_2), 42.8 (CH_2), 88.3 (C), 92.7 (C), 113.6 (d, *J* = 22 Hz, CH), 116.4 (d, *J* = 22 Hz, CH), 118.5 (d, *J* = 3 Hz, C), 121.4 (q, *J* = 1 Hz, C), 123.6 (q, *J* = 273 Hz, CF_3), 125.9 (q, *J* = 5 Hz, CH), 128.0 (CH), 130.9 (d, *J* = 30 Hz, C), 131.5 (CH), 133.9 (CH), 134.5 (d, *J* = 9 Hz, CH), 145.0 (d, *J* = 8 Hz, C), 162.8 (d, *J* = 251 Hz, CF) ppm.

IR (neat): $\tilde{\nu}$ = 2932, 2867, 2217, 1601, 1574, 1498, 1319, 1172, 1125, 1055, 1032, 817, 763 cm^{-1}.

MS (EI): *m/z* (%) = 307 (39) $[M]^+$, 306 (35), 278 (22), 256 (49), 238 (40), 207 (22), 162 (100).
HRMS: calcd. ($C_{17}H_{13}F_4N$) 307.0984; found 307.0989.



$C_{17}H_{16}FNO$
MW: 269.31

2-(5-Fluoro-2-((2-methoxyphenyl)ethynyl)phenyl)ethanamine (**145**): A solution of $AlCl_3$ (667 mg, 5.00 mmol) in Et_2O (7 mL) was rapidly added to a suspension of $LiAlH_4$ (190 mg, 5.00 mmol) in Et_2O (7 mL) and the mixture was stirred at 25 °C for 30 minutes. Then, a solution of nitrile **117** (1.35 mg, 5.00 mmol) in Et_2O (10 mL) was slowly added. After the mixture had been stirred at 25 °C for additional 2 h, aqueous KOH (5 N, 5 mL) and saturated K_2SO_4 solution (5 mL) was added dropwise to decompose the excess of $LiAlH_4$. The mixture was filtrated and the precipitate was washed with CH_2Cl_2 (2 × 50 mL). The filtrate was extracted with CH_2Cl_2 (5 × 30 mL) and the combined organic layers were dried ($MgSO_4$). After concentration under vacuum and purification by flash chromatography (SiO_2, 110 g, MTBE/7 N NH_3 in MeOH 95:5, R_f = 0.22), **145** (1.23 g, 4.55 mmol, 91 %) was isolated as a light yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.21 (br. s, 2 H), 2.98-3.09 (m, 4 H), 3.91 (s, 3 H), 6.88-6.97 (m, 4 H), 7.30 (t, *J* = 7.9 Hz, 1 H), 7.46 (dd, *J* = 7.6, 1.2 Hz, 1 H), 7.51 (dd, *J* = 8.5, 5.9 Hz, 1 H) ppm.

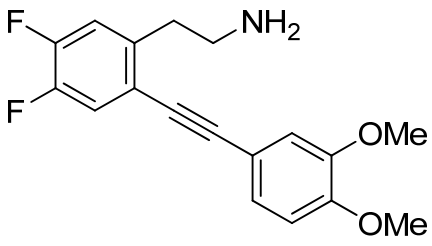
^{13}C NMR (126 MHz, DEPT, $CDCl_3$): δ = 39.1 (CH_2), 43.0 (CH_2), 55.7 (CH_3), 88.9 (C), 91.3 (C), 110.5 (CH), 112.4 (C), 113.3 (d, *J* = 22 Hz, CH), 116.2 (d, *J* = 22 Hz, CH),

119.5 (d, *J* = 3 Hz, C), 120.4 (CH), 129.7 (CH), 133.0 (CH), 133.7 (d, *J* = 9 Hz, CH), 144.7 (d, *J* = 8 Hz, C), 159.9 (C), 162.3 (d, *J* = 249 Hz, CF) ppm.

IR (neat): $\tilde{\nu}$ = 2940, 2837, 1596, 1575, 1497, 1483, 1273, 1245, 1225, 1022, 816, 748 cm^{-1}.

MS (EI): *m/z* (%) = 269 (93) $[M]^+$, 268 (88), 238 (50), 207 (43), 196 (68), 162 (100), 148 (50), 121 (29).

HRMS: calcd. ($C_{17}H_{16}FNO$) 269.1216; found 269.1213.



$C_{18}H_{17}F_2NO_2$
MW: 317.33

2-(2-((3,4-Dimethoxyphenyl)ethynyl)-4,5-difluorophenyl)ethanamine (**146**): A solution of $AlCl_3$ (467 mg, 3.50 mmol) in Et_2O (5 mL) was rapidly added to a suspension of $LiAlH_4$ (133 mg, 3.50 mmol) in Et_2O (4 mL) and the mixture was stirred at 25 °C for 30 minutes. Then, a solution of nitrile **118** (1.10 g, 3.50 mmol) in Et_2O (7 mL) was slowly added. After the mixture had been stirred at 25 °C for additional 2 h, water was added dropwise to decompose the excess of $LiAlH_4$ and aqueous (5 N, 10 mL) was then added. The colloidal mixture was extracted with Et_2O (10 × 30 mL) and the combined organic layers were dried ($MgSO_4$). After concentration under vacuum and purification by flash chromatography (SiO_2, 120 g, MTBE/7 N NH_3 in MeOH 90:10, R_f = 0.33), **146** (1.01 g, 3.18 mmol, 91 %) was isolated as a yellow solid.

M.p.: 61 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.37 (br. s, 2 H), 2.95 (t, *J* = 6.4 Hz, 2 H), 3.05 (t, *J* = 6.1 Hz, 2 H), 3.91 (s, 6 H), 6.84 (d, *J* = 8,3 Hz, 1 H), 7.00 (d, *J* = 1.7 Hz, 1 H), 7.05

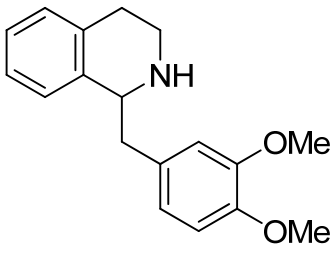
(dd, *J* = 11.0, 8.0 Hz, 1 H), 7.12 (dd, *J* = 8.3, 1.9 Hz, 1 H), 7.31 (dd, *J* = 10.7, 7.9 Hz, 1 H) ppm.

^{13}C NMR (75 MHz, DEPT, $CDCl_3$): δ = 38.3 (CH_2), 42.5 (CH_2), 55.9 (CH_3), 56.0 (CH_3), 84.6 (C), 93.5 (C), 111.1 (CH), 114.1 (CH), 114.9 (C), 118.0 (d, *J* = 18 Hz, CH), 119.7 (dd, *J* = 7, 4 Hz, C), 120.6 (d, *J* = 19 Hz, CH), 124.9 (CH), 139.0 (dd, *J* = 5, 4 Hz, C), 148.4 (dd, *J* = 247, 13 Hz, CF), 148.8 (C), 149.9 (C), 149.9 (dd, *J* = 251, 13 Hz, CF) ppm.

IR (KBr): $\tilde{\nu}$ = 3441, 3040, 3012, 2935, 2834, 2794, 1609, 1591, 1517, 1461, 1417, 1329, 1303, 1259, 1241, 1208, 1155, 1137, 1102, 1029, 861, 807, 766 cm^{-1}.

MS (EI): *m/z* (%) = 317 (100) $[M]^+$, 302 (12), 288 (27), 286 (21), 243 (10), 241 (11), 225 (12), 214 (16), 201 (36), 180 (21), 175 (12), 166 (21), 151 (75), 138 (8), 113 (6).

HRMS: calcd. ($C_{18}H_{17}NO_2F_2$) 317.1227; found 317.1234.



$C_{18}H_{21}NO_2$
MW: 283.36

1-(3,4-dimethoxybenzyl)-1,2,3,4-tetrahydroisoquinoline (***rac*-147**): In a Schlenk tube, a mixture of aminoalkyne **119** (281 mg, 1.00 mmol) and Ind_2TiMe_2 (15 mg, 0.05 mmol, 5 mol%) in toluene (1.00 mL) was stirred at 105 °C for 16 h. The resulting dark brown solution was cooled to room temperature and a mixture of $NaBH_3CN$ (126 mg, 2.00 mmol) and $ZnCl_2$ (136 mg, 1.00 mmol) in MeOH (5.0 mL) was added. After this had been stirred at 25 C for 24 h, saturated $NaCO_3$ solution (30 mL) was added and the mixture was extracted with CH_2Cl_2 (5 × 25 mL). The combined organic layers were dried ($MgSO_4$) and concentrated under vacuum. After purification by flash chromatography (SiO_2, 23 g, MTBE/7 N NH_3 in MeOH 98:2, R_f = 0.27), ***rac*-147** (190 mg, 0.67 mmol, 67 %) was isolated as a yellow oil.

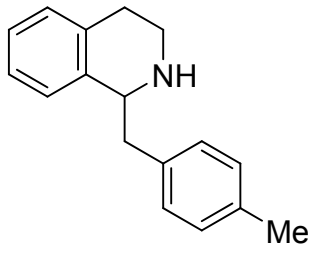
^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.29 (br. s, 1 H), 2.75-2.99 (m, 4 H), 3.18-3.27 (m, 2 H), 3.83 (s, 3 H), 3.87 (s, 3 H), 4.22-4.28 (m, 1 H), 6.73 (s, 1 H), 6.80 (d, *J* = 8.6 Hz, 1 H), 6.83 (d, *J* = 8.1 Hz, 1 H), 7.11 (d, *J* = 7.0 Hz, 1 H), 7.14-7.21 (m, 2 H), 7.24 (d, *J* = 6.9 Hz, 1 H) ppm.

^{13}C NMR (126 MHz, DEPT, $CDCl_3$) δ = 29.9 (CH_2), 40.9 (CH_2), 41.9 (CH_2), 55.8 (CH_3), 55.9 (CH_3), 57.2 (CH), 111.3 (CH), 112.3 (CH), 121.3 (CH), 125.7 (CH), 126.1 (CH), 126.2 (CH), 129.3 (CH), 131.3 (C), 135.3 (C), 138.4 (C), 147.6 (C), 148.9 (C) ppm.

IR (neat): $\tilde{\nu}$ = 2932, 2833, 1513, 1453, 1260, 1235, 1155, 1138, 1027, 743 cm^{-1}.

MS (CI): *m/z* (%) = 284 (21) $[M + H]^+$, 132 (100), 117 (8).

HRMS: calcd. ($C_{18}H_{22}NO_2$) 284.1651; found 284.1653.



$C_{17}H_{19}N$
MW: 237.34

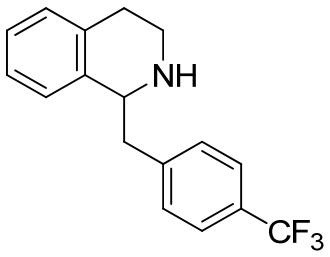
1-(4-Methylbenzyl)-1,2,3,4-tetrahydroisoquinoline (***rac*-148**): In a Schlenk tube, a mixture of aminoalkyne **120** (153 mg, 0.65 mmol) and Ind_2TiMe_2 (10 mg, 0.03 mmol, 5 mol%) in toluene (1 mL) was stirred at 105 °C for 16 h. The resulting dark brown solution was cooled to room temperature and a mixture of $NaBH_3CN$ (82 mg, 1.30 mmol) and $ZnCl_2$ (89 mg, 0.65 mmol) in MeOH (5.0 mL) was added. After this had been stirred at 25 °C for 24 h, saturated NH_4Cl solution (25 mL) was added and the mixture was extracted with CH_2Cl_2 (5 × 25 mL). The combined organic layers were dried ($MgSO_4$) and concentrated under vacuum. After purification by flash chromatography (SiO_2, 28 g, MTBE/7 N NH_3 in MeOH 95:5, R_f = 0.46), ***rac*-148** (124 mg, 0.52 mmol, 80 %) was isolated as a yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.01 (br. s, 1 H), 2.34 (s, 3 H), 2.74-2.96 (m, 4 H), 3.18-3.28 (m, 2 H), 4.16-4.22 (m, 1 H), 7.05-7.20 (m, 7 H), 7.23-7.29 (m, 1 H) ppm.
^{13}C NMR (126 MHz, DEPT, $CDCl_3$) δ = 21.0 (CH_3), 29.8 (CH_2), 40.6 (CH_2), 41.9 (CH_2), 57.2 (CH), 125.7 (CH), 126.1 (CH), 126.2 (CH), 129.2 (CH), 129.3 (CH), 129.3 (CH), 135.2 (C), 135.9 (C), 136.0 (C), 138.6 (C) ppm.

IR (neat): $\tilde{\nu}$ = 2923, 1671, 1604, 1514, 1491, 1454, 1317, 1265, 1216, 1123, 736 cm^{-1}.

MS (CI): *m/z* (%) = 238 (53) $[M + H]^+$, 150 (11), 132 (100), 150 (9).

HRMS: (CI) calcd. ($C_{17}H_{20}N$) 238.1596; found 238.1600.



$C_{17}H_{16}F_3N$
MW: 291.31

1-(4-(Trifluoromethyl)benzyl)-1,2,3,4-tetrahydroisoquinoline (***rac*-149**): In a Schlenk tube, a mixture of aminoalkyne **121** (275 mg, 0.95 mmol) and Ind_2TiMe_2 (15 mg, 0.05 mmol, 5 mol%) in toluene (1 mL) was stirred at 105 °C for 16 h. The resulting dark brown solution was cooled to room temperature and a mixture of $NaBH_3CN$ (119 mg, 1.90 mmol) and $ZnCl_2$ (129 mg, 0.95 mmol) in MeOH (5.0 mL) was added. After this had been stirred at 25 C for 24 h, saturated NH_4Cl solution (25 mL) was added and the mixture was extracted with CH_2Cl_2 (5 × 25 mL). The combined organic layers were dried ($MgSO_4$) and concentrated under vacuum. After purification by flash chromatography (SiO_2, 28 g, MTBE/7 N NH_3 in MeOH 98:2, R_f = 0.25), ***rac*-149** (193 mg, 0.66 mmol, 70 %) was isolated as a yellow-orange oil.

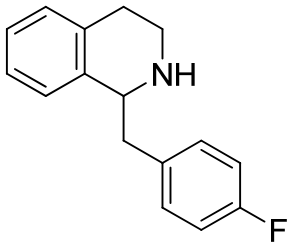
^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.57 (br. s, 1 H), 2.73-2.89 (m, 2 H), 2.91-3.01 (m, 2 H), 3.18-3.25 (m, 1 H), 3.30 (dd, *J* = 13.8, 3.6 Hz, 1 H), 4.25 (dd, *J* = 10.0, 3.6 Hz, 1 H), 7.10-7.24 (m, 4 H), 7.39 (d, *J* = 7.9 Hz, 2 H), 7.58 (d, *J* = 7.9 Hz, 2 H) ppm.

^{13}C NMR (126 MHz, DEPT, $CDCl_3$): δ = 29.9 (CH_2), 40.7 (CH_2), 42.6 (CH_2), 57.1 (CH), 124.3 (q, J = 272 Hz, CF_3), 125.5 (q, J = 4 Hz, CH), 125.8 (CH), 126.1 (CH), 126.3 (CH), 128.8 (q, J = 33 Hz, C), 129.5 (CH), 129.7 (CH), 135.4 (C), 138.3 (C), 143.5 (C) ppm.

IR (neat): $\tilde{\nu}$ = 2929, 1322, 1163, 1120, 1066, 1019, 907, 727 cm^{-1}.

MS (CI): *m/z* (%) = 292 (49) $[M + H]^+$, 159 (3), 132 (100), 117 (4).

HRMS: (CI) calcd. ($C_{17}H_{17}F_3N$) 292.1313; found 292.1319.



$C_{16}H_{16}FN$
MW: 241.30

1-(4-Fluorobenzyl)-1,2,3,4-tetrahydroisoquinoline (***rac*-150**): In a Schlenk tube, a mixture of aminoalkyne **122** (239 mg, 1.00 mmol) and Ind_2TiMe_2 (15 mg, 0.05 mmol, 5 mol%) in toluene (1 mL) was stirred at 105 °C for 16 h. The resulting dark brown solution was cooled to room temperature and a mixture of $NaBH_3CN$ (126 mg, 2.00 mmol) and $ZnCl_2$ (136 mg, 1.00 mmol) in MeOH (5.0 mL) was added. After this had been stirred at 25 °C for 24 h, saturated NH_4Cl solution (25 mL) was added and the mixture was extracted with CH_2Cl_2 (5 × 25 mL). The combined organic layers were dried ($MgSO_4$) and concentrated under vacuum. After purification by flash chromatography (SiO_2, 20 g, MTBE/7 N NH_3 in MeOH 98:2, R_f = 0.58), ***rac*-150** (180 mg, 0.75 mmol, 75 %) was isolated as a yellow oil.

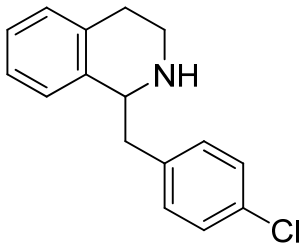
^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.77 (br. s, 1 H), 2.72-2.96 (m, 4 H), 3.16-3.27 (m, 2 H), 4.17 (dd, J = 10.0, 3.6 Hz, 1 H), 7.01 (t, J = 8.7 Hz, 2 H), 7.09-7.25 (m, 6 H) ppm.

^{13}C NMR (126 MHz, DEPT, $CDCl_3$): δ = 29.9 (CH_2), 40.6 (CH_2), 41.7 (CH_2), 57.2 (CH), 115.3 (d, *J* = 21 Hz, CH), 125.7 (CH), 126.1 (CH), 126.2 (CH), 129.4 (CH), 130.7 (d, *J* = 8 Hz, CH), 134.7 (d, *J* = 3 Hz, C), 135.3 (C), 138.4 (C), 161.6 (d, *J* = 244 Hz, CF) ppm.

IR (neat): $\tilde{\nu}$ = 3019, 2923, 2803, 1601, 1508, 1454, 1219, 1157, 1123, 744 cm^{-1}.

MS (CI): *m/z* (%) = 242 (100) $[M + H]^+$, 132 (94), 109 (6).

HRMS: (CI) calcd. ($C_{16}H_{17}FN$) 242.1345; found 242.1341.



$C_{16}H_{16}ClN$
MW: 257.76

1-(4-Chlorobenzyl)-1,2,3,4-tetrahydroisoquinoline (***rac*-151**): In a Schlenk tube, a mixture of aminoalkyne **123** (256 mg, 1.00 mmol) and Ind_2TiMe_2 (15 mg, 0.05 mmol, 5 mol%) in toluene (1 mL) was stirred at 105 °C for 16 h. The resulting dark brown solution was cooled to room temperature and a mixture of $NaBH_3CN$ (126 mg, 2.00 mmol) and $ZnCl_2$ (136 mg, 1.00 mmol) in MeOH (5.0 mL) was added. After this had been stirred at 25 °C for 24 h, saturated NH_4Cl solution (25 mL) was added and the mixture was extracted with CH_2Cl_2 (5 × 25 mL). The combined organic layers were dried ($MgSO_4$) and concentrated under vacuum. After purification by flash chromatography (SiO_2, 25 g, MTBE/7 N NH_3 in MeOH 99:1, R_f = 0.28), ***rac*-151** (215 mg, 0.84 mmol, 84 %) was isolated as a orange-yellow oil.

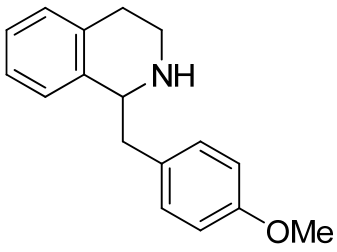
^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.71 (br. s, 1 H), 2.73-2.96 (m, 4 H), 3.17-3.26 (m, 2 H), 4.19 (dd, *J* = 10.0, 3.6 Hz, 1 H), 7.09-7.13 (m, 1 H), 7.14-7.23 (m, 5 H), 7.29 (d, *J* = 8.4 Hz, 2 H) ppm.

^{13}C NMR (126 MHz, DEPT, $CDCl_3$) δ = 29.9 (CH_2), 40.7 (CH_2), 41.9 (CH_2), 57.1 (C), 125.7 (CH), 126.1 (CH), 126.2 (CH), 128.7 (CH), 129.4 (CH), 130.7 (CH), 132.2 (C), 135.3 (C), 137.6 (C), 138.3 (CH) ppm.

IR (neat): $\tilde{\nu}$ = 3020, 2923, 2832, 2802, 1489, 1454, 1123, 1091, 1015, 804, 740, 718 cm^{-1}.

MS (CI): *m/z* (%) = 260 (15) [M + H, ^{37}Cl]$^+$, 258 (47) [M + H, ^{35}Cl]$^+$, 130 (100).

HRMS: (CI) calcd. ($C_{16}H_{17}ClN$) 258.1050; found 258.1053.



$C_{17}H_{19}NO$
MW: 253.34

1-(4-Methoxybenzyl)-1,2,3,4-tetrahydroisoquinoline (***rac*-152**): In a Schlenk tube, a mixture of aminoalkyne **124** (188 mg, 0.75 mmol) and Ind_2TiMe_2 (12 mg, 0.04 mmol, 5 mol%) in toluene (1 mL) was stirred at 105 °C for 16 h. The resulting dark brown solution was cooled to room temperature and a mixture of $NaBH_3CN$ (94 mg, 1.50 mmol) and $ZnCl_2$ (102 mg, 0.75 mmol) in MeOH (5.0 mL) was added. After this had been stirred at 25 C for 24 h, saturated NH_4Cl solution (25 mL) was added and the mixture was extracted with CH_2Cl_2 (5 × 25 mL). The combined organic layers were dried ($MgSO_4$) and concentrated under vacuum. After purification by flash chromatography (SiO_2, 16 g, MTBE/7 N NH_3 in MeOH 98:2, R_f = 0.42), ***rac*-152** (179 mg, 0.71 mmol, 90 %) was isolated as a light yellow oil.

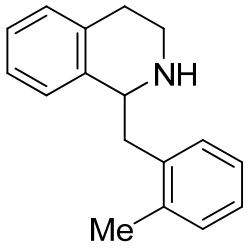
^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.09 (br. s, 1 H), 2.73-2.95 (m, 4 H), 3.18-3.24 (m, 2 H), 3.80 (s, 3 H), 4.16 (dd, *J* = 10.1, 3.7 Hz, 1 H), 6.87 (d, *J* = 8.5 Hz, 2 H), 7.10 (d, *J* = 6.7 Hz, 1 H), 7.13-7.20 (m, 4 H), 7.22-7.25 (m, 1 H) ppm.

^{13}C NMR (126 MHz, DEPT, $CDCl_3$) δ = 29.8 (CH_2), 40.6 (CH_2), 41.5 (CH_2), 55.2 (CH_3), 57.3 (CH), 114.0 (CH), 125.7 (CH), 126.1 (CH), 126.1 (CH), 129.3 (CH), 130.2 (CH), 130.9 (C), 135.2 (C), 138.5 (C), 158.2 (C) ppm.

IR (neat): $\tilde{\nu}$ = 2919, 2833, 1610, 1510, 1454, 1244, 1176, 1034, 743 cm^{-1}.

MS (CI): *m/z* (%) = 254 (100) $[M + H]^+$, 132 (65).

HRMS: (CI) calcd. ($C_{17}H_{20}NO$) 254.1545; found 254.1551.



$C_{17}H_{19}N$
MW: 237.34

1-(2-Methylbenzyl)-1,2,3,4-tetrahydroisoquinoline (***rac*-153**): In a Schlenk tube, a mixture of aminoalkyne **125** (235 mg, 1.00 mmol) and Ind_2TiMe_2 (15 mg, 0.05 mmol, 5 mol%) in toluene (1 mL) was stirred at 105 °C for 16 h. The resulting dark brown solution was cooled to room temperature and a mixture of $NaBH_3CN$ (126 mg, 2.00 mmol) and $ZnCl_2$ (136 mg, 1.00 mmol) in MeOH (5.0 mL) was added. After this had been stirred at 25 °C for 24 h, saturated NH_4Cl solution (25 mL) was added and the mixture was extracted with CH_2Cl_2 (5 × 25 mL). The combined organic layers were dried ($MgSO_4$) and concentrated under vacuum. After purification by flash chromatography (SiO_2, 27 g, MTBE/7 N NH_3 in MeOH 98:2, R_f = 0.36), ***rac*-153** (187 mg, 0.79 mmol, 79 %) was isolated as a light brown oil.

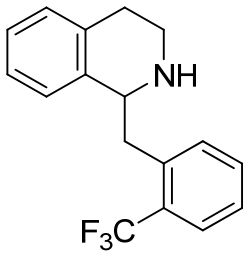
^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.72 (br. s, 1 H), 2.41 (s, 3 H), 2.77-2.98 (m, 4 H), 3.22-3.31 (m, 2 H), 4.20 (dd, *J* = 10.5, 3.4 Hz, 1 H), 7.11-7.24 (m, 8 H) ppm.

^{13}C NMR (126 MHz, DEPT, $CDCl_3$) δ = 19.7 (CH_3), 30.0 (CH_2), 39.9 (CH_2), 40.4 (CH_2), 55.8 (CH), 125.7 (CH), 126.0 (CH), 126.1 (CH), 126.2 (CH), 126.6 (CH), 129.3 (CH), 130.2 (CH), 130.6 (CH), 135.2 (C), 136.6 (C), 137.5 (C), 138.9 (C) ppm.

IR (neat): $\tilde{\nu}$ = 3061, 3017, 2922, 2802, 1492, 1454, 1316, 1125, 961, 751 cm^{-1}.

MS (CI): *m/z* (%) = 238 (65) $[M + H]^+$, 132 (100).

HRMS: (CI) calcd. ($C_{17}H_{20}N$) 238.1596; found 238.1593.



$C_{17}H_{16}F_3N$
MW: 291.31

1-(2-(Trifluoromethyl)benzyl)-1,2,3,4-tetrahydroisoquinoline (***rac*-154**): In a Schlenk tube, a mixture of aminoalkyne **126** (289 mg, 1.00 mmol) and Ind_2TiMe_2 (15 mg, 0.05 mmol, 5 mol%) in toluene (1 mL) was stirred at 105 °C for 15 h. The resulting dark brown solution was cooled to room temperature and a mixture of $NaBH_3CN$ (126 mg, 2.00 mmol) and $ZnCl_2$ (136 mg, 1.00 mmol) in MeOH (5.0 mL) was added. After this had been stirred at 25 C for 24 h, saturated NH_4Cl solution (25 mL) was added and the mixture was extracted with CH_2Cl_2 (5 × 25 mL). The combined organic layers were dried ($MgSO_4$) and concentrated under vacuum. After purification by flash chromatography (SiO_2, 30 g, MTBE/7 N NH_3 in MeOH 95:5, R_f = 0.45), ***rac*-154** (246 mg, 0.85 mmol, 85 %) was isolated as a light brown solid.

M.p.: 60 °C.

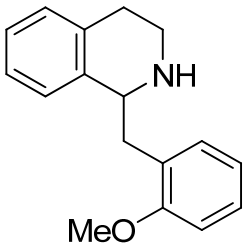
^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.74 (br. s, 1 H), 2.77-2.90 (m, 2 H), 2.95-3.08 (m, 2 H), 3.23-3.30 (m, 1 H), 3.41-3.49 (m, 1 H), 4.27 (dd, *J* = 10.6, 2.7 Hz, 1 H), 7.09-7.25 (m, 4 H), 7.35 (t, *J* = 7.6 Hz, 1 H), 7.44 (d, *J* = 7.6 Hz, 1 H), 7.51 (t, *J* = 7.5 Hz, 1 H), 7.69 (d, *J* = 7.9 Hz, 1 H) ppm.

^{13}C NMR (126 MHz, DEPT, $CDCl_3$): δ = 29.9 (CH_2), 39.1 (CH_2), 39.7 (CH_2), 56.2 (CH), 124.8 (q, *J* = 274 Hz, CF_3), 125.9 (CH), 126.3 (CH), 126.4 (q , *J* = 6 Hz, CH),

126.5 (CH), 126.6 (CH), 128.9 (q, *J* = 30 Hz, C), 129.3 (CH), 131.6 (CH), 132.4 (CH), 135.12 (C), 138.1 (C), 138.6 (C) ppm.

IR (neat): $\tilde{\nu}$ = 3324, 3072, 2940, 2913, 2865, 1606, 1581, 1492, 1453, 1306, 1157, 1119, 1060, 1034, 753 cm^{-1}.
MS (CI): *m/z* (%) = 292 (54) $[M + H]^+$, 290 (6), 132 (100).

HRMS: (CI) calcd. ($C_{17}H_{17}F_3N$) 292.1313; found 292.1307.



$C_{17}H_{19}NO$
MW: 253.34

1-(2-Methoxybenzyl)-1,2,3,4-tetrahydroisoquinoline (***rac*-155**): In a Schlenk tube, a mixture of aminoalkyne **127** (251 mg, 1.00 mmol) and Ind_2TiMe_2 (15 mg, 0.05 mmol, 5 mol%) in toluene (1 mL) was stirred at 105 °C for 16 h. The resulting dark brown solution was cooled to room temperature and a mixture of $NaBH_3CN$ (126 mg, 2.00 mmol) and $ZnCl_2$ (136 mg, 1.00 mmol) in MeOH (5.0 mL) was added. After this had been stirred at 25 °C for 24 h, saturated NH_4Cl solution (25 mL) was added and the mixture was extracted with CH_2Cl_2 (5 × 25 mL). The combined organic layers were dried ($MgSO_4$) and concentrated under vacuum. After purification by flash chromatography (SiO_2, 30 g, MTBE/7 N NH_3 in MeOH 98:2, R_f = 0.53), ***rac*-155** (195 mg, 0.76 mmol, 76 %) was isolated as a dark yellow oil.

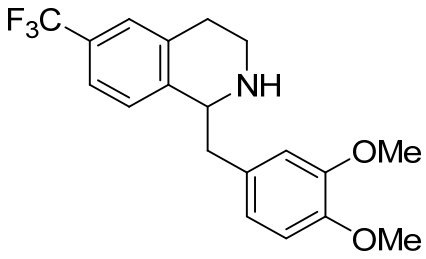
^1H NMR (500 MHz, $CDCl_3$): δ = 1.83 (br. s, 1 H), 2.77-2.88 (m, 3 H), 2.89-2.95 (m, 1 H), 3.22-3.29 (m, 1 H), 3.34 (dd, *J* = 13.4, 3.2 Hz, 1 H), 3.86 (s, 3 H), 4.27 (dd, *J* = 10.3, 2.7 Hz, 1 H), 6.88-6.94 (m, 2 H), 7.11 (t, *J* = 8.1 Hz, 1 H), 7.15 (d, *J* = 8.7 Hz, 1 H), 7.16-7.21 (m, 2 H), 7.22-7.27 (m, 1 H), 7.29 (d, *J* = 7.4 Hz, 1 H) ppm.

^{13}C NMR (126 MHz, DEPT, $CDCl_3$) δ = 29.9 (CH_2), 37.6 (CH_2), 40.1 (CH_2), 55.3 (CH_3), 55.4 (CH), 110.4 (CH), 120.4 (CH), 125.6 (CH), 125.9 (CH), 126.6 (CH), 127.7 (CH), 127.8 (C), 129.1 (CH), 131.2 (CH), 135.1 (C), 139.4 (C), 157.8 (C) ppm.

IR (neat): $\tilde{\nu}$ = 3021, 2924, 2834, 1493, 1456, 1242, 1126, 1031, 747 cm^{-1}.

MS (CI): *m/z* (%) = 254 (94) $[M + H]^+$, 146 (15), 132 (100).

HRMS: (CI) calcd. ($C_{17}H_{20}NO$) 254.1545; found 254.1541.



$C_{19}H_{20}F_3NO_2$
MW: 351.36

1-(3,4-Dimethoxybenzyl)-6-(trifluoromethyl)-1,2,3,4-tetrahydroisoquinoline (***rac*-156**): In a Schlenk tube, a mixture of aminoalkyne **128** (175 mg, 0.50 mmol) and Ind_2TiMe_2 (9 mg, 0.025 mmol, 5 mol%) in toluene (0.25 mL) was stirred at 105 °C for 16 h. The resulting dark brown solution was cooled to room temperature and a mixture of $NaBH_3CN$ (63 mg, 1.00 mmol) and $ZnCl_2$ (68 mg, 0.50 mmol) in MeOH (5.0 mL) was added. After this had been stirred at 25 °C for 24 h, saturated NH_4Cl solution (25 mL) was added and the mixture was extracted with CH_2Cl_2 (5 × 25 mL). The combined organic layers were dried ($MgSO_4$) and concentrated under vacuum. After purification by flash chromatography (SiO_2, 110 g, MTBE/7 N NH_3 in MeOH 95:5, R_f = 0.18), ***rac*-156** (169 mg, 0.48 mmol, 96 %) was isolated as a yellow solid.

M.p.: 93 °C.

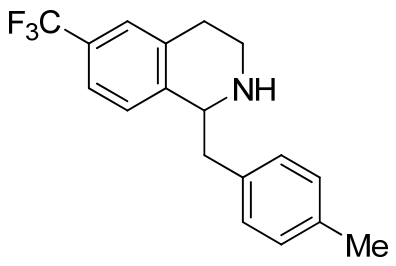
^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.13 (br s, 1 H), 2.80-2.96 (m, 4 H), 3.19-3.26 (m, 2 H), 3.84 (s, 3 H), 3.87 (s, 3 H), 4.21 (dd, *J* = 9.5, 3.2 Hz, 1 H), 6.71 (d, *J* = 1.7 Hz, 1 H), 6.79 (dd, *J* = 8.1, 1.7 Hz, 1 H), 6.84 (d, *J* = 8.0 Hz, 1 H), 7.33-7.43 (m, 3 H) ppm.

^{13}C NMR (75 MHz, DEPT, $CDCl_3$): δ = 29.9 (CH_2), 40.5 (CH_2), 41.8 (CH_2), 55.7 (CH_3), 55.8 (CH_3), 57.1 (CH), 111.2 (CH), 112.1 (CH), 121.3 (CH), 122.2 (q, J = 4 Hz, CH), 124.2 (q, J = 272 Hz, CF_3), 126.1 (q, J = 4 Hz, CH), 126.6 (CH), 128.3 (q, J = 32 Hz, C), 130.7 (C), 136.2 (C), 142.5 (C), 147.7 (C), 148.9 (C) ppm.

IR (neat): $\tilde{\nu}$ = 3443, 2936, 2835, 1621, 1590, 1516, 1466, 1425, 1338, 1323, 1266, 1237, 1160, 1126, 1077, 1030, 828, 813, 764 cm^{-1}.

MS (EI): *m/z* (%) = 351 (1) $[M]^+$, 350 (3), 349 (4), 334 (4), 332 (11), 214 (6), 201 (94), 200 (100), 198 (23), 185 (22), 173 (7), 151 (35), 131 (11), 113 (7), 107 (7).

HRMS: calcd. ($C_{19}H_{20}NO_2F_3$) 351.1446; found 351.1401.



$C_{18}H_{18}F_3N$
MW: 305.34

1-(4-Methylbenzyl)-6-(trifluoromethyl)-1,2,3,4-tetrahydroisoquinoline (***rac*-157**): In a Schlenk tube, a mixture of aminoalkyne **129** (303 mg, 1.00 mmol) and Ind_2TiMe_2 (15 mg, 0.05 mmol, 5 mol%) in toluene (1 mL) was stirred at 105 °C for 16 h. The resulting dark brown solution was cooled to room temperature and a mixture of $NaBH_3CN$ (126 mg, 2.00 mmol) and $ZnCl_2$ (136 mg, 1.00 mmol) in MeOH (5.0 mL) was added. After this had been stirred at 25 C for 24 h, saturated NH_4Cl solution (25 mL) was added and the mixture was extracted with CH_2Cl_2 (5 × 25 mL). The combined organic layers were dried ($MgSO_4$) and concentrated under vacuum. After purification by flash chromatography (SiO_2, 35 g, MTBE/7 N NH_3 in MeOH 99:1, R_f = 0.38), ***rac*-157** (238 mg, 0.78 mmol, 78 %) was isolated as a yellow oil.

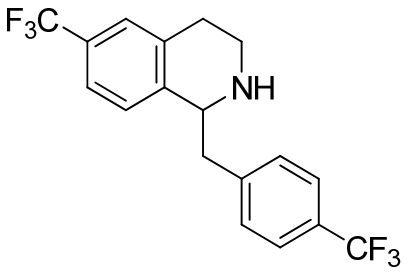
^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.75 (br. s, 1 H), 2.34 (s, 3 H), 2.77-2.97 (m, 4 H), 3.17-3.28 (m, 2 H), 4.20 (dd, *J* = 10.1, 3.1 Hz, 1 H), 7.15 (br. s, 4 H), 7.31-7.43 (m, 3 H) ppm.

^{13}C NMR (126 MHz, DEPT, $CDCl_3$): δ = 21.0 (CH_3), 30.0 (CH_2), 40.3 (CH_2), 41.8 (CH_2), 57.2 (CH), 122.3 (q, *J* = 3 Hz, CH), 124.3 (q, *J* = 272 Hz, CF_3), 126.1 (q, *J* = 4 Hz, CH), 126.7 (CH), 128.32(q, *J* = 32 Hz, C), 129.1 (CH), 129.4 (CH), 135.4 (C), 136.1 (C), 136.2 (C), 142.7 (C) ppm.

IR (neat): $\tilde{\nu}$ = 2925, 1516, 1448, 1428, 1339, 1322, 1162, 1118, 1077, 827 cm^{-1}.

MS (CI): *m/z* (%) = 306 (82) $[M + H]^+$, 200 (100), 105 (5), 119 (9).

HRMS: (CI) calcd. ($C_{18}H_{19}F_3N$) 306.1470; found 306.1464.



$C_{18}H_{15}F_6N$
MW: 359.31

6-(Trifluoromethyl)-1-(4-(trifluoromethyl)benzyl)-1,2,3,4-tetrahydroisoquinoline (***rac*-158**): In a Schlenk tube, a mixture of aminoalkyne **130** (268 mg, 0.75 mmol) and Ind_2TiMe_2 (12 mg, 0.04 mmol, 5 mol%) in toluene (1 mL) was stirred at 105 °C for 16 h. The resulting dark brown solution was cooled to room temperature and a mixture of $NaBH_3CN$ (94 mg, 1.50 mmol) and $ZnCl_2$ (102 mg, 0.75 mmol) in MeOH (5.0 mL) was added. After this had been stirred at 25 °C for 24 h, saturated NH_4Cl solution (25 mL) was added and the mixture was extracted with CH_2Cl_2 (5 × 25 mL). The combined organic layers were dried ($MgSO_4$) and concentrated under vacuum. After purification by flash chromatography (SiO_2, 40 g, MTBE/7 N NH_3 in MeOH 98:2, R_f = 0.51), ***rac*-158** (235 mg, 0.65 mmol, 87 %) was isolated as a light yellow solid.

M.p.: 65 °C.

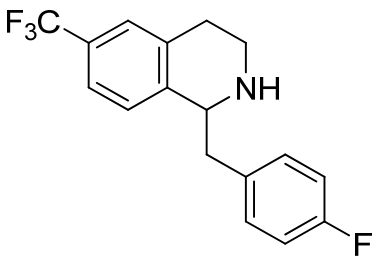
^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.73 (br. s, 1 H), 2.77-3.02 (m, 4 H), 3.19-3.32 (m, 2 H), 4.28 (dd, *J* = 9.9, 3.3 Hz, 1 H), 7.31 (d, *J* = 8.1 Hz, 1 H), 7.36-7.40 (m, 3 H), 7.42 (d, *J* = 8.2 Hz, 1 H), 7.59 (d, *J* = 8.0 Hz, 2 H) ppm.

^{13}C NMR (126 MHz, DEPT, $CDCl_3$): δ = 29.9 (CH_2), 40.3 (CH_2), 42.3 (CH_2), 56.9 (CH), 122.5 (q, *J* = 4 Hz, CH), 124.2 (q, *J* = 272 Hz, CF_3), 124.2 (q, *J* = 272 Hz, CF_3), 125.6 (q, *J* = 4 Hz, CH), 126.3 (q, *J* = 4 Hz, CH), 126.6 (CH), 128.7 (q, *J* = 32 Hz, C), 129.1 (q, *J* = 32 Hz, C), 129.7 (CH), 136.2 (C), 142.2 (C), 142.9 (C) ppm.

IR (neat): $\tilde{\nu}$ = 2932, 2847, 1616, 1426, 1319, 1164, 1115, 1075, 1066, 1018, 830, 738 cm^{-1}.

MS (CI): *m/z* (%) = 360 (90) $[M + H]^+$, 340 (3), 200 (100), 181 (2).

HRMS: (CI) calcd. ($C_{18}H_{16}F_6N$) 360.1187; found 360.1184.



$C_{17}H_{15}F_4N$
MW: 309.30

1-(4-Fluorobenzyl)-6-(trifluoromethyl)-1,2,3,4-tetrahydroisoquinoline (***rac*-159**): In a Schlenk tube, a mixture of aminoalkyne **131** (307 mg, 1.00 mmol) and Ind_2TiMe_2 (15 mg, 0.05 mmol, 5 mol%) in toluene (1 mL) was stirred at 105 °C for 16 h. The resulting dark brown solution was cooled to room temperature and a mixture of $NaBH_3CN$ (126 mg, 2.00 mmol) and $ZnCl_2$ (136 mg, 1.00 mmol) in MeOH (5.0 mL) was added. After this had been stirred at 25 C for 24 h, saturated NH_4Cl solution (25 mL) was added and the mixture was extracted with CH_2Cl_2 (5 × 25 mL). The combined organic layers were dried ($MgSO_4$) and concentrated under vacuum. After

purification by flash chromatography (SiO_2, 30 g, MTBE/7 N NH_3 in MeOH 99:1, R_f = 0.39), ***rac*-159** (268 mg, 0.87 mmol, 87 %) was isolated as a yellow solid.

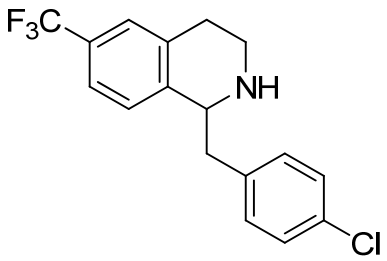
^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.74 (br. s, 1 H), 2.77-2.98 (m, 4 H), 3.19-3.26 (m, 2 H), 4.21 (dd, *J* = 9.8, 2.9 Hz, 1 H), 7.03 (t, *J* = 8.7 Hz, 2 H), 7.19-7.24 (m, 2 H), 7.31 (d, *J* = 8.1 Hz, 1 H), 7.38 (s, 1 H), 7.41 (d, *J* = 8.1 Hz, 1 H) ppm.

^{13}C NMR (126 MHz, DEPT, $CDCl_3$): δ = 29.9 (CH_2), 40.3 (CH_2), 41.5 (CH_2), 57.1 (CH), 115.5 (d, *J* = 21 Hz, CH), 122.4 (q, *J* = 4 Hz, CH), 124.2 (q, *J* = 272 Hz, CF_3), 126.2 (q, *J* = 3 Hz, CH), 126.6 (CH), 128.5 (q, *J* = 32 Hz, C), 130.7 (d, *J* = 8 Hz, CH), 134.2 (d, *J* = 3 Hz, C), 136.2 (C), 142.4 (C), 161.7 (d, *J* = 245 Hz, CF) ppm.

IR (neat): $\tilde{\nu}$ = 3040, 2928, 2812, 1509, 1427, 1338, 1321, 1260, 1221, 1158, 1115, 1074, 827 cm^{-1}.

MS (CI): *m/z* (%) = 310 (100) $[M + H]^+$, 200 (87), 109 (4).

HRMS: (CI) calcd. ($C_{17}H_{16}F_4N$) 310.1219; found 310.1223.



$C_{17}H_{15}ClF_3N$
MW: 325.76

1-(4-Chlorobenzyl)-6-(trifluoromethyl)-1,2,3,4-tetrahydroisoquinoline (***rac*-160**): In a Schlenk tube, a mixture of aminoalkyne **132** (324 mg, 1.00 mmol) and Ind_2TiMe_2 (15 mg, 0.05 mmol, 5 mol%) in toluene (1 mL) was stirred at 105 °C for 12 h. The resulting dark brown solution was cooled to room temperature and a mixture of $NaBH_3CN$ (126 mg, 2.00 mmol) and $ZnCl_2$ (136 mg, 1.00 mmol) in MeOH (5.0 mL) was added. After this had been stirred at 25 C for 24 h, saturated NH_4Cl solution (25 mL) was added and the mixture was extracted with CH_2Cl_2 (5 × 25 mL). The

combined organic layers were dried ($MgSO_4$) and concentrated under vacuum. After purification by flash chromatography (SiO_2, 25 g, MTBE/7 N NH_3 in MeOH 99:1, R_f = 0.30), ***rac*-160** (269 mg, 0.83 mmol, 83 %) was isolated as a dark yellow oil.

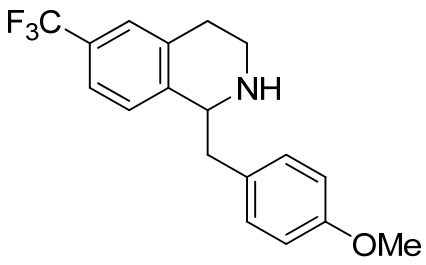
^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.78 (br. s, 1 H), 2.75-2.97 (m, 4 H), 3.19-3.25 (m, 2 H), 4.22 (dd, *J* = 9.9, 3.4 Hz, 1 H), 7.19 (d, *J* = 8.3 Hz, 2 H), 7.29-7.32 (m, 3 H), 7.38 (s, 1 H), 7.41 (d, *J* = 8.1 Hz, 1 H) ppm.

^{13}C NMR (126 MHz, DEPT, $CDCl_3$): δ = 29.9 (CH_2), 40.3 (CH_2), 41.7 (CH_2), 57.0 (CH), 122.4 (q, *J* = 3 Hz, CH), 124.2 (q, *J* = 272 Hz, CF_3), 126.2 (d, *J* = 3 Hz, CH), 126.6 (CH), 128.5 (q, *J* = 32 Hz, C), 128.8 (CH), 130.6 (CH), 132.5 (C), 136.1 (C), 137.0 (C), 142.2 (C) ppm.

IR (neat): $\tilde{\nu}$ = 2928, 2811, 1491, 1426, 1337, 1320, 1161, 1116, 1074, 1015, 826 cm^{-1}.

MS (CI): *m/z* (%) = 328 (24) [M + H, ^{37}Cl]$^+$, 326 (80) [M + H, ^{35}Cl]$^+$, 200 (100), 61 (10).

HRMS: (CI) calcd. ($C_{17}H_{16}ClF_3N$) 326.0923; found 326.0916.



$C_{18}H_{18}F_3NO$
MW: 321.34

1-(4-Methoxybenzyl)-6-(trifluoromethyl)-1,2,3,4-tetrahydroisoquinoline (***rac*-161**): In a Schlenk tube, a mixture of aminoalkyne **133** (239 mg, 0.75 mmol) and Ind_2TiMe_2 (12 mg, 0.04 mmol, 5 mol%) in toluene (1 mL) was stirred at 105 °C for 16 h. The resulting dark brown solution was cooled to room temperature and a mixture of $NaBH_3CN$ (94 mg, 1.50 mmol) and $ZnCl_2$ (102 mg, 0.75 mmol) in MeOH (5.0 mL) was added. After this had been stirred at 25 °C for 24 h, saturated NH_4Cl solution (25

mL) was added and the mixture was extracted with CH_2Cl_2 (5 × 25 mL). The combined organic layers were dried ($MgSO_4$) and concentrated under vacuum. After purification by flash chromatography (SiO_2, 40 g, MTBE/7 N NH_3 in MeOH 98:2, R_f = 0.42), ***rac*-161** (203 mg, 0.63 mmol, 84 %) was isolated as a light yellow oil.

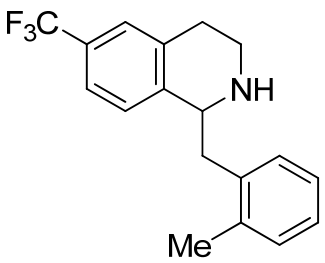
^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.21 (br. s, 1 H), 2.75-2.98 (m, 4 H), 3.12-3.30 (m, 2 H), 3.80 (s, 3 H), 4.19 (dd, *J* = 9.8, 3.5 Hz, 1 H), 6.87 (d, *J* = 8.5 Hz, 2 H), 7.16 (d, *J* = 8.5 Hz, 2 H), 7.31 (d, *J* = 8.1 Hz, 1 H), 7.36 (s, 1 H), 7.40 (d, *J* = 8.2 Hz, 1 H) ppm.

^{13}C NMR (126 MHz, DEPT, $CDCl_3$): δ = 29.9 (CH_2), 40.3 (CH_2), 41.4 (CH_2), 55.2 (CH_3), 57.2 (CH), 114.2 (CH), 122.4 (q, *J* = 4 Hz, CH), 124.3 (q, *J* = 272 Hz, CF_3), 126.1 (q, *J* = 4 Hz, CH), 126.7 (CH), 128.4 (q, *J* = 32 Hz, C), 130.2 (CH), 130.4 (C), 136.1 (C), 142.6 (C), 158.5 (C) ppm.

IR (neat): $\tilde{\nu}$ = 2935, 2838, 1513, 1428, 1339, 1323, 1248, 1163, 1118, 1077, 1036, 830 cm^{-1}.

MS (CI): *m/z* (%) = 322 (100) $[M + H]^+$, 302 (10), 200 (32), 121 (2).

HRMS: (CI) calcd. ($C_{18}H_{19}F_3NO$) 322.1419; found 322.1417



$C_{18}H_{18}F_3N$
MW: 305.34

1-(2-Methylbenzyl)-6-(trifluoromethyl)-1,2,3,4-tetrahydroisoquinoline (***rac*-162**): In a Schlenk tube, a mixture of aminoalkyne **134** (303 mg, 1.00 mmol) and Ind_2TiMe_2 (15 mg, 0.05 mmol, 5 mol%) in toluene (1 mL) was stirred at 105 °C for 16 h. The resulting dark brown solution was cooled to room temperature and a mixture of $NaBH_3CN$ (126 mg, 2.00 mmol) and $ZnCl_2$ (136 mg, 1.00 mmol) in MeOH (5.0 mL)

was added. After this had been stirred at 25 °C for 24 h, saturated NH_4Cl solution (25 mL) was added and the mixture was extracted with CH_2Cl_2 (5 × 25 mL). The combined organic layers were dried ($MgSO_4$) and concentrated under vacuum. After purification by flash chromatography (SiO_2, 27 g, MTBE/7 N NH_3 in MeOH 98:2, R_f = 0.43), ***rac*-162** (255 mg, 0.84 mmol, 84 %) was isolated as a light brown oil.

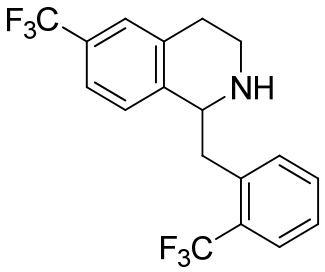
^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.73 (br. s, 1 H), 2.40 (s, 3 H), 2.81-2.99 (m, 4 H), 3.23-3.30 (m, 2 H), 4.22 (dd, *J* = 10.3, 2.8 Hz, 1 H), 7.16-7.23 (m, 4 H), 7.29 (d, *J* = 8.0 Hz, 1 H), 7.40 (d, *J* = 9.8 Hz, 2 H) ppm.

^{13}C NMR (126 MHz, DEPT, $CDCl_3$): δ = 19.7 (CH_3), 30.0 (CH_2), 39.7 (CH_2), 40.1 (CH_2), 55.8 (CH_3), 122.3 (q, *J* = 3 Hz, CH), 124.2 (q, *J* = 272 Hz, CF_3), 126.1 (CH), 126.1 (q, *J* = 5 Hz, CH), 126.7 (CH), 126.8 (CH), 128.4 (q, *J* = 32 Hz, C), 130.2 (CH), 130.7 (CH), 136.1 (C), 136.6 (C), 136.9 (C), 142.9 (C) ppm.

IR (neat): $\tilde{\nu}$ = 3018, 2927, 2809, 1426, 1337, 1320, 1161, 1115, 1075, 751, 739 cm^{-1}.

MS (CI): *m/z* (%) = 306 (86) $[M + H]^+$, 304 (7), 200 (100).

HRMS: (CI) calcd. ($C_{18}H_{19}F_3N$) 306.1470; found 306.1465.



$C_{18}H_{15}F_6N$
MW: 359.31

6-(Trifluoromethyl)-1-(2-(trifluoromethyl)benzyl)-1,2,3,4-tetrahydroisoquinoline (***rac*-163**): In a Schlenk tube, a mixture of aminoalkyne **135** (357 mg, 1.00 mmol) and Ind_2TiMe_2 (15 mg, 0.05 mmol, 5 mol%) in toluene (1 mL) was stirred at 105 °C for 15 h. The resulting dark brown solution was cooled to room temperature and a mixture

of $NaBH_3CN$ (126 mg, 2.00 mmol) and $ZnCl_2$ (136 mg, 1.00 mmol) in MeOH (5.0 mL) was added. After this had been stirred at 25 °C for 24 h, saturated NH_4Cl solution (25 mL) was added and the mixture was extracted with CH_2Cl_2 (5 × 25 mL). The combined organic layers were dried ($MgSO_4$) and concentrated under vacuum. After purification by flash chromatography (SiO_2, 30 g, MTBE/7 N NH_3 in MeOH 95:5, R_f = 0.47), ***rac*-163** (282 mg, 0.79 mmol, 79 %) was isolated as a light brown oil.

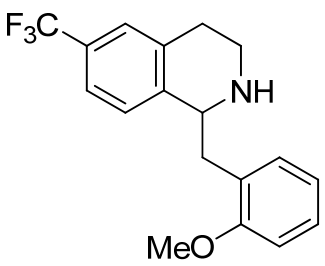
^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.65 (br. s, 1 H), 2.82-2.95 (m, 2 H), 2.98-3.07 (m, 2 H), 3.24-3.32 (m, 1 H), 3.39-3.46 (m, 1 H), 4.29 (d, *J* = 10.4 Hz, 1 H), 7.32 (d, *J* = 8.1 Hz, 1 H), 7.35-7.44 (m, 4 H), 7.53 (t, *J* = 7.5 Hz, 1 H), 7.71 (d, *J* = 7.9 Hz, 1 H) ppm.

^{13}C NMR (126 MHz, DEPT, $CDCl_3$): δ = 29.9 (CH_2), 39.0 (CH_2), 39.3 (CH_2), 56.2 (CH), 122.6 (q, *J* = 3 Hz, CH), 124.2 (q, *J* = 272 Hz, CF_3), 124.7 (q, *J* = 274 Hz, CF_3), 126.2 (q, *J* = 4 Hz, CH), 126.5 (q, *J* = 6 Hz, CH), 126.8 (CH), 127.1 (CH), 128.5 (q, *J* = 32 Hz, C), 129.0 (q, *J* = 30 Hz, C), 131.7 (CH), 132.4 (CH), 136.0 (C), 137.5 (C), 142.6 (C) ppm.

IR (neat): $\tilde{\nu}$ = 2930, 2836, 1607, 1582, 1453, 1427, 1311, 1158, 1107, 1075, 1060, 1037, 766 cm^{-1}.

MS (CI): *m/z* (%) = 360 (100) $[M + H]^+$, 200 (55).

HRMS: (CI) calcd. ($C_{18}H_{16}F_6N$) 360.1187; found 360.1192.



$C_{18}H_{18}F_3NO$
MW: 321.34

1-(2-Methoxybenzyl)-6-(trifluoromethyl)-1,2,3,4-tetrahydroisoquinoline (***rac*-164**): In a Schlenk tube, a mixture of aminoalkyne **136** (319 mg, 1.00 mmol) and

Ind_2TiMe_2 (15 mg, 0.05 mmol, 5 mol%) in toluene (1 mL) was stirred at 105 °C for 16 h. The resulting dark brown solution was cooled to room temperature and a mixture of $NaBH_3CN$ (126 mg, 2.00 mmol) and $ZnCl_2$ (136 mg, 1.00 mmol) in MeOH (5.0 mL) was added. After this had been stirred at 25 °C for 24 h, saturated NH_4Cl solution (25 mL) was added and the mixture was extracted with CH_2Cl_2 (5 × 25 mL). The combined organic layers were dried ($MgSO_4$) and concentrated under vacuum. After purification by flash chromatography (SiO_2, 30 g, MTBE/7 N NH_3 in MeOH 98:2, R_f = 0.61), ***rac*-164** (275 mg, 0.86 mmol, 86 %) was isolated as a yellow oil.

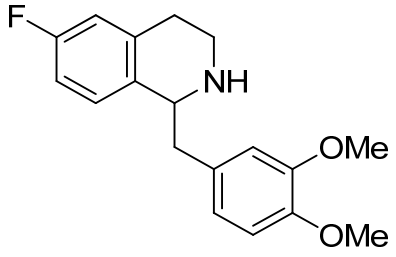
^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.84 (br. s, 1 H), 2.83 (dd, *J* = 11.6, 8.5 Hz, 1 H), 2.85-2.89 (m, 2 H), 2.91-2.97 (m, 1 H), 3.24-3.29 (m, 1 H), 3.31 (dd, *J* = 13.5, 3.6 Hz, 1 H), 3.86 (s, 3 H), 4.30 (dd, *J* = 10.0, 2.4 Hz, 1 H), 6.89-6.95 (m, 2 H), 7.17 (dd, *J* = 7.3, 1.1 Hz, 1 H), 7.26 (dt, *J* = 8.0, 1.5 Hz, 1 H), 7.35-7.38 (m, 2 H), 7.40 (d, *J* = 8.3 Hz, 1 H) ppm.

^{13}C NMR (126 MHz, DEPT, $CDCl_3$): δ = 29.9 (CH_2), 37.5 (CH_2), 39.6 (CH_2), 55.3 (CH_3), 55.4 (CH), 110.4 (CH), 120.5 (CH), 122.2 (q, *J* = 3 Hz, CH), 124.3 (q, *J* = 272 Hz, CF_3), 125.9 (q, *J* = 4 Hz, CH), 127.2 (CH), 127.2 (C), 128.0 (CH), 128.1 (q, *J* = 32 Hz, C), 131.2 (CH), 135.9 (C), 143.4 (C), 157.7 (C) ppm.

IR (neat): $\tilde{\nu}$ = 2927, 2836, 1493, 1427, 1337, 1320, 1242, 1160, 1112, 1074, 752 cm^{-1}.

MS (CI): *m/z* (%) = 322 (100) $[M + H]^+$, 320 (6), 200 (77).

HRMS: (CI) calcd. ($C_{18}H_{19}F_3NO$) 322.1419; found 322.1415.



$C_{18}H_{20}FNO_2$
MW: 301.36

1-(3,4-Dimethoxybenzyl)-6-fluoro-1,2,3,4-tetrahydroisoquinoline (***rac*-165**): In a Schlenk tube, a mixture of aminoalkyne **137** (209 mg, 0.70 mmol) and Ind_2TiMe_2 (11 mg, 0.04 mmol, 5 mol%) in toluene (0.10 mL) was stirred at 105 °C for 16 h. The resulting dark brown solution was cooled to room temperature and a mixture of $NaBH_3CN$ (88 mg, 1.40 mmol) and $ZnCl_2$ (95 mg, 0.70 mmol) in MeOH (5.0 mL) was added. After this had been stirred at 25 °C for 24 h, saturated NH_4Cl solution (25 mL) was added and the mixture was extracted with CH_2Cl_2 (5 × 25 mL). The combined organic layers were dried ($MgSO_4$) and concentrated under vacuum. After purification by flash chromatography (SiO_2, 20 g, MTBE/7 N NH_3 in MeOH 95:5, R_f = 0.20), ***rac*-165** (198 mg, 0.66 mmol, 94 %) was isolated as a yellow oil.

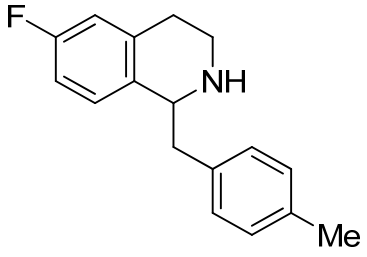
^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.88-1.96 (br s, 1 H), 2.70-2.92 (m, 4 H), 3.16-3.22 (m, 2 H), 3.85 (s, 3 H), 3.87 (s, 3 H), 4.14 (dd, *J* = 9.6, 3.6 Hz, 1 H), 6.74 (d, *J* = 1.6 Hz, 1 H), 6.84 (m, 4 H), 7.18 (dd, *J* = 8.5, 5.8 Hz, 1 H) ppm.

^{13}C NMR (126 MHz, DEPT, $CDCl_3$): δ = 30.5 (CH_2), 41.0 (CH_2), 42.5 (CH_2), 56.3 (CH_3), 56.3 (CH_3), 111.8 (CH), 112.8 (CH), 113.1 (d, *J* = 21 Hz, CH), 115.8 (d, *J* = 20 Hz, CH), 121.8 (CH), 128.1 (d, *J* = 8 Hz, CH), 131.6 (C), 134.7 (d, *J* = 3 Hz, C), 138.0 (d, *J* = 7 Hz, C), 148.2 (C), 149.4 (C), 161.5 (d, *J* = 244 Hz, CF) ppm.

IR (neat): $\tilde{\nu}$ = 3000, 2933, 2834, 2360, 2341, 1612, 1589, 1514, 1497, 1463, 1450, 1418, 1330, 1261, 1239, 1027, 935, 914, 857, 810, 763 cm^{-1}.

MS (ESI, CH_2Cl_2): *m/z* (%) = 302 (30) $[M + H]^+$, 151 (5), 150 (100), 147 (5).

HRMS (ESI, CH_2Cl_2): calcd. ($C_{18}H_{20}NO_2F$ + H) 302.1556; found 302.1555.



$C_{17}H_{18}FN$
MW: 255.33

6-Fluoro-1-(4-methylbenzyl)-1,2,3,4-tetrahydroisoquinoline (***rac*-166**): In a Schlenk tube, a mixture of aminoalkyne **138** (228 mg, 0.90 mmol) and Ind_2TiMe_2 (14 mg, 0.05 mmol, 5 mol%) in toluene (1 mL) was stirred at 105 °C for 16 h. The resulting dark brown solution was cooled to room temperature and a mixture of $NaBH_3CN$ (113 mg, 1.80 mmol) and $ZnCl_2$ (123 mg, 0.90 mmol) in MeOH (5.0 mL) was added. After this had been stirred at 25 °C for 24 h, saturated NH_4Cl solution (25 mL) was added and the mixture was extracted with CH_2Cl_2 (5 × 25 mL). The combined organic layers were dried ($MgSO_4$) and concentrated under vacuum. After purification by flash chromatography (SiO_2, 30 g, MTBE/7 N NH_3 in MeOH 99:1, R_f = 0.42), ***rac*-166** (201 mg, 0.79 mmol, 88 %) was isolated as a yellow oil.

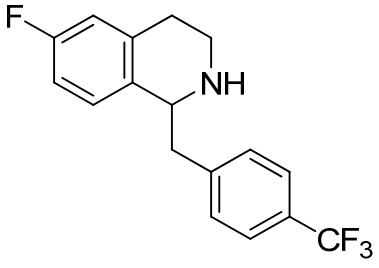
^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.89 (br. s, 1 H), 2.34 (s, 3 H), 2.71-2.92 (m, 4 H), 3.15-3.22 (m, 2 H), 4.10-4.16 (m, 1 H), 6.79 (dd, *J* = 9.6, 2.3 Hz, 1 H), 6.86 (dt, *J* = 8.5, 2.3 Hz, 1 H), 7.14 (s, 4 H), 7.18 (dd, *J* = 8.4, 5.9 Hz, 1 H) ppm.

^{13}C NMR (126 MHz, DEPT, $CDCl_3$): δ = 21.0 (CH_3), 30.1 (CH_2), 40.3 (CH_2), 42.0 (CH_2), 56.9 (CH), 112.7 (d, *J* = 21 Hz, CH), 115.3 (d, *J* = 20 Hz, CH), 127.6 (d, *J* = 8 Hz, CH), 129.1 (CH), 129.3 (CH), 134.4 (d, *J* = 3 Hz, C), 135.7 (C), 136.0 (C), 137.4 (d, *J* = 7 Hz, C), 161.0 (d, *J* = 245 Hz, CF) ppm.

IR (neat): $\tilde{\nu}$ = 3020, 2921, 2833, 1615, 1590, 1514, 1496, 1445, 1427, 1252, 1233, 1142, 1111, 810 cm^{-1}.

MS (CI): *m/z* (%) = 256 (100) $[M + H]^+$, 150 (95), 105 (3).

HRMS: (CI) calcd. ($C_{17}H_{19}F_3N$) 256.1502; found 256.1507.



$C_{17}H_{15}F_4N$
MW: 309.30

6-Fluoro-1-(4-(trifluoromethyl)benzyl)-1,2,3,4-tetrahydroisoquinoline (***rac*-167**): In a Schlenk tube, a mixture of aminoalkyne **139** (200 mg, 0.65 mmol) and Ind_2TiMe_2 (10 mg, 0.03 mmol, 5 mol%) in toluene (1 mL) was stirred at 105 °C for 16 h. The resulting dark brown solution was cooled to room temperature and a mixture of $NaBH_3CN$ (82 mg, 1.30 mmol) and $ZnCl_2$ (89 mg, 0.65 mmol) in MeOH (5.0 mL) was added. After this had been stirred at 25 C for 24 h, saturated NH_4Cl solution (25 mL) was added and the mixture was extracted with CH_2Cl_2 (5 × 25 mL). The combined organic layers were dried ($MgSO_4$) and concentrated under vacuum. After purification by flash chromatography (SiO_2, 16 g, MTBE/7 N NH_3 in MeOH 99:1, R_f = 0.23), ***rac*-167** (166 mg, 0.54 mmol, 83 %) was isolated as a light yellow oil.

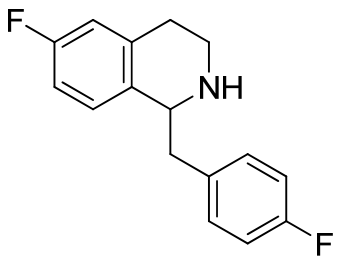
^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.66 (br. s, 1 H), 2.69-2.85 (m, 2 H), 2.88-2.97 (m, 2 H), 3.15-3.28 (m, 2 H), 4.20 (dd, *J* = 9.9, 3.7 Hz, 1 H), 6.80 (dd, *J* = 9.5, 2.6 Hz, 1 H), 6.86 (td, *J* = 8.5, 2.7 Hz, 1 H), 7.15 (dd, *J* = 8.6, 5.7 Hz, 1 H), 7.36 (d, *J* = 8.0 Hz, 2 H), 7.58 (d, *J* = 8.1 Hz, 2 H) ppm.

^{13}C NMR (126 MHz, DEPT, $CDCl_3$): δ = 30.0 (CH_2), 40.3 (CH_2), 42.5 (CH_2), 56.6 (CH), 112.9 (d, *J* = 22 Hz, CH), 115.5 (d, *J* = 21 Hz, CH), 124.3 (q, *J* = 272 Hz, CF_3), 125.4 (q, *J* = 4 Hz, CH), 127.6 (d, *J* = 8 Hz, CH), 128.9 (q, *J* = 33 Hz, C), 129.6 (CH), 133.9 (d, *J* = 3 Hz, C), 137.6 (d, *J* = 7 Hz, C), 143.2 (C), 161.1 (d, *J* = 245 Hz, CF) ppm.

IR (neat): $\tilde{\nu}$ = 3358, 3260, 3173, 2929, 2211, 1604, 1596, 1507, 1440, 1286, 1246, 1176, 1106, 1024, 997, 897, 832, 762 cm^{-1}.

MS (CI): *m/z* (%) = 310 (100) $[M + H]^+$, 150 (93).

HRMS: (CI) calcd. ($C_{17}H_{16}F_4N$) 310.1219; found 310.1222.



$C_{16}H_{15}F_2N$
MW: 259.29

6-Fluoro-1-(4-fluorobenzyl)-1,2,3,4-tetrahydroisoquinoline (***rac*-168**): In a Schlenk tube, a mixture of aminoalkyne **140** (257 mg, 1.00 mmol) and Ind_2TiMe_2 (15 mg, 0.05 mmol, 5 mol%) in toluene (1 mL) was stirred at 105 °C for 16 h. The resulting dark brown solution was cooled to room temperature and a mixture of $NaBH_3CN$ (126 mg, 2.00 mmol) and $ZnCl_2$ (136 mg, 1.00 mmol) in MeOH (5.0 mL) was added. After this had been stirred at 25 °C for 24 h, saturated NH_4Cl solution (25 mL) was added and the mixture was extracted with CH_2Cl_2 (5 × 25 mL). The combined organic layers were dried ($MgSO_4$) and concentrated under vacuum. After purification by flash chromatography (SiO_2, 30 g, MTBE/7 N NH_3 in MeOH 98:2, R_f = 0.55), ***rac*-168** (200 mg, 0.77 mmol, 77 %) was isolated as a yellow oil.

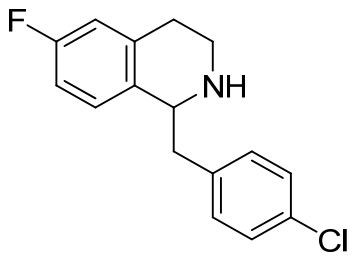
^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.73 (br. s, 1 H), 2.71-2.78 (m, 1 H), 2.79-2.93 (m, 3 H), 4.13 (dd, *J* = 9.9, 3.6 Hz, 1 H), 6.80 (dd, *J* = 9.5, 2.3 Hz, 1 H), 6.86 (dt, *J* = 8.5, 2.6 Hz, 1 H), 7.01 (t, *J* = 8.6 Hz, 2 H), 7.15 (dd, *J* = 8.5, 5.8 Hz, 1 H), 7.20 (dd, *J* = 8.3, 5.6 Hz, 2 H) ppm.

^{13}C NMR (126 MHz, DEPT, $CDCl_3$): δ = 30.0 (CH_2), 40.3 (CH_2), 41.7 (CH_2), 56.8 (CH), 112.8 (d, *J* = 21 Hz, CH), 115.4 (d, *J* = 21 Hz, CH), 115.4 (d, *J* = 20 Hz, CH), 127.6 (d, *J* = 8 Hz, CH), 130.7 (d, *J* = 8 Hz, CH), 134.1 (d, *J* = 2 Hz, C), 134.4 (d, *J* = 3 Hz, C), 137.5 (d, *J* = 7 Hz, C), 161.0 (d, *J* = 244 Hz, CF), 161.6 (d, *J* = 245 Hz, CF) ppm.

IR (neat): $\tilde{\nu}$ = 3040, 2926, 2834, 1600, 1508, 1427, 1220, 1157, 815 cm^{-1}.

MS (CI): *m/z* (%) = 260 (79) $[M + H]^+$, 150 (100), 109 (6).

HRMS: (CI) calcd. ($C_{16}H_{16}F_2N$) 260.1251; found 260.1254.



$C_{16}H_{15}ClFN$
MW: 275.75

1-(4-Chlorobenzyl)-6-fluoro-1,2,3,4-tetrahydroisoquinoline (***rac*-169**): In a Schlenk tube, a mixture of aminoalkyne **141** (252 mg, 0.92 mmol) and Ind_2TiMe_2 (14 mg, 0.05 mmol, 5 mol%) in toluene (1 mL) was stirred at 105 °C for 12 h. The resulting dark brown solution was cooled to room temperature and a mixture of $NaBH_3CN$ (116 mg, 1.84 mmol) and $ZnCl_2$ (125 mg, 0.92 mmol) in MeOH (5.0 mL) was added. After this had been stirred at 25 C for 24 h, saturated NH_4Cl solution (25 mL) was added and the mixture was extracted with CH_2Cl_2 (5 × 25 mL). The combined organic layers were dried ($MgSO_4$) and concentrated under vacuum. After purification by flash chromatography (SiO_2, 20 g, MTBE/7 N NH_3 in MeOH 95:5, R_f = 0.34), ***rac*-169** (192 mg, 0.70 mmol, 76 %) was isolated as a light yellow oil.

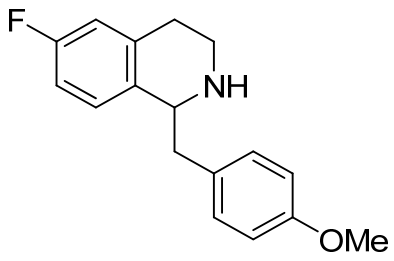
^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.76 (br. s, 1 H), 2.68-2.97 (m, 4 H), 3.11-3.24 (m, 2 H), 4.14 (dd, *J* = 9.8, 3.5 Hz, 1 H), 6.81 (dd, *J* = 9.5, 2.4 Hz, 1 H), 6.86 (dt, *J* = 8.5, 2.6 Hz, 1 H), 7.15 (dd, *J* = 8.6, 5.8 Hz, 1 H), 7.18 (d, *J* = 8.3 Hz, 2 H), 7.29 (d, *J* = 8.2 Hz, 2 H) ppm.

^{13}C NMR (126 MHz, DEPT,$CDCl_3$): δ = 30.0 (CH_2), 40.3 (CH_2), 41.9 (CH_2), 56.7 (CH), 112.8 (d, *J* = 21 Hz, CH), 115.5 (d, *J* = 20 Hz, CH), 127.6 (d, *J* = 8 Hz, CH), 128.7 (CH), 130.6 (CH), 132.4 (C), 134.0 (d, *J* = 2 Hz, C), 137.3 (C), 137.5 (d, *J* = 7 Hz, C), 161.1 (d, *J* = 245 Hz, CF) ppm.

IR (neat): $\tilde{\nu}$ = 2930, 2841, 1613, 1588, 1491, 1237, 1228, 1090, 857, 811 cm^{-1}.

MS (CI): *m/z* (%) = 278 (10) [M + H, $^{37}Cl]^+$, 276 (21) [M + H, $^{35}Cl]^+$, 150 (100).

HRMS: (CI) calcd. ($C_{16}H_{16}ClFN$) 276.0955; found 276.0951.



$C_{17}H_{18}FNO$
MW: 271.33

6-Fluoro-1-(4-methoxybenzyl)-1,2,3,4-tetrahydroisoquinoline (***rac*-170**): In a Schlenk tube, a mixture of aminoalkyne **142** (199 mg, 0.74 mmol) and Ind_2TiMe_2 (11 mg, 0.04 mmol, 5 mol%) in toluene (1 mL) was stirred at 105 °C for 16 h. The resulting dark brown solution was cooled to room temperature and a mixture of $NaBH_3CN$ (93 mg, 1.48 mmol) and $ZnCl_2$ (101 mg, 0.74 mmol) in MeOH (5.0 mL) was added. After this had been stirred at 25 °C for 24 h, saturated NH_4Cl solution (25 mL) was added and the mixture was extracted with CH_2Cl_2 (5 × 25 mL). The combined organic layers were dried ($MgSO_4$) and concentrated under vacuum. After purification by flash chromatography (SiO_2, 23 g, MTBE/7 N NH_3 in MeOH 99:1, R_f = 0.25), ***rac*-170** (171 mg, 0.63 mmol, 85 %) was isolated as a light yellow oil.

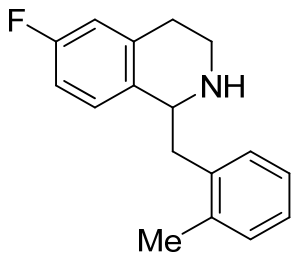
^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.91 (br. s, 1 H), 2.68-2.92 (m, 4 H), 3.11-3.21 (m, 2 H), 3.78 (s, 3 H), 4.10 (dd, *J* = 9.9, 3.8 Hz, 1 H), 6.78 (dd, *J* = 9.5, 2.6 Hz, 1 H), 6.81-6.88 (m, 3 H), 7.12-7.17 (m, 3 H) ppm.

^{13}C NMR (126 MHz, DEPT, $CDCl_3$): δ = 30.0 (CH_2), 40.3 (CH_2), 41.5 (CH_2), 55.1 (CH_3), 56.8 (CH), 112.6 (d, *J* = 21 Hz, CH), 114.0 (CH), 115.3 (d, *J* = 20 Hz, CH), 127.6 (d, *J* = 8 Hz, CH), 130.2 (CH), 130.7 (C), 134.3 (C), 137.4 (d, *J* = 7 Hz, C), 158.3 (C), 161.0 (d, *J* = 245 Hz, CF) ppm.

IR (neat): $\tilde{\nu}$ = 2969, 2912, 2835, 1610, 1511, 1497, 1450, 1276, 1240, 1179, 1121, 1111, 1037, 991, 934, 852, 832, 821, 791, 772 cm^{-1}.

MS (CI): *m/z* (%) = 272 (100) $[M + H]^+$, 231 (5), 180 (2), 166 (12), 150 (46), 121 (3).

HRMS: (CI) calcd. ($C_{17}H_{19}FNO$) 272.1451; found 272.1447.



$C_{17}H_{18}FN$
MW: 255.33

6-Fluoro-1-(2-methylbenzyl)-1,2,3,4-tetrahydroisoquinoline (***rac*-171**): In a Schlenk tube, a mixture of aminoalkyne **143** (253 mg, 1.00 mmol) and Ind_2TiMe_2 (15 mg, 0.05 mmol, 5 mol%) in toluene (1 mL) was stirred at 105 °C for 16 h. The resulting dark brown solution was cooled to room temperature and a mixture of $NaBH_3CN$ (126 mg, 2.00 mmol) and $ZnCl_2$ (136 mg, 1.00 mmol) in MeOH (5.0 mL) was added. After this had been stirred at 25 C for 24 h, saturated NH_4Cl solution (25 mL) was added and the mixture was extracted with CH_2Cl_2 (5 × 25 mL). The combined organic layers were dried ($MgSO_4$) and concentrated under vacuum. After purification by flash chromatography (SiO_2, 27 g, MTBE/7 N NH_3 in MeOH 98:2, R_f = 0.36), ***rac*-171** (194 mg, 0.76 mmol, 76 %) was isolated as a light brown oil.

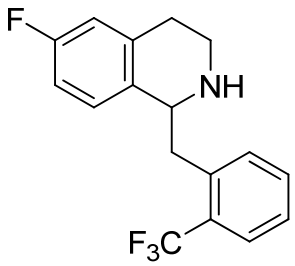
^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.95 (br. s, 1 H), 2.39 (s, 3 H), 2.76-2.96 (m, 4 H), 3.22 (d, *J* = 3.7 Hz, 1 H), 3.24 (d, *J* = 4.3 Hz, 1 H), 4.16 (dd, *J* = 10.2, 3.4 Hz, 1 H), 6.80-6.88 (m, 2 H), 7.12 (dd, *J* = 8.4, 5.8 Hz, 1 H), 7.15-7.22 (m, 4 H) ppm.

^{13}C NMR (126 MHz, DEPT, $CDCl_3$): δ = 19.6 (CH_3), 30.0 (CH_2), 39.9 (CH_2), 40.0 (CH_2), 55.4 (CH), 112.8 (d, *J* = 21 Hz, CH), 115.4 (d, *J* = 20 Hz, CH), 126.1 (CH), 126.7 (CH), 127.8 (d, *J* = 8 Hz, CH), 130.2 (CH), 130.6 (CH), 134.5 (d, *J* = 2 Hz, C), 136.6 (C), 137.2 (C), 137.4 (d, *J* = 7 Hz, C), 161.1 (d, *J* = 244 Hz, CF) ppm.

IR (neat): $\tilde{\nu}$ = 3019, 2925, 2806, 1614, 1589, 1496, 1446, 1252, 1232, 1124, 814, 746 cm^{-1}.

MS (CI): *m/z* (%) = 256 (84) $[M + H]^+$, 254 (4), 150 (100).

HRMS: (CI) calcd. ($C_{17}H_{19}FN$) 256.1502; found 256.1495.



$C_{17}H_{15}F_4N$
MW: 309.30

6-Fluoro-1-(2-(trifluoromethyl)benzyl)-1,2,3,4-tetrahydroisoquinoline (***rac*-172**): In a Schlenk tube, a mixture of aminoalkyne **144** (307 mg, 1.00 mmol) and Ind_2TiMe_2 (15 mg, 0.05 mmol, 5 mol%) in toluene (1 mL) was stirred at 105 °C for 15 h. The resulting dark brown solution was cooled to room temperature and a mixture of $NaBH_3CN$ (126 mg, 2.00 mmol) and $ZnCl_2$ (136 mg, 1.00 mmol) in MeOH (5.0 mL) was added. After this had been stirred at 25 C for 24 h, saturated NH_4Cl solution (25 mL) was added and the mixture was extracted with CH_2Cl_2 (5 × 25 mL). The combined organic layers were dried ($MgSO_4$) and concentrated under vacuum. After purification by flash chromatography (SiO_2, 30 g, MTBE/7 N NH_3 in MeOH 95:5, R_f = 0.43), ***rac*-172** (248 mg, 0.80 mmol, 80 %) was isolated as a light brown solid.
M.p.: 64 °C.

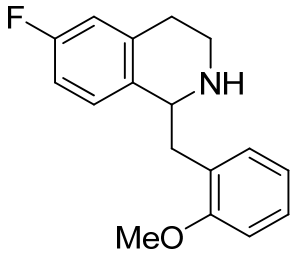
^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.64 (br. s, 1 H), 2.76-2.87 (m, 2 H), 2.95-3.05 (m, 2 H), 3.21-3.28 (m, 1 H), 3.37-3.43 (m, 1 H), 4.22 (dd, *J* = 10.3, 2.4 Hz, 1 H), 6.81 (dd, *J* = 9.5, 2.5 Hz, 1 H), 6.87 (dt, *J* = 8.5, 2.6 Hz, 1 H), 7.16 (dd, *J* = 8.5, 5.8 Hz, 1 H), 7.36 (t, *J* = 7.6 Hz, 1 H), 7.41 (d, *J* = 7.6 Hz, 1 H), 7.52 (t, *J* = 7.4 Hz, 1 H), 7.70 (d, *J* = 7.8 Hz, 1 H) ppm.

^{13}C NMR (126 MHz, DEPT, $CDCl_3$): δ = 30.0 (CH_2), 39.2 (CH_2), 39.3 (CH_2), 55.9 (CH), 113.0 (d, *J* = 21 Hz, CH), 115.4 (d, *J* = 20 Hz, CH), 124.7 (q, *J* = 274 Hz, CF_3), 126.4 (q, *J* = 6 Hz, CH), 126.6 (CH), 128.1 (d, *J* = 8 Hz, CH), 128.9 (q, *J* = 30 Hz, C), 131.6 (CH), 132.4 (CH), 134.3 (d, *J* = 3 Hz, C), 137.4 (d, *J* = 7 Hz, C), 137.8 (C), 161.1 (d, *J* = 245 Hz, CF) ppm.

IR (neat): $\tilde{\nu}$ = 3339, 3039, 2940, 2835, 1611, 1582, 1494, 1455, 1305, 1228, 1155, 1120, 1100, 1063, 1035, 983, 861, 760 cm^{-1}.

MS (CI): *m/z* (%) = 310 (67) $[M + H]^+$, 150 (100).

HRMS: (CI) calcd. ($C_{17}H_{16}F_4N$) 310.1219; found 310.1214.



$C_{17}H_{18}FNO$
MW: 271.33

6-Fluoro-1-(2-methoxybenzyl)-1,2,3,4-tetrahydroisoquinoline (***rac*-173**): In a Schlenk tube, a mixture of aminoalkyne **145** (269 mg, 1.00 mmol) and Ind_2TiMe_2 (15 mg, 0.05 mmol, 5 mol%) in toluene (1 mL) was stirred at 105 °C for 15 h. The resulting dark brown solution was cooled to room temperature and a mixture of $NaBH_3CN$ (126 mg, 2.00 mmol) and $ZnCl_2$ (136 mg, 1.00 mmol) in MeOH (5.0 mL) was added. After this had been stirred at 25 C for 24 h, saturated NH_4Cl solution (25 mL) was added and the mixture was extracted with CH_2Cl_2 (5 × 25 mL). The combined organic layers were dried ($MgSO_4$) and concentrated under vacuum. After purification by flash chromatography (SiO_2, 30 g, MTBE/7 N NH_3 in MeOH 98:2, R_f = 0.54), ***rac*-173** (184 mg, 0.68 mmol, 68 %) was isolated as a orange-yellow oil.

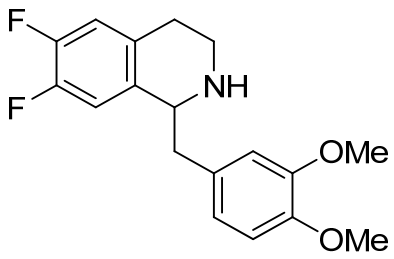
^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.88 (br. s, 1 H), 2.75-2.86 (m, 3 H), 2.87-2.93 (m, 1 H), 3.20-3.26 (m, 1 H), 3.28 (dd, *J* = 13.4, 3.5 Hz, 1 H), 3.85 (s, 3 H), 4.22 (dd, *J* = 10.0, 2.9 Hz, 1 H), 6.80 (dd, *J* = 9.5, 2.5 Hz, 1 H), 6.86 (dt, *J* = 8.5, 2.6 Hz, 1 H), 6.91 (dd, *J* = 13.3, 7.6 Hz, 2 H), 7.17 (dd, *J* = 7.3, 1.4 Hz, 1 H), 7.19-7.27 (m, 2 H) ppm.

^{13}C NMR (126 MHz, DEPT, $CDCl_3$): δ = 30.0 (CH_2), 37.6 (CH_2), 39.7 (CH_2), 55.0 (CH), 55.3 (CH_3), 110.4 (CH), 112.7 (d, *J* = 21 Hz, CH), 115.1 (d, *J* = 20 Hz, CH), 120.5 (CH), 127.5 (C), 127.8 (CH), 128.2 (d, *J* = 8 Hz, CH), 131.2 (CH), 135.0 (d, *J* = 3 Hz, C), 137.2 (d, *J* = 7 Hz, C), 157.7 (C), 161.0 (d, *J* = 244 Hz, CF) ppm.

IR (neat): $\tilde{\nu}$ = 2926, 2836, 1589, 1494, 1241, 1121, 1031, 815, 753 cm^{-1}.

MS (CI): *m/z* (%) = 272 (76) $[M + H]^+$, 150 (100).

HRMS: (CI) calcd. ($C_{17}H_{19}FNO$) 272.1451; found 272.1448.



$C_{18}H_{19}F_2NO_2$
MW: 319.35

1-(3,4-Dimethoxybenzyl)-6,7-difluoro-1,2,3,4-tetrahydroisoquinoline (***rac*-174**): In a Schlenk tube, a mixture of aminoalkyne **146** (159 mg, 0.50 mmol) and Ind_2TiMe_2 (9 mg, 0.03 mmol, 5 mol%) in toluene (0.25 mL) was stirred at 105 °C for 16 h. The resulting dark brown solution was cooled to room temperature and a mixture of $NaBH_3CN$ (63 mg, 1.00 mmol) and $ZnCl_2$ (68 mg, 0.50 mmol) in MeOH (5.0 mL) was added. After this had been stirred at 25 C for 24 h, saturated NH_4Cl solution (25 mL) was added and the mixture was extracted with CH_2Cl_2 (5 × 25 mL). The combined organic layers were dried ($MgSO_4$) and concentrated under vacuum. After purification by flash chromatography (SiO_2, 20 g, MTBE/7 N NH_3 in MeOH 95:5, R_f = 0.19), ***rac*-174** (154 mg, 0.48 mmol, 96 %) was isolated as a yellow solid.

M.p.: 61 °C

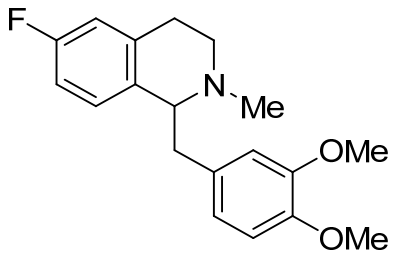
^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.88 (br s, 1 H), 2.63-2.93 (m, 4 H), 3.10-3.24 (m, 2 H), 3.86 (s, 3 H), 3.87 (s, 3 H), 4.08 (dd, *J* = 9.5, 3.3 Hz, 1 H), 6.74 (d, *J* = 1.7 Hz, 1 H), 6.78 (dd, *J* = 8.1, 1.7 Hz, 1 H), 6.84 (d, *J* = 8.1 Hz, 1 H), 6.89 (dd, *J* = 10.6, 8.5 Hz, 1 H), 7.03 (dd, *J* = 11.1, 8.3 Hz, 1 H) ppm.

^{13}C NMR (75 MHz, DEPT, $CDCl_3$): δ = 29.3 (CH_2), 40.7 (CH_2), 41.9 (CH_2), 55.8 (CH_3), 55.9 (CH_3), 56.7 (CH), 111.4 (CH), 112.3 (CH), 114.6 (dd, *J* = 16, 2 Hz, CH), 117.3 (dd, *J* = 14, 3 Hz, CH), 121.3 (CH), 130.7 (C), 131.9 (dd, *J* = 5, 4 Hz, C), 135.0 (t, *J* = 4 Hz, C), 147.8 (C), 148.3 (dd, *J* = 248, 12 Hz, CF), 148.5 (dd, *J* = 248, 12 Hz, CF), 149.0 (C) ppm.

IR (neat): $\tilde{\nu}$ = 3007, 2944, 2840, 2211, 1598, 1578, 1517, 1465, 1442, 1407, 1342, 1283, 1266, 1247, 1221, 1189, 1174, 1134, 1023, 882, 863, 808, 765 cm^{-1}.

MS (EI): *m/z* (%) = 319 (2) $[M]^+$, 318 (2), 317 (3), 316 (3), 302 (4), 267 (5), 236 (4), 212 (4), 182 (18), 169 (41), 168 (100), 166 (15), 153 (16), 151 (17), 141 (7), 113 (6).

HRMS: calcd. ($C_{18}H_{19}NO_2F_2$) 319.1384; found 319.1399.



$C_{19}H_{22}FNO_2$
MW: 315.38

1-(3,4-Dimethoxybenzyl)-6-fluoro-2-methyl-1,2,3,4-tetrahydroisoquinoline (***rac*-175**): Aqueous CH_2O (0.5 mL, *c* = 37 %, 6.7 mmol) was added to a solution of ***rac*-165** (75 mg, 0.25 mmol) in MeOH (2.0 mL). After this mixture had been stirred at 25 °C for 3 h, $NaBH_4$ (95 mg, 2.50 mmol) was slowly added. Subsequently, the reaction mixture was stirred at 25 °C for additional 16 h. Then, saturated aqueous NH_4Cl (15 mL) was added and the mixture was extracted with CH_2Cl_2 (5 × 30 mL). The combined organic layers were dried with $MgSO_4$ and the solvent was removed under vacuum. After purification by flash chromatography (SiO_2, 10 g, MTBE/7 N NH_3 in MeOH 95:5, R_f = 0.21), ***rac*-176** (64 mg, 0.20 mmol, 81 %) was isolated as a yellow oil.

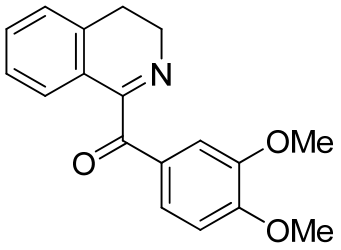
^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.52 (s, 3 H), 2.91-2.56 (m, 4 H), 3.19-3.04 (m, 2 H), 3.73-3.76 m (1 H), 3.76 (s, 3 H), 3.85 (s, 3 H), 6.51 (d, *J* = 1.7 Hz, 1 H), 6.61-6.78 (m, 5 H) ppm.

^{13}C NMR (126 MHz, DEPT, $CDCl_3$): δ = 26.4 (CH_2), 40.5 (CH_2), 42.8 (CH_3), 46.7 (CH_2), 55.7 (CH_3), 55.8 (CH_3), 64.6 (CH), 110.9 (CH), 112.2 (d, *J* = 21 Hz, CH), 112.9 (CH), 114.8 (d, *J* = 20 Hz, CH), 121.7 (CH), 129.5 (d, *J* = 8 Hz, CH), 132.0 (C), 133.2 (C), 136.6 (d, *J* = 7 Hz, C), 147.3 (C), 148.4 (C), 161.0 (d, *J* = 244 Hz, CF) ppm.

IR (neat): $\tilde{\nu}$ = 2934, 2834, 2787, 2359, 1613, 1590, 1514, 1496, 1464, 1417, 1374, 1260, 1235, 1155, 1139, 1029, 864, 808, 764 cm^{-1}.

MS (ESI, CH_2Cl_2): *m/z* (%) = 316 (38) [M^+ + H], 164 (100).

HRMS (ESI, CH_2Cl_2): calcd. ($C_{19}H_{22}NO_2F$ + H) 316.1713; found 316.1710.



$C_{18}H_{17}NO_3$
MW: 295.33

(3,4-Dihydroisoquinolin-1-yl)(3,4-dimethoxyphenyl)methanone (**187**): In a Schlenk tube, a mixture of aminoalkyne **119** (281 mg, 1.00 mmol) and Ind_2TiMe_2 (15 mg, 0.05 mmol, 5 mol%) in toluene (1.00 mL) was stirred at 105 °C for 16 h. The resulting dark brown solution was cooled to room temperature and treated with CH_3CN (3 mL) and 10% Pd/C (106 mg, 0.10 mmol Pd). After this had been stirred at 25 °C under O_2 atmosphere for 24 h, the reaction mixture was filtered over Celite and concentrated under vacuum. After purification by flash chromatography (SiO_2, 22 g, PE/EtOAc 50:50, R_f = 0.24), **187** (163 mg, 0.55 mmol, 55 %) was isolated as a yellow solid.

M.p.: 111.8 °C.

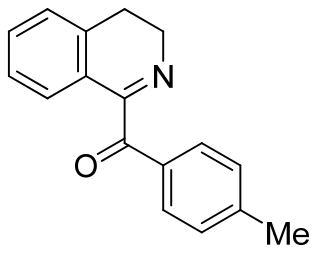
^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.89 (br. t, *J* = 7.6 Hz, 2 H), 3.91-4.01 (m, 9 H), 7.23-7.27 (m, 2 H), 7.33 (d, *J* = 7.4 Hz, 1 H), 7.40 (t, *J* = 7.4 Hz, 1 H), 7.59 (dd, *J* = 8.5, 1.8 Hz, 1 H), 7.68 (d, *J* = 1.7 Hz, 1 H) ppm.

^{13}C NMR (126 MHz, DEPT, $CDCl_3$) δ = 25.6 (CH_2), 47.3 (CH_2), 56.0 (CH_3), 56.1 (CH_3), 110.0 (CH), 111.0 (CH), 126.5 (CH), 126.6 (CH), 126.8 (C), 127.2 (CH), 127.8 (CH), 128.6 (C), 131.6 (CH), 137.1 (C), 149.2 (C), 154.2 (C), 165.5 (C), 192.7 (C) ppm.

IR (neat): $\tilde{\nu}$ = 3007, 2934, 2843, 1659, 1594, 1584, 1511, 1450, 1417, 1258, 1239, 1164, 1147, 1129, 1020, 741 cm^{-1}.

MS (CI): *m/z* (%) = 296 (100) $[M + H]^+$, 295 (21), 267 (11), 264 (36), 252 (11), 165 (17).

HRMS: (CI) calcd. ($C_{18}H_{18}NO_3$) 296.1287; found 296.1289.



$C_{17}H_{15}NO$
MW: 249.31

(3,4-Dihydroisoquinolin-1-yl)(p-tolyl)methanone (**188**): In a Schlenk tube, a mixture of aminoalkyne **120** (235 mg, 1.00 mmol) and Ind_2TiMe_2 (15 mg, 0.05 mmol, 5 mol%) in toluene (1 mL) was stirred at 105 °C for 12 h. The resulting dark brown solution was cooled to room temperature and treated with CH_3CN (3 mL) and 10% Pd/C (106 mg, 0.10 mmol Pd). After this had been stirred at 25 °C under O_2 atmosphere for 24 h, the reaction mixture was filtered over Celite and concentrated under vacuum. After purification by flash chromatography (SiO_2, 20 g, PE/EtOAc 80:20, R_f = 0.19), **214** (219 mg, 0.88 mmol, 88 %) was isolated as a yellow solid.

M.p.: 84 °C.

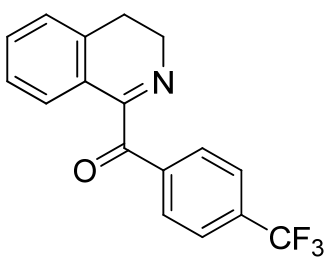
^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.27 (s, 3 H), 2.73 (t, *J* = 7.7 Hz, 2 H), 3.81-3.85 (m, 2 H), 7.06-7.16 (m, 4 H), 7.19-7.28 (m, 2 H), 7.82 (d, *J* = 8.2 Hz, 2 H) ppm.

^{13}C NMR (126 MHz, DEPT, $CDCl_3$) δ = 21.6 (CH_3), 25.3 (CH_2), 47.0 (CH_2), 126.3 (CH), 126.4 (C), 126.9 (CH), 127.6 (CH), 129.1 (CH), 130.2 (CH), 131.3 (CH), 132.8 (C), 136.9 (C), 144.7 (C), 165.2 (C), 193.4 (C) ppm.

IR (neat): $\tilde{\nu}$ = 2975, 2888, 2840, 1658, 1603, 1572, 1232, 1220, 1211, 1179, 1015, 904, 744 cm^{-1}.

MS (CI): *m/z* (%) = 250 (100) $[M + H]^+$, 249 (20), 221 (14), 119 (9).

HRMS: (CI) calcd. ($C_{17}H_{16}NO$) 250.1232; found 250.1263.



$C_{17}H_{12}F_3NO$
MW: 303.28

(3,4-Dihydroisoquinolin-1-yl)(4-(trifluoromethyl)phenyl)methanone (**189**): In a Schlenk tube, a mixture of aminoalkyne **121** (231 mg, 0.80 mmol) and Ind_2TiMe_2 (12 mg, 0.04 mmol, 5 mol%) in toluene (1 mL) was stirred at 105 °C for 16 h. The resulting dark brown solution was cooled to room temperature and treated with CH_3CN (3 mL) and 10% Pd/C (85 mg, 0.08 mmol Pd). After this had been stirred at 25 °C under O_2 atmosphere for 24 h, the reaction mixture was filtered over Celite and concentrated under vacuum. After purification by flash chromatography (SiO_2, 20 g, PE/EtOAc 80:20, R_f = 0.11), **189** (176 mg, 0.58 mmol, 73 %) was isolated as a yellow oil.

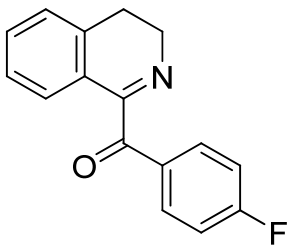
^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.88 (br. t, *J* = 7.7 Hz, 2 H), 3.99 (br. t, *J* = 7.7 Hz, 2 H), 7.26-7.31 (m, 2 H), 7.39-7.45 (m, 2 H), 7.74 (d, *J* = 8.3 Hz, 2 H), 8.15 (d, *J* = 8.2 Hz, 2 H) ppm.

^{13}C NMR (126 MHz, DEPT, $CDCl_3$): δ = 25.4 (CH_2), 47.5 (CH_2), 123.5 (q, *J* = 273 Hz, CF_3), 125.5 (q, *J* = 4 Hz, CH), 126.3 (C), 126.5 (CH), 127.2 (CH), 127.9 (CH), 130.7 (CH), 131.9 (CH), 134.8 (q, *J* = 33 Hz, C), 137.3 (C), 138.4 (C), 164.5 (C), 192.4 (C) ppm.

IR (neat): $\tilde{\nu}$ = 3068, 2949, 1680, 1409, 1322, 1166, 1124, 1068, 1016, 904, 761 cm^{-1}.

MS (CI): *m/z* (%) = 304 (100) $[M + H]^+$, 275 (13), 132 (3), 150 (9).

HRMS: (CI) calcd. ($C_{17}H_{13}F_3NO$) 304.0949; found 304.0953.



$C_{16}H_{12}FNO$
MW: 253.27

(3,4-Dihydroisoquinolin-1-yl)(4-fluorophenyl)methanone (**190**): In a Schlenk tube, a mixture of aminoalkyne **122** (239 mg, 1.00 mmol) and Ind_2TiMe_2 (15 mg, 0.05 mmol, 5 mol%) in toluene (1 mL) was stirred at 105 °C for 16 h. The resulting dark brown solution was cooled to room temperature and treated with CH_3CN (3 mL) and 10% Pd/C (106 mg, 0.10 mmol Pd). After this had been stirred at 25 °C under O_2 atmosphere for 24 h, the reaction mixture was filtered over Celite and concentrated under vacuum. After purification by flash chromatography (SiO_2, 20 g, PE/EtOAc 80:20, R_f = 0.42), **190** (197 mg, 0.78 mmol, 78 %) was isolated as a light yellow oil.

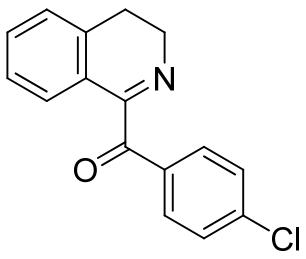
^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.88 (br. t, *J* = 7.7 Hz, 2 H), 3.97 (d, *J* = 6.1 Hz, 1 H), 3.98 (d, *J* = 7.6 Hz, 1 H), 7.14 (t, *J* = 8.6 Hz, 2 H), 7.24-7.28 (m, 2 H), 7.35 (d, *J* = 7.6 Hz, 1 H), 7.41 (dt, *J* = 7.4, 0.8 Hz, 1 H), 8.06-8.12 (m, 2 H) ppm.

^{13}C NMR (126 MHz, DEPT, $CDCl_3$): δ = 25.5 (CH_2), 47.3 (CH_2), 115.8 (d, *J* = 22 Hz, CH), 126.5 (CH), 127.2 (CH), 127.9 (CH), 131.7 (CH), 131.8 (C), 131.9 (C), 133.1 (d, *J* = 10 Hz, CH), 137.2 (C), 165.0 (C), 166.2 (d, *J* = 256 Hz, CF), 192.1 (C) ppm.

IR (neat): $\tilde{\nu}$ = 3071, 2946, 2896, 2846, 1669, 1594, 1504, 1411, 1316, 1226, 1210, 1153, 1016, 904, 846, 756, 738 cm^{-1}.

MS (CI): *m/z* (%) = 254 (100) $[M + H]^+$, 225 (12), 112 (13), 95 (12).

HRMS: (CI) calcd. ($C_{16}H_{13}FNO$) 254.0981; found 254.0987.



$C_{16}H_{12}ClNO$
MW: 269.73

(4-Chlorophenyl)(3,4-dihydroisoquinolin-1-yl)methanone (**191**): In a Schlenk tube, a mixture of aminoalkyne **123** (256 mg, 1.00 mmol) and Ind_2TiMe_2 (15 mg, 0.05 mmol, 5 mol%) in toluene (1 mL) was stirred at 105 °C for 16 h. The resulting dark brown solution was cooled to room temperature and treated with CH_3CN (3 mL) and 10% Pd/C (106 mg, 0.10 mmol Pd). After this had been stirred at 25 °C under O_2 atmosphere for 24 h, the reaction mixture was filtered over Celite and concentrated under vacuum. After purification by flash chromatography (SiO_2, 24 g, PE/EtOAc 80:20, R_f = 0.34), **191** (205 mg, 0.76 mmol, 76 %) was isolated as a light yellow oil.

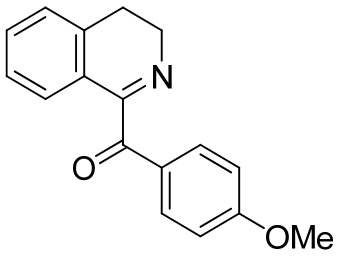
^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.88 (br. t, *J* = 7.6 Hz, 2 H), 3.98 (br. t, *J* = 7.7 Hz, 2 H), 7.24-7.29 (m, 2 H), 7.35 (d, *J* = 7.5 Hz, 1 H), 7.41 (t, *J* = 7.5 Hz, 1 H), 7.45 (d, *J* = 8.5 Hz, 2 H), 7.99 (d, *J* = 8.5 Hz, 2 H) ppm.

^{13}C NMR (126 MHz, DEPT, $CDCl_3$) δ = 25.5 (CH_2), 47.4 (CH_2), 126.5 (C), 126.5 (CH), 127.2 (CH), 127.9 (CH), 128.9 (CH), 131.8 (CH), 131.8 (CH), 133.8 (C), 137.2 (C), 140.4 (CCl), 164.8 (C), 192.4 (C) ppm.

IR (neat): $\tilde{\nu}$ = 3070, 2950, 2896, 2846, 1672, 1585, 1210, 1088, 1014, 903, 727 cm^{-1}.

MS (CI): *m/z* (%) = 272 (32) [M + H, ^{37}Cl]$^+$, 270 (100) [M + H, ^{35}Cl]$^+$, 268 (12), 241 (14).

HRMS: (CI) calcd. ($C_{16}H_{13}ClNO$) 270.0686; found 270.0681.



$C_{17}H_{15}NO_2$
MW: 265.31

(3,4-Dihydroisoquinolin-1-yl)(4-methoxyphenyl)methanone (**192**): In a Schlenk tube, a mixture of aminoalkyne **124** (201 mg, 0.80 mmol) and Ind_2TiMe_2 (12 mg, 0.04 mmol, 5 mol%) in toluene (1 mL) was stirred at 105 °C for 16 h. The resulting dark brown solution was cooled to room temperature and treated with CH_3CN (3 mL) and 10% Pd/C (85 mg, 0.08 mmol Pd). After this had been stirred at 25 °C under O_2 atmosphere for 24 h, the reaction mixture was filtered over Celite and concentrated under vacuum. After purification by flash chromatography (SiO_2, 19 g, PE/EtOAc 50:50, R_f = 0.400), **192** (172 mg, 0.65 mmol, 81 %) was isolated as an orange oil.

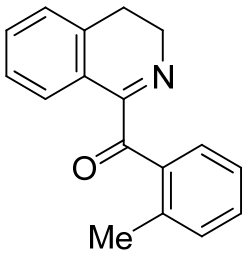
^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.88 (br. t, *J* = 7.6 Hz, 2 H), 3.85 (s, 3 H), 3.96 (br. t, *J* = 7.6 Hz, 2 H), 6.94 (d, *J* = 8.7 Hz, 2 H), 7.20-7.25 (m, 2 H), 7.31-7.41 (m, 2 H), 8.02 (d, *J* = 8.7 Hz, 2 H) ppm.

^{13}C NMR (126 MHz, DEPT, $CDCl_3$) δ = 25.5 (CH_2), 47.1 (CH_2), 55.5 (CH_3), 113.8 (CH), 126.6 (CH), 126.7 (C), 127.1 (CH), 127.7 (CH), 128.4 (C), 131.5 (CH), 132.7 (CH), 137.1 (C), 164.2 (C), 165.5 (C), 192.4 (C) ppm.

IR (neat): $\tilde{\nu}$ = 2942, 2842, 1662, 1596, 1574, 1511, 1423, 1313, 1589, 1218, 1166, 1020, 906, 844, 760, 740 cm^{-1}.

MS (CI): *m/z* (%) = 266 (100) $[M + H]^+$, 135 (12).

HRMS: (CI) calcd. ($C_{17}H_{16}NO_2$) 266.1181; found 266.1185.



$C_{17}H_{15}NO$
MW: 249.31

(3,4-Dihydroisoquinolin-1-yl)(o-tolyl)methanone (**193**): In a Schlenk tube, a mixture of aminoalkyne **125** (235 mg, 1.00 mmol) and Ind_2TiMe_2 (15 mg, 0.05 mmol, 5 mol%) in toluene (1 mL) was stirred at 105 °C for 14 h. The resulting dark brown solution was cooled to room temperature and treated with CH_3CN (3 mL) and 10% Pd/C (106 mg, 0.10 mmol Pd). After this had been stirred at 25 °C under O_2 atmosphere for 24 h, the reaction mixture was filtered over Celite and concentrated under vacuum. After purification by flash chromatography (SiO_2, 25 g, PE/EtOAc 50:50, R_f = 0.55), **193** (224 mg, 0.90 mmol, 90 %) was isolated as a light yellow oil.

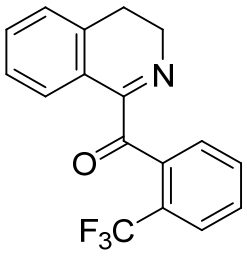
^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.59 (s, 3 H), 2.84 (br. t, J = 7.6 Hz, 2 H), 3.89-3.96 (m, 2 H), 7.22-7.31 (m, 4 H), 7.39-7.43 (m, 2 H), 7.47 (d, J = 7.7 Hz, 1 H), 7.64 (d, J = 7.9 Hz, 1 H) ppm.

^{13}C NMR (126 MHz, DEPT, $CDCl_3$) δ = 21.4 (CH_3), 25.5 (CH_2), 47.5 (CH_2), 125.6 (CH), 126.6 (C), 126.7 (CH), 127.1 (CH), 127.8 (CH), 131.5 (CH), 131.8 (CH), 131.8 (CH), 132.3 (CH), 135.8 (C), 137.4 (C), 139.9 (C), 166.2 (C), 196.4 (C) ppm.

IR (neat): $\tilde{\nu}$ = 3067, 3025, 2945, 2895, 2844, 1672, 1617, 1573, 1456, 1317, 1211, 1018, 904, 736 cm^{-1}.

MS (CI): *m/z* (%) = 250 (100) $[M + H]^+$, 249 (20), 234 (5), 221 (13).

HRMS: (CI) calcd. ($C_{17}H_{16}NO$) 250.1232; found 250.1230.



$C_{17}H_{12}F_3NO$
MW: 303.28

(3,4-Dihydroisoquinolin-1-yl)(2-(trifluoromethyl)phenyl)methanone (**194**): In a Schlenk tube, a mixture of aminoalkyne **126** (289 mg, 1.00 mmol) and Ind_2TiMe_2 (15 mg, 0.05 mmol, 5 mol%) in toluene (1 mL) was stirred at 105 °C for 15 h. The resulting dark brown solution was cooled to room temperature and treated with CH_3CN (3 mL) and 10% Pd/C (106 mg, 0.10 mmol Pd). After this had been stirred at 25 °C under O_2 atmosphere for 24 h, the reaction mixture was filtered over Celite and concentrated under vacuum. After purification by flash chromatography (SiO_2, 30 g, PE/EtOAc 50:50, R_f = 0.54), **194** (197 mg, 0.65 mmol, 65 %) was isolated as a yellow solid.

M.p.: 98 °C.

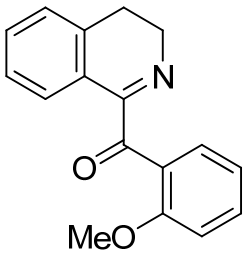
^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.75 (br. t, *J* = 7.5 Hz, 2 H), 3.86 (br. t, *J* = 7.5 Hz, 2 H), 7.23 (d, *J* = 7.4 Hz, 1 H), 7.36 (t, *J* = 7.5 Hz, 1 H), 7.40-7.46 (m, 1 H), 7.55-7.66 (m, 3 H), 7.71 (d, *J* = 7.6 Hz, 1 H), 7.86 (d, *J* = 7.6 Hz, 1 H) ppm.

^{13}C NMR (126 MHz, DEPT, $CDCl_3$): δ = 25.4 (CH_2), 47.9 (CH_2), 123.9 (q, *J* = 274 Hz, CF_3), 126.0 (C), 126.3 (q, *J* = 4 Hz, CH), 127.1 (CH), 127.4 (CH), 127.4 (CH), 127.9 (q, *J* = 32 Hz, C), 129.5 (CH), 130.4 (CH), 131.5 (CH), 131.6 (CH), 137.8 (C), 138.5 (C), 164.2 (C), 194.9 (C) ppm.

IR (neat): $\tilde{\nu}$ = 3030, 2960, 2842, 1692, 1607, 1572, 1315, 1165, 1108, 1076, 1032, 904, 773, 744 cm^{-1}.

MS (CI): *m/z* (%) = 304 (100) $[M + H]^+$, 275 (23), 234 (42), 173 (8).

HRMS: (CI) calcd. ($C_{17}H_{13}F_3NO$) 304.0949; found 304.0953.



$C_{17}H_{15}NO_2$
MW: 265.31

(3,4-Dihydroisoquinolin-1-yl)(2-methoxyphenyl)methanone (**195**): In a Schlenk tube, a mixture of aminoalkyne **127** (251 mg, 1.00 mmol) and Ind_2TiMe_2 (15 mg, 0.05 mmol, 5 mol%) in toluene (1 mL) was stirred at 105 °C for 16 h. The resulting dark brown solution was cooled to room temperature and treated with CH_3CN (3 mL) and 10% Pd/C (106 mg, 0.10 mmol Pd). After this had been stirred at 25 °C under O_2 atmosphere for 24 h, the reaction mixture was filtered over Celite and concentrated under vacuum. After purification by flash chromatography (SiO_2, 20 g, PE/EtOAc 50:50, R_f = 0.21), **195** (195 mg, 0.74 mmol, 74 %) was isolated as a yellow oil.

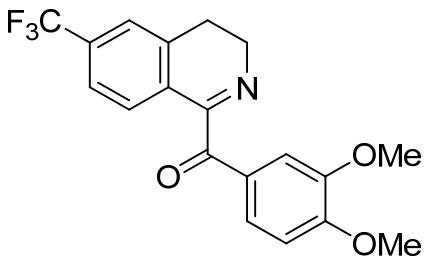
^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.82 (br. t, *J* = 7.5 Hz, 2 H), 3.62 (s, 3 H), 3.83 (br. t, *J* = 7.5 Hz, 2 H), 6.91 (d, *J* = 8.4 Hz, 1 H), 7.06 (t, *J* = 7.4 Hz, 1 H), 7.25 (t, *J* = 7.8 Hz, 2 H), 7.37-7.42 (m, 2 H), 7.48-7.53 (m, 1 H), 7.86 (dd, *J* = 7.7, 1.6 Hz, 1 H) ppm.

^{13}C NMR (126 MHz, DEPT, $CDCl_3$) δ = 25.6 (CH_2), 47.0 (CH_2), 55.5 (CH_3), 111.9 (CH), 120.9 (CH), 126.4 (CH), 126.4 (CH), 126.8 (C), 126.9 (CH), 127.5 (CH), 130.9 (CH), 131.1 (CH), 134.7 (CH), 137.3 (C), 159.3 (C), 166.9 (C), 194.7 (C) ppm.

IR (neat): $\tilde{\nu}$ = 3071, 2942, 2896, 2839, 1663, 1596, 1484, 1464, 1273, 1245, 1206, 1018, 905, 755, 738 cm^{-1}.

MS (CI): *m/z* (%) = 266 (100) $[M + H]^+$, 234 (56), 135 (11).

HRMS: (CI) calcd. ($C_{17}H_{16}NO_2$) 266.1181; found 266.1177.



$C_{19}H_{16}F_3NO_3$
MW: 363.33

(3,4-Dimethoxyphenyl)(6-(trifluoromethyl)-3,4-dihydroisoquinolin-1-yl)methanone (**196**): In a Schlenk tube, a mixture of aminoalkyne **128** (87 mg, 0.25 mmol) and Ind_2TiMe_2 (4 mg, 0.01 mmol, 5 mol%) in toluene (1 mL) was stirred at 105 °C for 14 h. The resulting dark brown solution was cooled to room temperature and treated with CH_3CN (3 mL) and 10% Pd/C (27 mg, 0.03 mmol Pd). After this had been stirred at 25 °C under O_2 atmosphere for 24 h, the reaction mixture was filtered over Celite and concentrated under vacuum. After purification by flash chromatography (SiO_2, 8 g, PE/EtOAc 50:50, R_f = 0.26), **196** (35 mg, 0.10 mmol, 39 %) was isolated as a yellow oil.

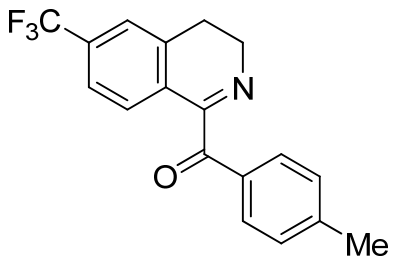
^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.95 (br. t, *J* = 7.6 Hz, 2 H), 3.95 (s, 3 H), 3.96 (s, 3 H), 4.03 (br. t, *J* = 7.6 Hz, 2 H), 6.89 (d, *J* = 8.4 Hz, 1 H), 7.48 (d, *J* = 8.5 Hz, 1 H), 7.50-7.54 (m, 2 H), 7.59 (dd, *J* = 8.3, 1.7 Hz, 1 H), 7.68 (s, 1 H) ppm.

^{13}C NMR (126 MHz, DEPT, $CDCl_3$): δ = 25.4 (CH_2), 47.0 (CH_2), 56.0 (CH_3), 56.2 (CH_3), 110.0 (CH), 111.1 (CH), 123.5 (q, *J* = 273 Hz, CF_3), 124.2 (q, *J* = 3 Hz, C), 124.7 (q, *J* = 4 Hz, CH), 126.6 (CH), 126.9 (CH), 128.2 (C), 129.3 (C), 132.9 (q, *J* = 33 Hz, C), 138.0 (C), 149.3 (C), 154.4 (C), 164.2 (C), 191.8 (C) ppm.

IR (neat): $\tilde{\nu}$ = 2942, 2842, 1658, 1583, 1511, 1420, 1321, 1260, 1165, 1119, 1080, 1018, 755 cm^{-1}.

MS (CI): *m/z* (%) = 364 (100) $[M + H]^+$, 263 (22), 360 (23), 332 (20), 200 (26), 165 (12).

HRMS: (CI) calcd. ($C_{19}H_{17}F_3NO_3$) 364.1161; found 364.1154.



$C_{18}H_{14}F_3NO$
MW: 317.31

p-Tolyl(6-(trifluoromethyl)-3,4-dihydroisoquinolin-1-yl)methanone (**197**): In a Schlenk tube, a mixture of aminoalkyne **129** (303 mg, 1.00 mmol) and Ind_2TiMe_2 (15 mg, 0.05 mmol, 5 mol%) in toluene (1 mL) was stirred at 105 °C for 12 h. The resulting dark brown solution was cooled to room temperature and treated with CH_3CN (3 mL) and 10% Pd/C (106 mg, 0.10 mmol Pd). After this had been stirred at 25 °C under O_2 atmosphere for 24 h, the reaction mixture was filtered over Celite and concentrated under vacuum. After purification by flash chromatography (SiO_2, 25 g, PE/EtOAc 80:20, R_f = 0.23), **197** (231 mg, 0.73 mmol, 73 %) was isolated as a yellow oil.

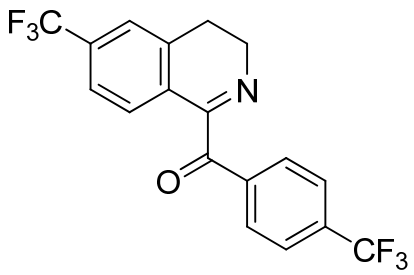
^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.42 (s, 3 H), 2.94 (br. t, *J* = 7.7 Hz, 2 H), 4.02 (br. t, *J* = 7.7 Hz, 2 H), 7.28 (d, *J* = 8.1 Hz, 1 H), 7.48-7.53 (m, 3 H), 7.94 (d, *J* = 8.2 Hz, 2 H) ppm.

^{13}C NMR (126 MHz, DEPT, $CDCl_3$): δ = 21.8 (CH_3), 25.3 (CH_2), 47.0 (CH_2), 123.5 (q, *J* = 273 Hz, CF_3), 124.1 (q, *J* = 4 Hz, CH), 124.7 (q, *J* = 4 Hz, CH), 126.9 (CH), 129.2 (C), 129.3 (CH), 130.5 (CH), 132.7 (C), 132.9 (q, *J* = 32 Hz, C), 138.0 (C), 145.3 (C), 164.1 (C), 192.8 (C) ppm.

IR (neat): $\tilde{\nu}$ = 2951, 2851, 1667, 1604, 1430, 1321, 1218, 1166, 1121, 1080, 1018, 904, 829, 748 cm^{-1}.

MS (CI): *m/z* (%) = 318 (100) $[M + H]^+$, 317 (34), 289 (14), 200 (9), 119 (16).

HRMS: (CI) calcd. ($C_{18}H_{15}F_3NO$) 318.1106; found 318.1110.



$C_{18}H_{11}F_6NO$
MW: 371.28

(6-(Trifluoromethyl)-3,4-dihydroisoquinolin-1-yl)(4-(trifluoromethyl)phenyl)methanone (**198**): In a Schlenk tube, a mixture of aminoalkyne **130** (268 mg, 0.75 mmol) and Ind_2TiMe_2 (12 mg, 0.04 mmol, 5 mol%) in toluene (1 mL) was stirred at 105 °C for 16 h. The resulting dark brown solution was cooled to room temperature and treated with CH_3CN (3 mL) and 10% Pd/C (80 mg, 0.08 mmol Pd). After this had been stirred at 25 °C under O_2 atmosphere for 24 h, the reaction mixture was filtered over Celite and concentrated under vacuum. After purification by flash chromatography (SiO_2, 17 g, PE/EtOAc 80:20, R_f = 0.39), **189** (159 mg, 0.43 mmol, 57 %) was isolated as a yellow solid.

M.p.: 103 °C.

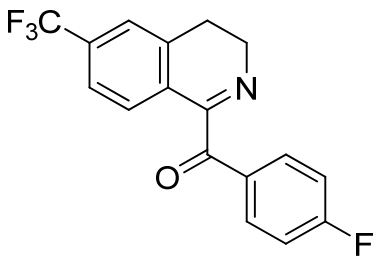
^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.94 (br. t, *J* = 7.7 Hz, 2 H), 4.05 (br. t, *J* = 7.7 Hz, 2 H), 7.51-7.63 (m, 3 H), 7.75 (d, *J* = 8.3 Hz, 2 H), 8.15 (d, *J* = 8.2 Hz, 2 H) ppm.

^{13}C NMR (126 MHz, DEPT, $CDCl_3$): δ = 25.3 (CH_2), 47.3 (CH_2), 123.5 (q, *J* = 273 Hz, 2 × CF_3), 124.3 (q, *J* = 4 Hz, CH), 124.8 (q, *J* = 3 Hz, CH), 125.5 (q, *J* = 3 Hz, CH), 127.0 (CH), 128.9 (C), 130.8 (CH), 133.3 (q, *J* = 33 Hz, C), 135.0 (q, *J* = 33 Hz, C), 138.2 (C), 138.3 (C), 163.2 (C), 191.6 (C) ppm.

IR (neat): $\tilde{\nu}$ = 2963, 1672, 1617, 1413, 1320, 1181, 1165, 1121, 1066, 1018, 903, 851 cm^{-1}.

MS (CI): *m/z* (%) = 372 (100) $[M + H]^+$, 343 (15), 302 (11), 173 (5), 145 (4).

HRMS: (CI) calcd. ($C_{18}H_{12}F_6NO$) 372.0823; found 372.0820.



$C_{17}H_{11}F_4NO$
MW: 321.27

(4-Fluorophenyl)(6-(trifluoromethyl)-3,4-dihydroisoquinolin-1-yl)methanone (**199**): In a Schlenk tube, a mixture of aminoalkyne **131** (307 mg, 1.00 mmol) and Ind_2TiMe_2 (15 mg, 0.05 mmol, 5 mol%) in toluene (1 mL) was stirred at 105 °C for 16 h. The resulting dark brown solution was cooled to room temperature and treated with CH_3CN (3 mL) and 10% Pd/C (106 mg, 0.10 mmol Pd). After this had been stirred at 25 °C under O_2 atmosphere for 24 h, the reaction mixture was filtered over Celite and concentrated under vacuum. After purification by flash chromatography (SiO_2, 22 g, PE/EtOAc 80:20, R_f = 0.51), **199** (266 mg, 0.83 mmol, 83 %) was isolated as a yellow solid.

M.p.: 70 °C.

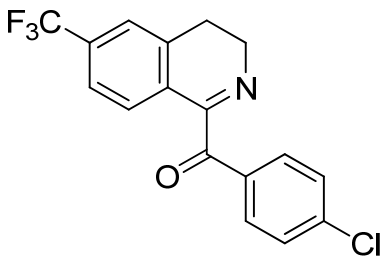
^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.94 (br. t, *J* = 7.7 Hz, 2 H), 4.03 (br. t, *J* = 7.7 Hz, 2 H), 7.16 (dt, *J* = 8.6, 1.7 Hz, 2 H), 7.50-7.56 (m, 3 H), 8.10 (dd, *J* = 8.6, 5.6 Hz, 2 H) ppm.

^{13}C NMR (126 MHz, DEPT, $CDCl_3$): δ = 25.3 (CH_2), 47.1 (CH_2), 115.8 (d, *J* = 22 Hz, CH), 123.5 (q, *J* = 273 Hz, CF_3), 124.2 (q, *J* = 4 Hz, CH), 124.7 (q, *J* = 4 Hz, CH), 126.9 (CH), 129.0 (C), 131.6 (d, *J* = 2 Hz, C), 133.0 (q, *J* = 33 Hz, C), 133.2 (d, *J* = 10 Hz, CH), 138.1 (C), 163.6 (C), 166.3 (d, *J* = 257 Hz, CF), 191.2 (C) ppm.

IR (neat): $\tilde{\nu}$ = 2963, 2857, 1671, 1596, 1505, 1318, 1213, 1169, 1144, 1112, 1078, 1060, 1016, 908, 845 cm^{-1}.

MS (CI): *m/z* (%) = 322 (100) $[M + H]^+$, 293 (4), 123 (7).

HRMS: (CI) calcd. ($C_{17}H_{12}F_4NO$) 322.0855; found 322.0860.



$C_{17}H_{11}ClF_3NO$
MW: 337.72

(4-Chlorophenyl)(6-(trifluoromethyl)-3,4-dihydroisoquinolin-1-yl)methanone (**200**): In a Schlenk tube, a mixture of aminoalkyne **132** (324 mg, 1.00 mmol) and Ind_2TiMe_2 (15 mg, 0.05 mmol, 5 mol%) in toluene (1 mL) was stirred at 105 °C for 16 h. The resulting dark brown solution was cooled to room temperature and treated with CH_3CN (3 mL) and 10% Pd/C (106 mg, 0.10 mmol Pd). After this had been stirred at 25 °C under O_2 atmosphere for 24 h, the reaction mixture was filtered over Celite and concentrated under vacuum. After purification by flash chromatography (SiO_2, 26 g, PE/EtOAc 50:50, R_f = 0.68), **200** (252 mg, 0.75 mmol, 75 %) was isolated as a yellow solid.

M.p.: 93 °C.

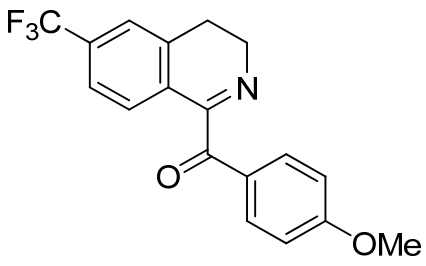
^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.94 (br. t, *J* = 7.7 Hz, 2 H), 4.04 (br. t, *J* = 7.7 Hz, 2 H), 7.46 (d, *J* = 8.6 Hz, 2 H), 7.51-7.56 (m, 3 H), 8.00 (d, *J* = 8.5 Hz, 2 H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$): δ = 25.3 (CH_2), 47.2 (CH_2), 123.5 (q, *J* = 273 Hz, CF_3), 124.2 (q, *J* = 4 Hz, CH), 124.8 (q, *J* = 3 Hz, CH), 127.0 (CH), 128.9 (C), 129.0 (CH), 131.8 (CH), 133.1 (q, *J* = 33 Hz, C), 133.6 (C), 138.1 (C), 140.7 (C), 163.5 (C), 191.6 (C) ppm.

IR (neat): $\tilde{\nu}$ = 3090, 2952, 2858, 1671, 1614, 1586, 1319, 1167, 1114, 1078, 900, 841, 822 cm^{-1}.

MS (CI): *m/z* (%) = 340 (33) [M + H, ^{37}Cl]$^+$, 338 (100) [M + H, ^{35}Cl]$^+$, 309 (11), 302 (8), 139 (8).

HRMS: (CI) calcd. ($C_{17}H_{12}ClF_3NO$) 338.0560; found 338.0552.



$C_{18}H_{14}F_3NO_2$
MW: 333.30

(4-Methoxyphenyl)(6-(trifluoromethyl)-3,4-dihydroisoquinolin-1-yl)methanone (**201**): In a Schlenk tube, a mixture of aminoalkyne **133** (239 mg, 0.75 mmol) and Ind_2TiMe_2 (12 mg, 0.04 mmol, 5 mol%) in toluene (1 mL) was stirred at 105 °C for 16 h. The resulting dark brown solution was cooled to room temperature and treated with CH_3CN (3 mL) and 10% Pd/C (80 mg, 0.08 mmol Pd). After this had been stirred at 25 °C under O_2 atmosphere for 24 h, the reaction mixture was filtered over Celite and concentrated under vacuum. After purification by flash chromatography (SiO_2, 13 g, PE/EtOAc 70:30, R_f = 0.13), **201** (119 mg, 0.37 mmol, 49 %) was isolated as an orange-yellow solid.

M.p.: 86 °C.

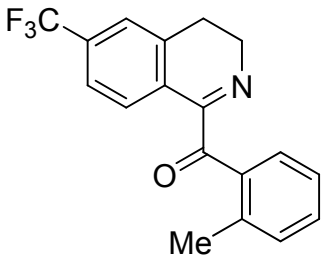
^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.94 (br. t, *J* = 7.7 Hz, 2 H), 3.88 (s, 3 H), 4.02 (br. t, *J* = 7.7 Hz, 2 H), 6.96 (d, *J* = 8.9 Hz, 2 H), 7.46-7.55 (m, 3 H), 8.03 (d, *J* = 8.8 Hz, 2 H) ppm.

^{13}C NMR (126 MHz, DEPT, $CDCl_3$): δ = 25.4 (CH_2), 47.0 (CH_2), 55. 6 (CH_3), 114.0 (CH), 123.6 (q, *J* = 272 Hz, CF_3), 124.2 (q, *J* = 4 Hz, CH), 124.7 (q, *J* = 4 Hz, CH), 127.0 (CH), 128.1 (C), 129.3 (C), 132.8 (CH), 132.9 (q, *J* = 33 Hz, C), 138.0 (C), 164.2 (C), 164.5 (C), 191.7 (C) ppm.

IR (neat): $\tilde{\nu}$ = 2964, 2845, 1656, 1595, 1511, 1430, 1349, 1323, 1265, 1163, 1113, 1081, 1030, 1019, 908, 837 cm^{-1}.

MS (CI): *m/z* (%) = 334 (100) $[M + H]^+$, 333 (12), 305 (3), 135 (3).

HRMS: (CI) calcd. ($C_{18}H_{15}F_3NO_2$) 334.1055; found 334.1057.



$C_{18}H_{14}F_3NO$
MW: 317.31

o-Tolyl(6-(trifluoromethyl)-3,4-dihydroisoquinolin-1-yl)methanone (**202**): In a Schlenk tube, a mixture of aminoalkyne **134** (303 mg, 1.00 mmol) and Ind_2TiMe_2 (15 mg, 0.05 mmol, 5 mol%) in toluene (1 mL) was stirred at 105 °C for 14 h. The resulting dark brown solution was cooled to room temperature and treated with CH_3CN (3 mL) and 10% Pd/C (106 mg, 0.10 mmol Pd). After this had been stirred at 25 °C under O_2 atmosphere for 24 h, the reaction mixture was filtered over Celite and concentrated under vacuum. After purification by flash chromatography (SiO_2, 25 g, PE/EtOAc 50:50, R_f = 0.62), **202** (266 mg, 0.84 mmol, 84 %) was isolated as a light yellow oil.

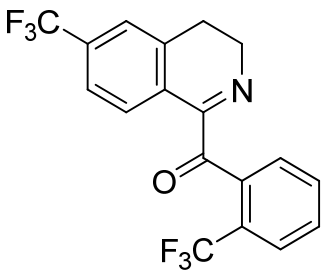
^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.57 (s, 3 H), 2.90 (br. t, *J* = 7.6 Hz, 2 H), 3.98 (br. t, *J* = 7.6 Hz, 2 H), 7.26 (t, *J* = 7.6 Hz, 1 H), 7.30 (d, *J* = 7.7 Hz, 1 H), 7.44 (t, *J* = 7.6 Hz, 1 H), 7.52 (s, 1 H), 7.56 (d, *J* = 8.3 Hz, 1 H), 7.61 (d, *J* = 7.9 Hz, 1 H), 7.63 (d, *J* = 8.1 Hz, 1 H) ppm.

^{13}C NMR (126 MHz, DEPT, $CDCl_3$): δ = 21.4 (CH_3), 25.3 (CH_2), 47.3 (CH_2), 123.6 (q, *J* = 272 Hz, CF_3), 124.2 (q, *J* = 4 Hz, CH), 124.7 (q, *J* = 3 Hz, CH), 125.6 (CH), 127.1 (CH), 129.1 (C), 131.7 (CH), 131.9 (CH), 132.5 (CH), 132.9 (q, *J* = 32 Hz, C), 135.6 (C), 138.3 (C), 139.9 (C), 164.9 (C), 195.7 (C) ppm.

IR (neat): $\tilde{\nu}$ = 3068, 2951, 1673, 1431, 1321, 1165, 1121, 1076, 903, 737 cm^{-1}.

MS (CI): *m/z* (%) = 318 (100) $[M + H]^+$, 317 (38), 289 (23), 119 (16).

HRMS: (CI) calcd. ($C_{18}H_{15}F_3NO$) 318.1106; found 318.1101.



$C_{18}H_{11}F_6NO$
MW: 371.28

(6-(Trifluoromethyl)-3,4-dihydroisoquinolin-1-yl)(2-(trifluoromethyl)phenyl)methanone (**203**): In a Schlenk tube, a mixture of aminoalkyne **135** (357 mg, 1.00 mmol) and Ind_2TiMe_2 (15 mg, 0.05 mmol, 5 mol%) in toluene (1 mL) was stirred at 105 °C for 15 h. The resulting dark brown solution was cooled to room temperature and treated with CH_3CN (3 mL) and 10% Pd/C (106 mg, 0.10 mmol Pd). After this had been stirred at 25 °C under O_2 atmosphere for 24 h, the reaction mixture was filtered over Celite and concentrated under vacuum. After purification by flash chromatography (SiO_2, 30 g, PE/EtOAc 50:50, R_f = 0.42), **203** (283 mg, 0.76 mmol, 76 %) was isolated as a brown-yellow oil.

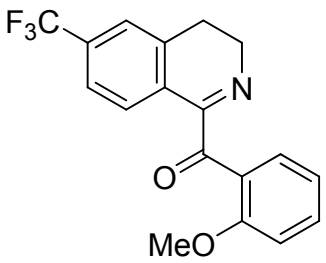
^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.81 (br. t, *J* = 7.5 Hz, 2 H), 3.91 (br. t, *J* = 7.6 Hz, 2 H), 7.51 (s, 1 H), 7.58 (d, *J* = 7.2 Hz, 1 H), 7.60-7.68 (m, 3 H), 7.71 (d, *J* = 7.5 Hz, 1 H), 8.01 (d, *J* = 8.1 Hz, 1 H) ppm.

^{13}C NMR (126 MHz, DEPT, $CDCl_3$): δ = 25.3 (CH_2), 47.7 (CH_2), 123.6 (q, *J* = 273 Hz, CF_3), 123.8 (q, *J* = 274 Hz, CF_3), 124.1 (q, *J* = 4 Hz, CH), 124.4 (q, *J* = 3 Hz, CH), 126.4 (q, *J* = 5 Hz, CH), 127.8 (CH), 127.9 (q, *J* = 32 Hz, C), 128.4 (C), 129.5 (CH), 130.6 (CH), 131.7 (CH), 132.9 (q, *J* = 33 Hz, C), 138.0 (C), 138.6 (C), 163.1 (C), 194.6 (C) ppm.

IR (neat): $\tilde{\nu}$ = 3087, 2957, 2843, 1686, 1620, 1431, 1310, 1158, 1124, 1067, 1036, 906 cm^{-1}.

MS (CI): *m/z* (%) = 372 (100) $[M + H]^+$, 343 (12), 302 (29), 173 (5).

HRMS: (CI) calcd. ($C_{18}H_{12}F_6NO$) 372.0823; found 372.0830.



$C_{18}H_{14}F_3NO_2$
MW: 333.30

(2-Methoxyphenyl)(6-(trifluoromethyl)-3,4-dihydroisoquinolin-1-yl)methanone (**204**): In a Schlenk tube, a mixture of aminoalkyne **136** (319 mg, 1.00 mmol) and Ind_2TiMe_2 (15 mg, 0.05 mmol, 5 mol%) in toluene (1 mL) was stirred at 105 °C for 16 h. The resulting dark brown solution was cooled to room temperature and treated with CH_3CN (3 mL) and 10% Pd/C (106 mg, 0.10 mmol Pd). After this had been stirred at 25 °C under O_2 atmosphere for 24 h, the reaction mixture was filtered over Celite and concentrated under vacuum. After purification by flash chromatography (SiO_2, 30 g, PE/EtOAc 50:50, R_f = 0.29), **204** (274 mg, 0.82 mmol, 82 %) was isolated as an orange-yellow oil.

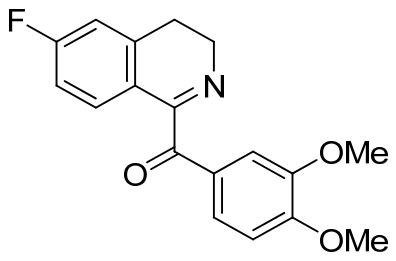
^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.87 (t, *J* = 7.5 Hz, 2 H), 3.63 (s, 3 H), 3.86 (br. t, *J* = 7.5 Hz, 2 H), 6.92 (d, *J* = 8.4 Hz, 1 H), 7.08 (t, *J* = 7.5 Hz, 1 H), 7.49-7.58 (m, 4 H), 7.85 (d, *J* = 7.7 Hz, 1 H) ppm.

^{13}C NMR (126 MHz, DEPT, $CDCl_3$): δ = 25.5 (CH_2), 46.9 (CH_2), 55.5 (CH_3), 111.9 (CH), 121.1 (CH), 123.7 (q, *J* = 273 Hz, CF_3), 123.9 (q, *J* = 4 Hz, CH), 124.4 (q, *J* = 4 Hz, CH), 126.7 (CH), 126.8 (C), 129.0 (C), 130.9 (CH), 132.4 (q, *J* = 32 Hz, C), 134.9 (CH), 138.2 (C), 159.3 (C), 165.5 (C), 194.4 (C) ppm.

IR (neat): $\tilde{\nu}$ = 2947, 2842, 1666, 1598, 1485, 1466, 1432, 1322, 1275, 1246, 1164, 1119, 1081, 1019, 906, 754 cm^{-1}.

MS (CI): *m/z* (%) = 334 (100) $[M + H]^+$, 302 (45), 135 (14).

HRMS: (CI) calcd. ($C_{18}H_{15}F_3NO_2$) 334.1055; found 334.1047.



$C_{18}H_{16}FNO_3$
MW: 313.32

(3,4-Dimethoxyphenyl)(6-fluoro-3,4-dihydroisoquinolin-1-yl)methanone (**205**): In a Schlenk tube, a mixture of aminoalkyne **137** (286 mg, 0.90 mmol) and Ind_2TiMe_2 (14 mg, 0.05 mmol, 5 mol%) in toluene (1 mL) was stirred at 105 °C for 14 h. The resulting dark brown solution was cooled to room temperature and treated with CH_3CN (3 mL) and 10% Pd/C (96 mg, 0.09 mmol Pd). After this had been stirred at 25 °C under O_2 atmosphere for 24 h, the reaction mixture was filtered over Celite and concentrated under vacuum. After purification by flash chromatography (SiO_2, 15 g, PE/EtOAc 50:50, R_f = 0.17), **205** (108 mg, 0.33 mmol, 36 %) was isolated as a yellow oil.

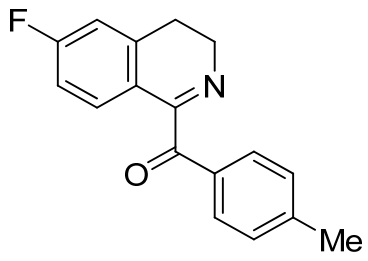
^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.83 (t, *J* = 7.6 Hz, 2 H), 3.93-3.99 (m, 8 H), 6.89 (d, *J* = 8.5 Hz, 1 H), 7.07 (t, *J* = 8.7 Hz, 1 H), 7.23-7.30 (m, 1 H), 7.60 (d, *J* = 8.4 Hz, 1 H), 7.67 (s, 1 H) ppm.

^{13}C NMR (126 MHz, DEPT, $CDCl_3$): δ = 24.8 (CH_2), 46.8 (CH_2), 56.0 (CH_3), 56.1 (CH_3), 109.9 (CH), 111.1 (CH), 116.1 (d, *J* = 19 Hz, CH), 116.7 (d, *J* = 18 Hz, CH), 122.9 (C), 126.6 (CH), 128.1 (C), 134.5 (dd, *J* = 4, 6 Hz, C), 148.9 (dd, *J* = 13, 248 Hz, CF), 149.2 (C), 151.9 (dd, *J* = 13, 255 Hz, CF), 154.4 (C), 163.1 (C), 191.6 (C) ppm.

IR (neat): $\tilde{\nu}$ = 3071, 2937, 1657, 1591, 1509, 1421, 1291, 1277, 1259, 1240, 1146, 1019, 813, 754 cm^{-1}.

MS (CI): *m/z* (%) = 332 (100) $[M + H]^+$, 300 (14), 165 (5).

HRMS: (CI) calcd. ($C_{18}H_{16}F_2NO_3$) 332.1098; found 332.1093.



$C_{17}H_{14}FNO$
MW: 267.30

(6-Fluoro-3,4-dihydroisoquinolin-1-yl)(p-tolyl)methanone (**206**): In a Schlenk tube, a mixture of aminoalkyne **138** (235 mg, 1.00 mmol) and Ind_2TiMe_2 (15 mg, 0.05 mmol, 5 mol%) in toluene (1 mL) was stirred at 105 °C for 12 h. The resulting dark brown solution was cooled to room temperature and treated with CH_3CN (3 mL) and 10% Pd/C (106 mg, 0.10 mmol Pd). After this had been stirred at 25 °C under O_2 atmosphere for 24 h, the reaction mixture was filtered over Celite and concentrated under vacuum. After purification by flash chromatography (SiO_2, 20 g, PE/EtOAc 80:20, R_f = 0.17), **214** (179 mg, 0.67 mmol, 67 %) was isolated as a yellow oil.

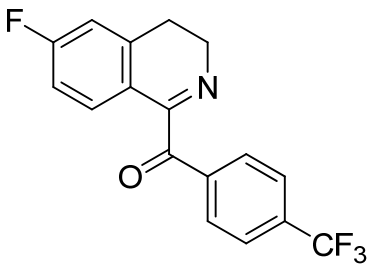
^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.41 (s, 3 H), 2.87 (br. t, *J* = 7.7 Hz, 2 H), 3.95 (br. t, *J* = 7.7 Hz, 2 H), 6.87-6.98 (m, 2 H), 7.27 (d, *J* = 8.0 Hz, 2 H), 7.34-7.40 (m, 1 H), 7.93 (d, *J* = 8.2 Hz, 2 H) ppm.

^{13}C NMR (126 MHz, DEPT, $CDCl_3$): δ = 21.7 (CH_3), 25.7 (CH_2), 46.8 (CH_2), 114.0 (d, *J* = 22 Hz, CH), 114.9 (d, *J* = 22 Hz, CH), 123.1 (d, *J* = 3 Hz, C), 128.9 (d, *J* = 9 Hz, CH), 129.3 (CH), 130.4 (CH), 132.8 (C), 140.3 (d, *J* = 9 Hz, C), 145.0 (C), 164.1 (d, *J* = 253 Hz, CF), 164.21 (C), 193.2 (C) ppm.

IR (neat): $\tilde{\nu}$ = 2948, 2847, 1666, 1603, 1579, 1490, 1244, 1207, 1176, 1118, 1020, 917, 902, 868, 822 cm^{-1}.

MS (CI): *m/z* (%) = 268 (100) $[M + H]^+$, 239 (3), 119 (2).

HRMS: (CI) calcd. ($C_{17}H_{16}NO$) 268.1138; found 268.1141.



$C_{17}H_{11}F_4NO$
MW: 321.27

(6-Fluoro-3,4-dihydroisoquinolin-1-yl)(4-(trifluoromethyl)phenyl)methanone (**207**): In a Schlenk tube, a mixture of aminoalkyne **139** (200 mg, 0.65 mmol) and Ind_2TiMe_2 (10 mg, 0.03 mmol, 5 mol%) in toluene (1 mL) was stirred at 105 °C for 16 h. The resulting dark brown solution was cooled to room temperature and treated with CH_3CN (3 mL) and 10% Pd/C (69 mg, 0.07 mmol, Pd). After this had been stirred at 25 °C under O_2 atmosphere for 24 h, the reaction mixture was filtered over Celite and concentrated under vacuum. After purification by flash chromatography (SiO_2, 12 g, PE/EtOAc 80:20, R_f = 0.34), **207** (136 mg, 0.42 mmol, 65 %) was isolated as a yellow oil.

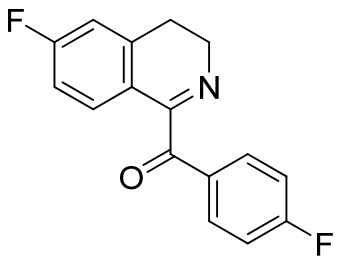
^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.88 (br. t, *J* = 7.7 Hz, 2 H), 3.98 (br. t, *J* = 7.7 Hz, 2 H), 6.94-7.02 (m, 1 H), 7.47 (dd, *J* = 8.1, 5.6 Hz, 0 H), 7.74 (d, *J* = 8.2 Hz, 2 H), 8.14 (d, *J* = 8.2 Hz, 2 H) ppm.

^{13}C NMR (126 MHz, DEPT, $CDCl_3$): δ = 25.7 (CH_2), 47.1 (CH_2), 114.2 (d, *J* = 22 Hz, CH), 115.1 (d, *J* = 22 Hz, CH), 122.8 (d, *J* = 2 Hz, C), 123.5 (q, *J* = 273 Hz, CF_3), 125.5 (q, *J* = 3 Hz, CH), 129.1 (d, *J* = 9 Hz, CH), 130.7 (CH), 134.8 (q, *J* = 33 Hz, C), 138.3 (C), 140.6 (d, *J* = 9 Hz, C), 163.4 (C), 164.3 (d, *J* = 254 Hz, CF), 192.1 (C) ppm.

IR (neat): $\tilde{\nu}$ = 2954, 1680, 1618, 1581, 1323, 1246, 1168, 1127, 1068, 1017, 903, 730 cm^{-1}.

MS (CI): *m/z* (%) = 322 (100) $[M + H]^+$, 293 (23), 252 (5), 173 (6), 145 (4).

HRMS: (CI) calcd. ($C_{17}H_{12}F_4NO$) 322.0855; found 322.0856.



$C_{16}H_{11}F_2NO$
MW: 271.26

(6-Fluoro-3,4-dihydroisoquinolin-1-yl)(4-fluorophenyl)methanone (**208**): In a Schlenk tube, a mixture of aminoalkyne **140** (257 mg, 1.00 mmol) and Ind_2TiMe_2 (15 mg, 0.05 mmol, 5 mol%) in toluene (1 mL) was stirred at 105 °C for 12 h. The resulting dark brown solution was cooled to room temperature and treated with CH_3CN (3 mL) and 10% Pd/C (106 mg, 0.10 mmol Pd). After this had been stirred at 25 °C under O_2 atmosphere for 24 h, the reaction mixture was filtered over Celite and concentrated under vacuum. After purification by flash chromatography (SiO_2, 20 g, PE/EtOAc 80:20, R_f = 0.38), **208** (195 mg, 0.72 mmol, 72 %) was isolated as a light yellow oil.

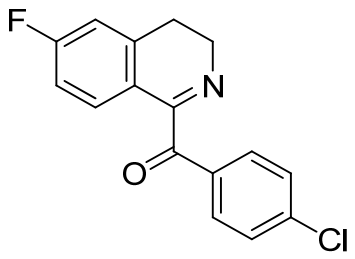
^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.88 (br. t, *J* = 6.7 Hz, 2 H), 3.96 (br. t, *J* = 7.7 Hz, 2 H), 6.91-6.99 (m, 2 H), 7.15 (t, *J* = 8.6 Hz, 2 H), 7.40 (dd, *J* = 8.4, 5.6 Hz, 1 H), 8.06-8.11 (m, 2 H) ppm.

^{13}C NMR (126 MHz, DEPT, $CDCl_3$): δ = 25.7 (CH_2), 46.9 (CH_2), 114.1 (d, *J* = 22 Hz, CH), 115.0 (d, *J* = 22 Hz, CH), 115.8 (d, *J* = 22 Hz, CH), 123.0 (d, *J* = 3 Hz, C), 129.0 (d, *J* = 9 Hz, CH), 131.7 (d, *J* = 3 Hz, C), 133.2 (d, *J* = 10 Hz, CH), 140.4 (d, *J* = 9 Hz, C), 163.8 (s, C), 164.2 (d, *J* = 254 Hz, CF), 166.3 (d, *J* = 257 Hz, CF), 191.8 (C) ppm.

IR (neat): $\tilde{\nu}$ = 3073, 2951, 2848, 1670, 1594, 1580, 1504, 1243, 1228, 1206, 1154, 1118, 902, 846 cm^{-1}.

MS (CI): *m/z* (%) = 272 (100) $[M + H]^+$, 243 (10), 123 (7).

HRMS: (CI) calcd. ($C_{16}H_{12}F_2NO$) 272.0887; found 272.0891.



$C_{16}H_{11}ClFNO$
MW: 287.72

(4-Chlorophenyl)(6-fluoro-3,4-dihydroisoquinolin-1-yl)methanone (**209**): In a Schlenk tube, a mixture of aminoalkyne **141** (274 mg, 1.00 mmol) and Ind_2TiMe_2 (15 mg, 0.05 mmol, 5 mol%) in toluene (1 mL) was stirred at 105 °C for 16 h. The resulting dark brown solution was cooled to room temperature and treated with CH_3CN (3 mL) and 10% Pd/C (106 mg, 0.10 mmol Pd). After this had been stirred at 25 °C under O_2 atmosphere for 24 h, the reaction mixture was filtered over Celite and concentrated under vacuum. After purification by flash chromatography (SiO_2, 30 g, PE/EtOAc 50:50, R_f = 0.61), **209** (205 mg, 0.74 mmol, 74 %) was isolated as a colorless oil.

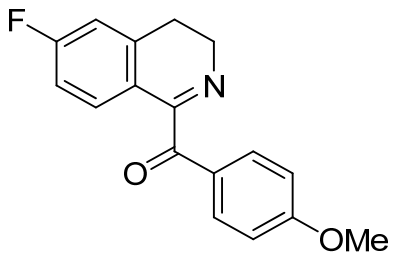
^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.87 (br. t, *J* = 7.7 Hz, 2 H), 3.96 (br. t, *J* = 7.7 Hz, 2 H), 6.91-6.99 (m, 2 H), 7.40 (dd, *J* = 8.4, 5.6 Hz, 1 H), 7.45 (d, *J* = 8.3 Hz, 2 H), 7.99 (d, *J* = 8.6 Hz, 2 H) ppm.

^{13}C NMR (126 MHz, DEPT, $CDCl_3$): δ = 25.7 (CH_2), 46.9 (CH_2), 114.1 (d, *J* = 22 Hz, CH), 115.0 (d, *J* = 22 Hz, CH), 122.9 (d, *J* = 3 Hz, C), 128.9 (CH), 129.0 (d, *J* = 9 Hz, CH), 131.8 (CH), 133.7 (C), 140.4 (C), 140.5 (C), 163.6 (C), 164.2 (d, *J* = 254 Hz, CF), 192.0 (C) ppm.

IR (neat): $\tilde{\nu}$ = 2949, 2898, 2846, 1671, 1618, 1581, 1487, 1400, 1244, 1206, 1087, 1014, 900, 825 cm^{-1}.

MS (CI): *m/z* (%) = 290 (31) [M + H, ^{37}Cl]$^+$, 288 (100) [M + H, ^{35}Cl]$^+$, 259 (28), 139 (12).

HRMS: (CI) calcd. ($C_{16}H_{12}ClFNO$) 288.0591; found 288.0588.



$C_{17}H_{14}FNO_2$
MW: 283.30

(6-Fluoro-3,4-dihydroisoquinolin-1-yl)(4-methoxyphenyl)methanone (**210**): In a Schlenk tube, a mixture of aminoalkyne **142** (199 mg, 0.74 mmol) and Ind_2TiMe_2 (11 mg, 0.04 mmol, 5 mol%) in toluene (1 mL) was stirred at 105 °C for 16 h. The resulting dark brown solution was cooled to room temperature and treated with CH_3CN (3 mL) and 10% Pd/C (79 mg, 0.07 mmol Pd). After this had been stirred at 25 °C under O_2 atmosphere for 24 h, the reaction mixture was filtered over Celite and concentrated under vacuum. After purification by flash chromatography (SiO_2, 14 g, PE/EtOAc 50:50, R_f = 0.30), **210** (130 mg, 0.46 mmol, 62 %) was isolated as a yellow solid.

M.p.: 93 °C.

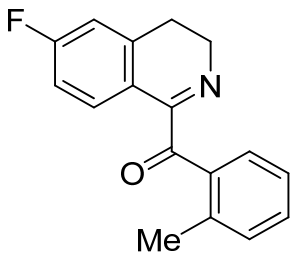
^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.89 (t, *J* = 7.5 Hz, 2 H), 3.88 (s, 3 H), 3.96 (t, *J* = 7.5 Hz, 2 H), 6.89-6.99 (m, 4 H), 7.34-7.41 (m, 1 H), 8.02 (d, *J* = 8.7 Hz, 2 H) ppm.

^{13}C NMR (126 MHz, DEPT, $CDCl_3$): δ = 25.7 (CH_2), 46.7 (CH_2), 55.5 (CH_3), 113.8 (CH), 114.0 (d, *J* = 22 Hz, CH), 114.9 (d, *J* = 22 Hz, CH), 123.1 (d, *J* = 3 Hz, C), 128.2 (C), 128.9 (d, *J* = 9 Hz, CH), 132.7 (CH), 140.3 (d, *J* = 9 Hz, C), 164.0 (d, *J* = 253 Hz, CF), 164.3 (C), 192.1 (C) ppm.

IR (neat): $\tilde{\nu}$ = 2967, 2839, 1649, 1600, 1573, 1497, 1421, 1318, 1260, 1244, 1216, 1172, 1117, 1019, 903, 858, 769 cm^{-1}.

MS (CI): *m/z* (%) = 284 (100) $[M + H]^+$, 255 (8), 135 (9).

HRMS: (CI) calcd. ($C_{17}H_{15}FNO_2$) 284.1087; found 284.1089.



$C_{17}H_{14}FNO$
MW: 267.30

(6-Fluoro-3,4-dihydroisoquinolin-1-yl)(o-tolyl)methanone (**211**): In a Schlenk tube, a mixture of aminoalkyne **143** (253 mg, 1.00 mmol) and Ind_2TiMe_2 (15 mg, 0.05 mmol, 5 mol%) in toluene (1 mL) was stirred at 105 °C for 14 h. The resulting dark brown solution was cooled to room temperature and treated with CH_3CN (3 mL) and 10% Pd/C (106 mg, 0.10 mmol Pd). After this had been stirred at 25 °C under O_2 atmosphere for 24 h, the reaction mixture was filtered over Celite and concentrated under vacuum. After purification by flash chromatography (SiO_2, 25 g, PE/EtOAc 50:50, R_f = 0.54), **211** (206 mg, 0.77 mmol, 77 %) was isolated as a light yellow oil.

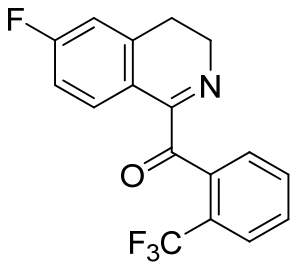
^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.57 (s, 3 H), 2.84 (br. t, *J* = 7.6 Hz, 2 H), 3.91 (br. t, *J*= 7.6 Hz, 2 H), 6.93-7.00 (m, 2 H), 7.22-7.30 (m, 2 H), 7.42 (t, *J* = 7.5Hz, 1 H), 7.52 (dd, *J* = 9.1, 5.8 Hz, 1 H), 7.61 (d, *J* = 7.8 Hz, 1H) ppm.

^{13}C NMR (126 MHz, DEPT, $CDCl_3$): δ = 21.4 (CH_3), 25.7 (CH_2), 47.1 (CH_2), 114.1 (d, *J* = 22 Hz, CH), 114.9 (d, *J* = 22 Hz, CH), 123.1 (d, *J* = 3 Hz, C), 125.6 (CH), 129.2 (d, *J* = 9 Hz, CH), 131.7 (CH), 131.9 (CH), 132.4 (CH), 135.8 (C), 139.8 (C), 140.7 (d, *J* = 9 Hz, C), 164.1 (d, *J* = 253 Hz, CF), 165.0 (C), 196.2 (C) ppm.

IR (neat): $\tilde{\nu}$ = 3063, 2949, 1672, 1615, 1580, 1493, 1430, 1243, 1208, 1113, 901, 868, 736 cm^{-1}.

MS (CI): *m/z* (%) = 268 (100) $[M + H]^+$, 267 (24), 266 (22), 252 (6), 239 (8).

HRMS: (CI) calcd. ($C_{17}H_{15}FNO$) 268.1138; found 268.1131.



$C_{17}H_{11}F_4NO$
MW: 321.27

(6-Fluoro-3,4-dihydroisoquinolin-1-yl)(2-(trifluoromethyl)phenyl)methanone (**212**): In a Schlenk tube, a mixture of aminoalkyne **144** (307 mg, 1.00 mmol) and Ind_2TiMe_2 (15 mg, 0.05 mmol, 5 mol%) in toluene (1 mL) was stirred at 105 °C for 15 h. The resulting dark brown solution was cooled to room temperature and treated with CH_3CN (3 mL) and 10% Pd/C (106 mg, 0.10 mmol Pd). After this had been stirred at 25 °C under O_2 atmosphere for 24 h, the reaction mixture was filtered over Celite and concentrated under vacuum. After purification by flash chromatography (SiO_2, 30 g, PE/EtOAc 60:40, R_f = 0.30), **212** (210 mg, 0.65 mmol, 65 %) was isolated as a yellow solid.

M.p.: 95 °C.

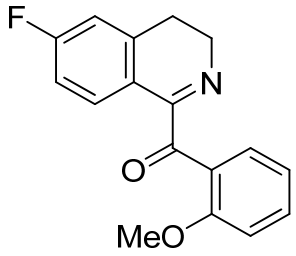
^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.74 (br. t, *J* = 7.6 Hz, 2 H), 3.84 (br. t, *J* = 7.6 Hz, 2 H), 6.94 (dd, *J* = 8.6, 1.9 Hz, 1 H), 7.04 (td, *J* = 8.6, 2.4 Hz, 1 H), 7.57 (t, *J* = 6.9 Hz, 1 H), 7.59-7.66 (m, 3 H), 7.70 (d, *J* = 7.6 Hz, 1 H), 7.91 (dd, *J* = 8.5, 5.8 Hz, 1 H) ppm.

^{13}C NMR (126 MHz, DEPT, $CDCl_3$): δ = 25.6 (CH_2), 47.5 (CH_2), 114.0 (d, *J* = 22 Hz, CH), 114.5 (d, *J* = 22 Hz, CH), 122.4 (d, *J* = 3 Hz, C), 123.8 (q, *J* = 274 Hz, CF_3), 126.3 (q, *J* = 5 Hz, CH), 127.8 (q, *J* = 32 Hz, C), 129.5 (CH), 129.9 (d, *J* = 9 Hz, CH), 130.5 (CH), 131.6 (CH), 138.3 (C), 140.9 (C), 141.0 (C), 164.11 (d, *J* = 253 Hz, CF), 194.9 (C) ppm.

IR (neat): $\tilde{\nu}$ = 3036, 2973, 2845, 1692, 1615, 1580, 1493, 1316, 1162, 1117, 1077, 1036, 872, 770 cm^{-1}.

MS (CI): *m/z* (%) = 322 (100) $[M + H]^+$, 293 (25), 252 (53), 173 (12).

HRMS: (CI) calcd. ($C_{17}H_{12}F_4NO$) 322.0855; found 322.0851.



$C_{17}H_{14}FNO_2$
MW: 283.30

(6-Fluoro-3,4-dihydroisoquinolin-1-yl)(2-methoxyphenyl)methanone (**213**): In a Schlenk tube, a mixture of aminoalkyne **145** (269 mg, 1.00 mmol) and Ind_2TiMe_2 (15 mg, 0.05 mmol, 5 mol%) in toluene (1 mL) was stirred at 105 °C for 16 h. The resulting dark brown solution was cooled to room temperature and treated with CH_3CN (3 mL) and 10% Pd/C (106 mg, 0.10 mmol Pd). After this had been stirred at 25 °C under O_2 atmosphere for 24 h, the reaction mixture was filtered over Celite and concentrated under vacuum. After purification by flash chromatography (SiO_2, 30 g, PE/EtOAc 50:50, R_f = 0.22), **213** (164 mg, 0.59 mmol, 59 %) was isolated as a yellow solid.

M.p.: 68 °C.

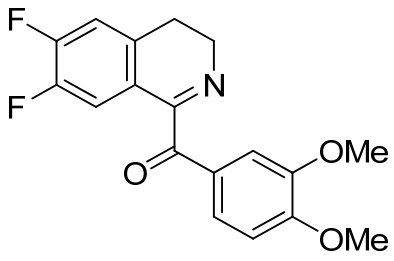
^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.82 (br. t, *J* = 7.5 Hz, 2 H), 3.64 (s, 3 H), 3.81 (br. t, *J* = 7.5 Hz, 2 H), 6.91-6.98 (m, 3 H), 7.07 (t, *J* = 7.6 Hz, 1 H), 7.45 (dd, *J* = 7.9, 5.8 Hz, 1 H), 7.49-7.55 (m, 1 H), 7.84 (dd, *J* = 7.7, 1.5 Hz, 1 H) ppm.

^{13}C NMR (126 MHz, DEPT, $CDCl_3$): δ = 25.8 (CH_2), 46.6 (CH_2), 55.5 (CH_3), 111.9 (CH), 113.9 (d, *J* = 22 Hz, CH), 114.7 (d, *J* = 22 Hz, CH), 121.0 (CH), 122.8 (C), 126.8 (C), 128.8 (d, *J* = 9 Hz, CH), 130.9 (CH), 134.8 (CH), 140.5 (d, *J* = 8 Hz, C), 159.3 (C), 163.9 (d, *J* = 253 Hz, CF), 165.8 (C), 194.6 (C) ppm.

IR (neat): $\tilde{\nu}$ = 3073, 2945, 2897, 2840, 1666, 1621, 1597, 1581, 1485, 1272, 1243, 1204, 1109, 1019, 903, 754 cm^{-1}.

MS (CI): *m/z* (%) = 284 (100) $[M + H]^+$, 252 (67), 135 (18).

HRMS: (CI) calcd. ($C_{17}H_{15}FNO_2$) 284.1087; found 284.1083.



$C_{18}H_{15}F_2NO_3$
MW: 331.31

(6,7-Difluoro-3,4-dihydroisoquinolin-1-yl)(3,4-dimethoxyphenyl)methanone (**214**): In a Schlenk tube, a mixture of aminoalkyne **146** (96 mg, 0.90 mmol) and Ind_2TiMe_2 (14 mg, 0.05 mmol, 5 mol%) in toluene (1 mL) was stirred at 105 °C for 14 h. The resulting dark brown solution was cooled to room temperature and treated with CH_3CN (3 mL) and 10% Pd/C (96 mg, 0.09 mmol Pd). After this had been stirred at 25 °C under O_2 atmosphere for 24 h, the reaction mixture was filtered over Celite and concentrated under vacuum. After purification by flash chromatography (SiO_2, 15 g, PE/EtOAc 50:50, R_f = 0.26), **214** (108 mg, 0.33 mmol, 36 %) was isolated as a yellow oil.

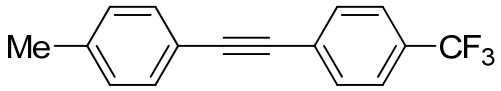
^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.83 (t, *J* = 7.6 Hz, 2 H), 3.93-3.99 (m, 8 H), 6.89 (d, *J* = 8.5 Hz, 1 H), 7.07 (t, *J* = 8.7 Hz, 1 H), 7.23-7.30 (m, 1 H), 7.60 (d, *J* = 8.4 Hz, 1 H), 7.67 (s, 1 H) ppm.

^{13}C NMR (126 MHz, DEPT, $CDCl_3$): δ = 24.8 (CH_2), 46.8 (CH_2), 56.0 (CH_3), 56.1 (CH_3), 109.9 (CH), 111.1 (CH), 116.1 (d, *J* = 19 Hz, CH), 116.7 (d, *J* = 18 Hz, CH), 122.9 (C), 126.6 (CH), 128.1 (C), 134.5 (dd, *J* = 4, 6 Hz, C), 148.9 (dd, *J* = 13, 248 Hz, CF), 149.2 (C), 151.9 (dd, *J* = 13, 255 Hz, CF), 154.4 (C), 163.1 (C), 191.6 (C) ppm.

IR (neat): $\tilde{\nu}$ = 3071, 2937, 1657, 1591, 1509, 1421, 1291, 1277, 1259, 1240, 1146, 1019, 813, 754 cm^{-1}.

MS (CI): *m/z* (%) = 332 (100) $[M + H]^+$, 300 (14), 165 (5).

HRMS: (CI) calcd. ($C_{18}H_{16}F_2NO_3$) 332.1098; found 332.1093.



$C_{16}H_{11}F_3$
MW: 260.25

1-Methyl-4-((4-(trifluoromethyl)phenyl)ethynyl)benzene (**219**): 1-Iodo-4-methylbenzene (**67**, 654 mg, 3.00 mmol), $Pd(PPh_3)_2Cl_2$ (42 mg, 0.06 mmol, 2 mol-%), CuI (11 mg, 0.06 mmol, 2 mol-%) and PPh_3 (31 mg, 0.12 mmol, 4 mol-%) were placed in an oven dried and argon-filled Schlenk tube. After addition of *i*Pr_2NH (1 mL) and toluene (5 mL) the mixture was stirred at 25 °C for 5 minutes, and ethynyltrimethylsilane (**64**, 354 mg, 3.60 mmol) was added. After this the mixture had been stirred at 25 °C for an additional 16 h. KOH (337 mg, 6 mmol), water (0,5 mL, 3.00 mmol) and methanol (2 mL) was added in one portion followed after stirring 3 h at room temperature by the addition of 1-iodo-4-(trifluoromethyl)benzene (**68**, 816 mg, 3.00 mmol). After another 16 h of stirring a saturated NH_4Cl solution (60 mL) was added. The mixture was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were washed with HCl (2 N, 50 mL), water (50 mL) and saturated NaCl solution (50 mL). The organic layer was dried ($MgSO_4$) and concentrated under vacuum. The residue was purified by flash chromatography (SiO_2, 115 g, PE, R_f = 0.30) to give **219** (662 mg, 2.5 mmol, 85 %) as a light yellow solid.

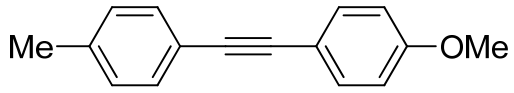
^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.37 (s, 3 H), 7.17 (d, *J* = 8.0 Hz, 2 H), 7.43 (d, *J* = 8.0 Hz, 2 H), 7.58 (d, *J* = 8.7 Hz, 2 H), 7.60 (d, *J* = 8.6 Hz, 2 H) ppm.

^{13}C NMR (126 MHz, DEPT, $CDCl_3$): δ = 21.5 (CH_3), 87.4 (C), 92.0 (C), 119.5 (C), 124.0 (q, *J* = 272 Hz, CF_3), 125.2 (q, *J* = 4 Hz, CH), 127.3 (C), 129.2 (CH), 129.7 (q, *J* = 33 Hz, C), 131.6 (CH), 131.7 (CH), 139.1 (C) ppm.

IR (neat): $\tilde{\nu}$ = 2923, 2218, 1315, 1164, 1122, 1104, 1063, 1013, 842, 819 cm^{-1}.

MS (EI): *m/z* (%) = 260 (100) $[M]^+$, 259 (32), 191 (12), 189 (16), 115 (4).

HRMS: calcd. ($C_{16}H_{11}F_3$) 260.0813; found 260.0811.



$C_{16}H_{14}O$
MW: 222.28

1-Methoxy-4-(p-tolylethynyl)benzene (**220**): 1-Iodo-4-methylbenzene (**67**, 654 mg, 3.00 mmol), $Pd(PPh_3)_2Cl_2$ (42 mg, 0.06 mmol, 2 mol-%), CuI (11 mg, 0.06 mmol, 2 mol-%) and PPh_3 (31 mg, 0.12 mmol, 4 mol-%) were placed in an oven dried and argon-filled Schlenk tube. After addition of *i*Pr_2NH (1 mL) and toluene (5 mL) the mixture was stirred at 25 °C for 5 minutes, and ethynyltrimethylsilane (**64**, 354 mg, 3.60 mmol) was added. After this the mixture had been stirred at 25 °C for an additional 16 h. KOH (337 mg, 6 mmol), water (0,5 mL, 3.00 mmol) and methanol (2 mL) was added in one portion followed after stirring 3 h at room temperature by the addition of 1-iodo-4-(trifluoromethyl)benzene (**71**, 702 mg, 3.00 mmol). After another 16 h of stirring a saturated NH_4Cl solution (60 mL) was added. The mixture was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were washed with HCl (2 N, 50 mL), water (50 mL) and saturated NaCl solution (50 mL). The organic layer was dried ($MgSO_4$) and concentrated under vacuum. The residue was purified by flash chromatography (SiO_2, 115 g, PE/EtOAc, 99:1, R_f = 0.35) to give **220** (510 mg, 2.29 mmol, 77 %) as a light brown solid.

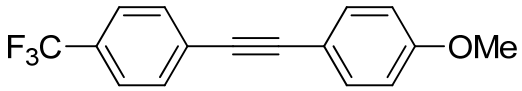
^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.35 (s, 3 H), 3.80 (s, 3 H), 6.86 (d, *J* = 8.6 Hz, 2 H), 7.13 (d, *J* = 7.9 Hz, 2 H), 7.40 (d, *J* = 8.0 Hz, 2 H), 7.45 (d, *J* = 8.6 Hz, 2 H) ppm.

^{13}C NMR (126 MHz, DEPT, $CDCl_3$): δ = 21.4 (CH_3), 55.2 (CH_3), 88.2 (C), 88.6 (C), 113.9 (CH), 115.5 (C), 120.5 (C), 129.0 (CH), 131.3 (CH), 132.9 (CH), 138.0 (C), 159.4 (C) ppm.

IR (neat): $\tilde{\nu}$ = 3005, 2968, 1510, 1451, 1286, 1244, 1173, 1106, 1027, 830, 817 cm^{-1}.

MS (EI): *m/z* (%) = 222 (100) $[M]^+$, 207 (48), 179 (18), 178 (20), 111 (6).

HRMS: calcd. ($C_{16}H_{14}O$) 22.1045; found 222.1040.



$C_{16}H_{11}F_3O$
MW: 276.25

1-Methoxy-4-((4-(trifluoromethyl)phenyl)ethynyl)benzene (**221**): 1-Iodo-4-methoxybenzene (**71**, 702 mg, 3.00 mmol), $Pd(PPh_3)_2Cl_2$ (42 mg, 0.06 mmol, 2 mol-%), CuI (11 mg, 0.06 mmol, 2 mol-%) and PPh_3 (31 mg, 0.12 mmol, 4 mol-%) were placed in an oven dried and argon-filled Schlenk tube. After addition of *i*Pr_2NH (1 mL) and toluene (5 mL) the mixture was stirred at 25 °C for 5 minutes, and ethynyltrimethylsilane (**64**, 354 mg, 3.60 mmol) was added. After this the mixture had been stirred at 25 °C for an additional 16 h. KOH (337 mg, 6 mmol), water (0,5 mL, 3.00 mmol) and methanol (2 mL) was added in one portion followed after stirring 3 h at room temperature by the addition of 1-iodo-4-(trifluoromethyl)benzene (**68**, 816 mg, 3.00 mmol). After another 16 h of stirring a saturated NH_4Cl solution (60 mL) was added. The mixture was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were washed with HCl (2 N, 50 mL), water (50 mL) and saturated NaCl solution (50 mL). The organic layer was dried ($MgSO_4$) and concentrated under vacuum. The residue was purified by flash chromatography (SiO_2, 100 g, PE/EtOAc, 99:1, R_f = 0.38) to give **221** (662 mg, 2.22 mmol, 74 %) as a light brown solid.

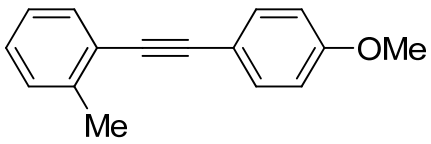
^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.83 (s, 3 H), 6.87–6.90 (m, 2 H), 7.46–7.50 (m, 2 H), 7.58 (d, *J* = 9.0 Hz, 2 H), 7.60 (d, *J* = 8.8 Hz, 2 H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$): δ = 55.3 (CH_3), 86.8 (C), 91.9 (C), 114.2 (CH), 114.6 (C), 124.0 (q, *J* = 272 Hz, CF_3), 125.2 (d, *J* = 3 Hz, CH), 129.5 (q, *J* = 33 Hz, C), 131.6 (CH), 133.3 (CH), 160.0 (C) ppm.

IR (neat): $\tilde{\nu}$ = 3027, 2970, 2845, 2217, 1600, 1503, 1319, 1290, 1252, 1165, 1124, 1103, 1065, 1030, 840 cm^{-1}.

MS (EI): *m/z* (%) = 276 (100) $[M]^+$, 261 (33), 233 (24), 232 (13), 183 (7), 138 (5).

HRMS: calcd. ($C_{16}H_{11}F_3O$) 276.0762; found 276.0756.



$C_{16}H_{14}O$
MW: 222.28

1-((4-Methoxyphenyl)ethynyl)-2-methylbenzene (**222**): 1-Iodo-2-methylbenzene (**72**, 654 mg, 3.00 mmol), $Pd(PPh_3)_2Cl_2$ (42 mg, 0.06 mmol, 2 mol-%), CuI (11 mg, 0.06 mmol, 2 mol-%) and PPh_3 (31 mg, 0.12 mmol, 4 mol-%) were placed in an oven dried and argon-filled Schlenk tube. After addition of *i*Pr_2NH (1 mL) and toluene (5 mL) the mixture was stirred at 25 °C for 5 minutes, and ethynyltrimethylsilane (**64**, 354 mg, 3.60 mmol) was added. After this the mixture had been stirred at 25 °C for an additional 16 h. KOH (337 mg, 6 mmol), water (0,5 mL, 3.00 mmol) and methanol (2 mL) was added in one portion followed after stirring 3 h at room temperature by the addition of 1-iodo-4-methoxybenzene (**71**, 702 mg, 3.00 mmol). After another 16 h of stirring a saturated NH_4Cl solution (60 mL) was added. The mixture was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were washed with HCl (2 N, 50 mL), water (50 mL) and saturated NaCl solution (50 mL). The organic layer was dried ($MgSO_4$) and concentrated under vacuum. The residue was purified by flash chromatography (SiO_2, 100 g, PE/EtOAc, 99:1, R_f = 0.22) to give **222** (547 mg, 2.46 mmol, 82 %) as a light brown solid.

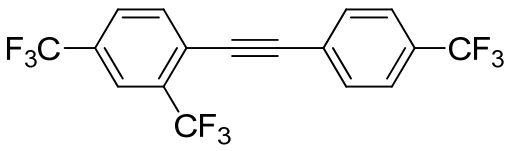
^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.50 (s, 3 H), 3.81 (s, 3 H), 6.85–6.89 (m, 2 H), 7.12–7.17 (m, 1 H), 7.18–7.24 (m, 2 H), 7.45–7.49 (m, 3 H) ppm.

^{13}C NMR (126 MHz, DEPT, $CDCl_3$): δ = 20.7 (CH_3), 55.3 (CH_3), 87.0 (C), 93.3 (C), 114.0 (CH), 115.6 (C), 123.3 (C), 125.5 (CH), 127.9 (CH), 129.4 (CH), 131.6 (CH), 132.9 (CH), 139.9 (C), 159.5 (C) ppm.

IR (neat): $\tilde{\nu}$ = 3013, 2961, 2838, 1596, 1506, 1456, 1286, 1256, 1172, 1029, 831, 755 cm^{-1}.

MS (EI): *m/z* (%) = 222 (100) $[M]^+$, 221 (22), 207 (48), 179 (33), 178 (63), 177 (15), 175 (13, 152 (12).

HRMS: calcd. ($C_{16}H_{14}O$) 222.1045; found 222.1051.



$C_{17}H_7F_9$
MW: 382.22

2,4-Bis(trifluoromethyl)-1-((4-(trifluoromethyl)phenyl)ethynyl)benzene (**223**): 1-Bromo-2,4-bis(trifluoromethyl)benzene (**217**, 879 mg, 3.00 mmol), $Pd(PPh_3)_2Cl_2$ (42 mg, 0.06 mmol, 2 mol-%), CuI (11 mg, 0.06 mmol, 2 mol-%) and PPh_3 (31 mg, 0.12 mmol, 4 mol-%) were placed in an oven dried and argon-filled Schlenk tube. After addition of *i*Pr_2NH (1 mL) and toluene (5 mL) the mixture was stirred at 25 °C for 5 minutes, and ethynyltrimethylsilane (**64**, 354 mg, 3.60 mmol) was added. After this the mixture had been stirred at 80 °C for an additional 16 h, then cooled to room temperature. KOH (337 mg, 6 mmol), water (0,5 mL, 3.00 mmol) and methanol (2 mL) was added in one portion followed after stirring 3 h at room temperature by the addition of 1-iodo-4-(trifluoromethyl)benzene (**68**, 816 mg, 3.00 mmol). After another 16 h of stirring a saturated NH_4Cl solution (60 mL) was added. The mixture was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were washed with HCl (2 N, 50 mL), water (50 mL) and saturated NaCl solution (50 mL). The organic layer was dried ($MgSO_4$) and concentrated under vacuum. The residue was purified by flash chromatography (SiO_2, 115 g, PE, R_f = 0.41) to give **223** (1000 mg, 2.62 mmol, 87 %) as a yellow solid.

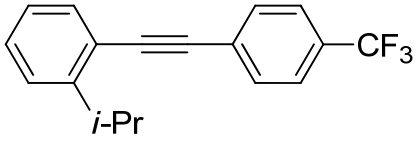
^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.64 (d, *J* = 8.6 Hz, 2 H), 7.67 (d, *J* = 8.5 Hz, 2 H), 7.81 (s, 2 H), 7.95 (s, 1 H) ppm.

^{13}C NMR (126 MHz, JMOD, $CDCl_3$): δ = 86.1 (C), 95.9 (C), 122.8 (q, *J* = 275 Hz, CF_3), 123.1 (q, *J* = 273 Hz, CF_3), 123.2–123.4 (m, CH), 123.8 (q, *J* = 272 Hz,), 124.8 (C), 125.5 (q, *J* = 4 Hz, CH), 125.8 (C), 128.4 (q, *J* = 3 Hz, CH), 130.5 (q, *J* = 34 Hz, C), 131.2 (q, *J* = 33 Hz, C), 132.1 (CH), 132.6 (q, *J* = 32 Hz, C), 134.4 (CH) ppm.

IR (neat): $\tilde{\nu}$ = 2231, 1341, 1321, 1275, 1260, 1105, 1065, 1052, 839 cm^{-1}.

MS (EI): *m/z* (%) = 382 (100) $[M]^+$, 363 (21), 313 (37), 293 (9), 243 (9), 166 (7), 141 (8).

HRMS: calcd. ($C_{25}H_6F_4$) 382.0404; found 382.0399.



$C_{18}H_{15}F_3$
MW: 288.31

1-Isopropyl-2-((4-(trifluoromethyl)phenyl)ethynyl)benzene (**224**): 1-Iodo-2-isopropylbenzene (**218**, 738 mg, 3.00 mmol), $Pd(PPh_3)_2Cl_2$ (42 mg, 0.06 mmol, 2 mol-%), CuI (11 mg, 0.06 mmol, 2 mol-%) and PPh_3 (31 mg, 0.12 mmol, 4 mol-%) were placed in an oven dried and argon-filled Schlenk tube. After addition of *i*Pr_2NH (1 mL) and toluene (5 mL) the mixture was stirred at 25 °C for 5 minutes, and ethynyltrimethylsilane (**64**, 354 mg, 3.60 mmol) was added. After this the mixture had been stirred at 25 °C for an additional 16 h. KOH (337 mg, 6 mmol), water (0,5 mL, 3.00 mmol) and methanol (2 mL) was added in one portion followed after stirring 3 h at room temperature by the addition of 1-iodo-4-(trifluoromethyl)benzene (**68**, 816 mg, 3.00 mmol). After another 16 h of stirring a saturated NH_4Cl solution (60 mL) was added. The mixture was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were washed with HCl (2 N, 50 mL), water (50 mL) and saturated NaCl solution (50 mL). The organic layer was dried ($MgSO_4$) and concentrated under vacuum. The residue was purified by flash chromatography (SiO_2, 115 g, PE, R_f = 0.46) to give **219** (717 mg, 2.49 mmol, 83 %) as a light yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.31 (s, 3 H), 1.32 (s, 3 H), 3.47–3.56 (m, 1 H), 7.13–7.20 (m, 1 H), 7.27–7.36 (m, 2 H), 7.52 (d, *J* = 7.8 Hz, 1 H), 7.58–7.65 (m, 4 H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$): δ = 23.1 (CH_3), 31.8 (CH), 90.8 (C), 91.6 (C), 121.3 (C), 124.5 (q, *J* = 273 Hz, CF_3), 125.1 (CH), 125.3 (q, *J* = 4 Hz, CH), 125.7 (CH), 127.5 (C), 129.3 (CH), 129.8 (q, *J* = 33 Hz, C), 131.7 (CH), 132.5 (CH), 150.8 (C) ppm.

IR (neat): $\tilde{\nu}$ = 2964, 1614, 1319, 1166, 1124, 1104, 1064, 839, 755 cm^{-1}.

MS (EI): *m/z* (%) = 288 (87) $[M]^+$, 274 (19), 273 (100), 233 (53), 204 (32), 129 (23).

HRMS: calcd. ($C_{18}H_{15}F_3$) 276.0762; found 276.0756.

6. Kristallographischer Anhang

Kristalldaten, Angaben zur Messung und zur Strukturlösung von **109**.

Identification code	R08036	
Empirical formula	C_{18} H_{14} F N O_2	
Formula weight	295.30	
Temperature	153(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	$P2_1/c$	
Unit cell dimensions	a = 7.7363(6) Å	α = 90°.
	b = 17.3543(8) Å	β = 96.878(9)°.
	c = 10.9986(8) Å	γ = 90°.
Volume	1466.02(17) $Å^3$	
Z	4	
Density (calculated)	1.338 Mg/m^3	
Absorption coefficient	0.096 mm^{-1}	
F(000)	616	
Crystal size	0.60 x 0.27 x 0.20 mm^3	
Theta range for data collection	2.35 to 26.16°.	
Index ranges	-9<=h<=9, -21<=k<=21, -13<=l<=13	
Reflections collected	15703	
Independent reflections	2910 [R(int) = 0.0691]	
Observed reflections	1796 [I>2sigma(I)]	
Completeness to theta = 26.16°	99.0 %	
Absorption correction	None	
Max. and min. transmission	0.9811 and 0.9446	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2910 / 0 / 201	
Goodness-of-fit on F^2	0.806	
Final R indices [I>2sigma(I)]	R1 = 0.0287, wR2 = 0.0621	
R indices (all data)	R1 = 0.0558, wR2 = 0.0662	
Largest diff. peak and hole	0.195 and -0.131 $e.Å^{-3}$	

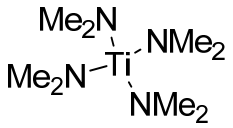
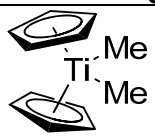
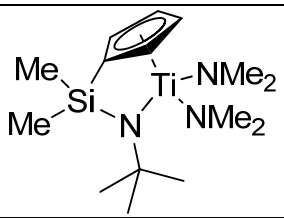
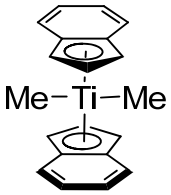
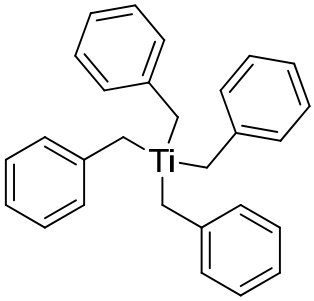
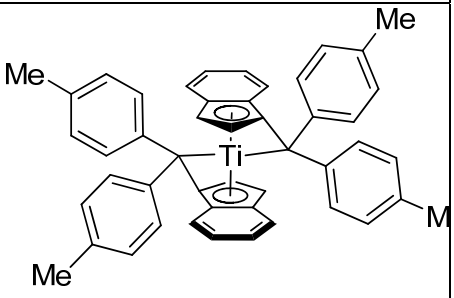
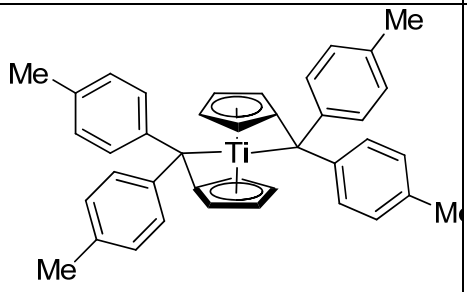
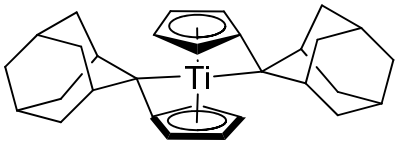
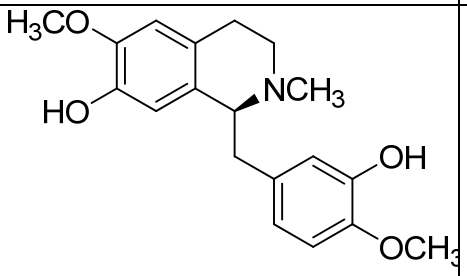
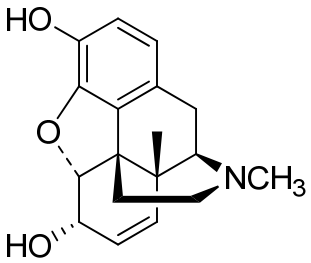
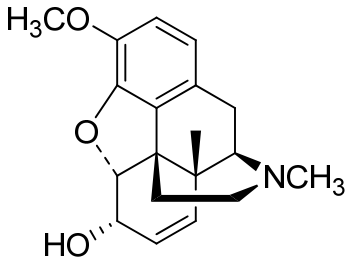
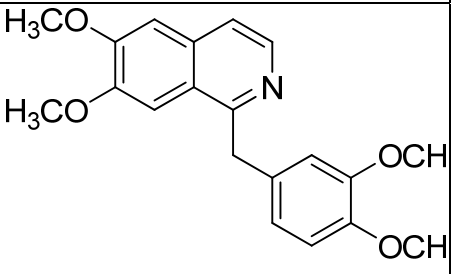
Kristalldaten, Angaben zur Messung und zur Strukturlösung von **182**.

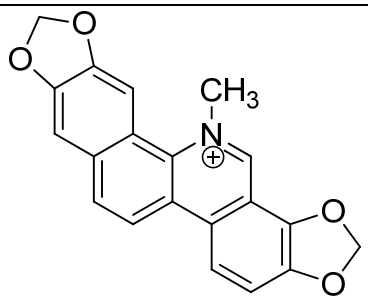
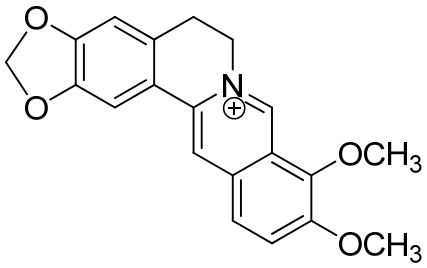
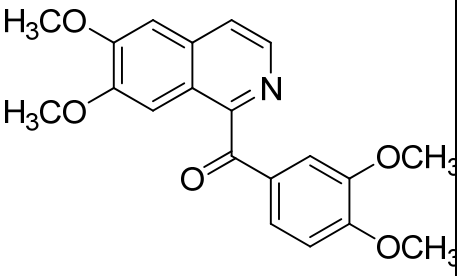
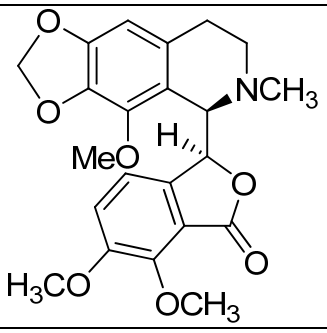
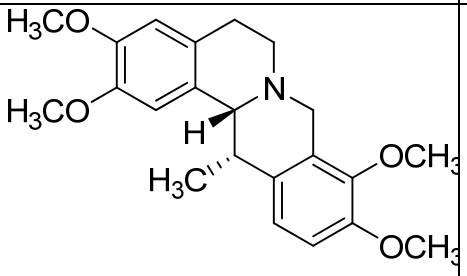
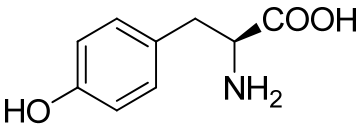
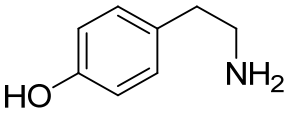
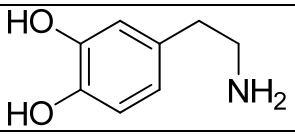
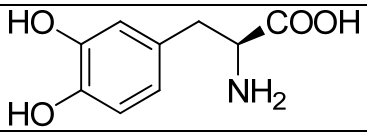
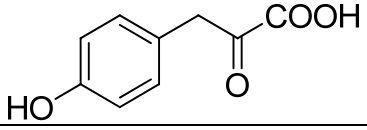
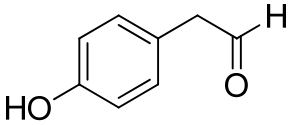
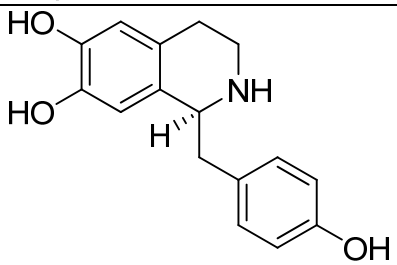
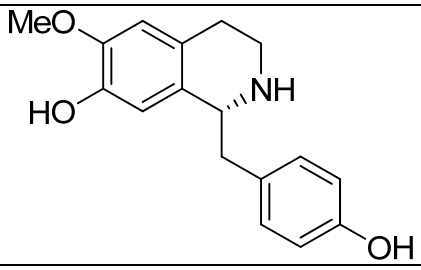
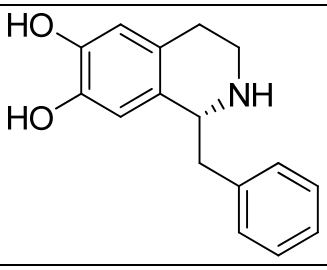
Identification code	R07099	
Empirical formula	C_{18} H_{15} F_2 N O_2	
Formula weight	315.31	
Temperature	153(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	P-1	
Unit cell dimensions	a = 4.9111(5) Å	α = 81.075(15)°.
	b = 11.5278(13) Å	β = 87.779(15)°.
	c = 13.2030(19) Å	γ = 89.756(13)°.
Volume	737.87(15) $Å^3$	
Z	2	
Density (calculated)	1.419 Mg/m^3	
Absorption coefficient	0.109 mm^{-1}	
F(000)	328	
Crystal size	1.00 x 0.19 x 0.07 mm^3	
Theta range for data collection	2.55 to 28.28°.	
Index ranges	-5<=h<=5, -15<=k<=15, -17<=l<=17	
Reflections collected	11315	
Independent reflections	3369 [R(int) = 0.0646]	
Observed reflections	1728 [I>2sigma(I)]	
Completeness to theta = 25.00°	94.2 %	
Absorption correction	None	
Max. and min. transmission	0.9924 and 0.8984	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3369 / 0 / 253	
Goodness-of-fit on F^2	0.780	
Final R indices [I>2sigma(I)]	R1 = 0.0376, wR2 = 0.0831	
R indices (all data)	R1 = 0.0822, wR2 = 0.0924	
Largest diff. peak and hole	0.201 and -0.267 $e.Å^{-3}$	

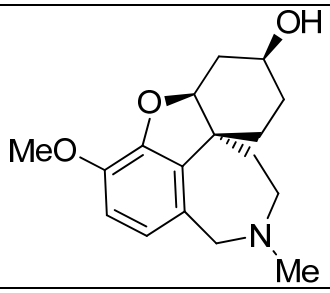
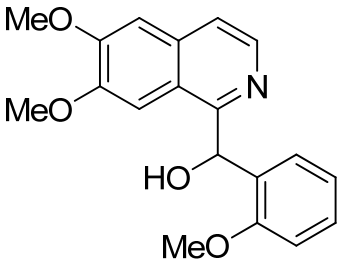
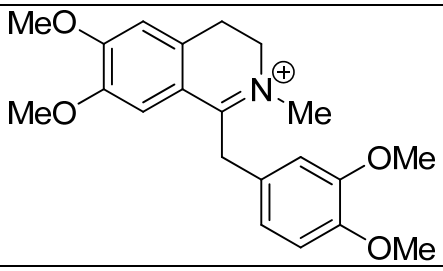
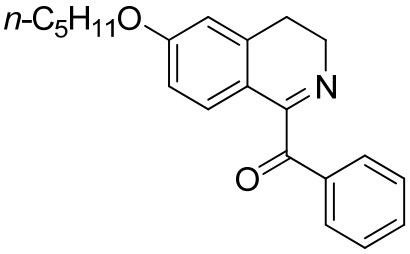
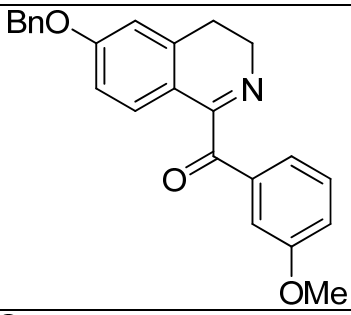
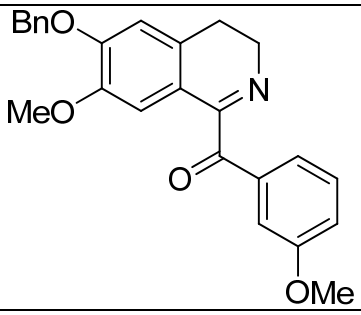
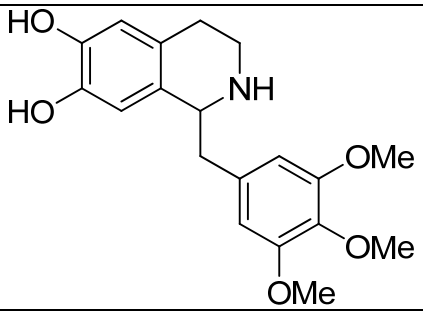
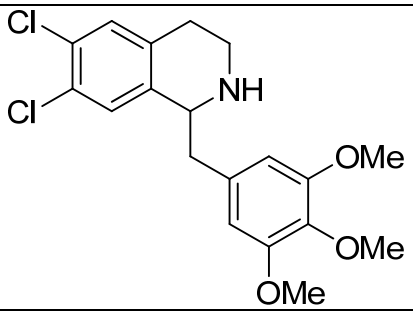
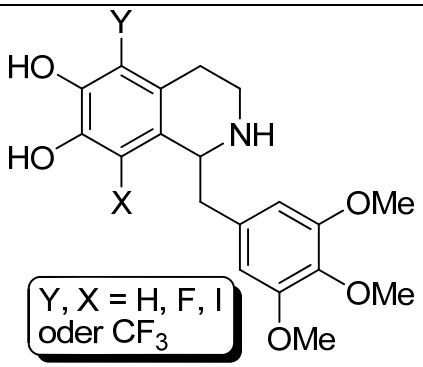
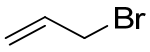
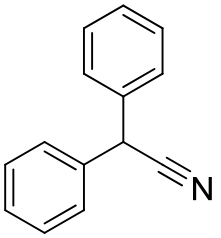
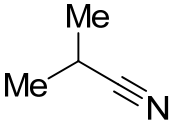
Kristalldaten, Angaben zur Messung und zur Strukturlösung von **187**.

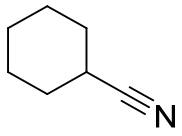
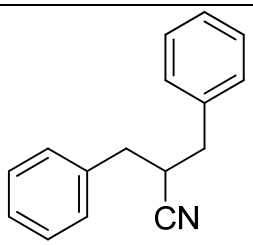
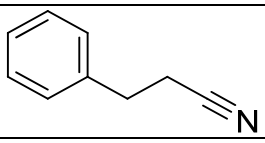
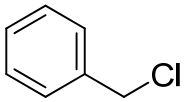
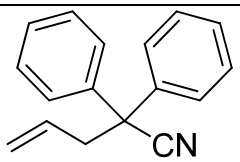
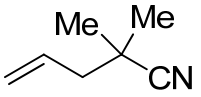
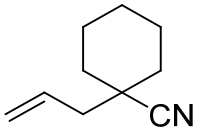
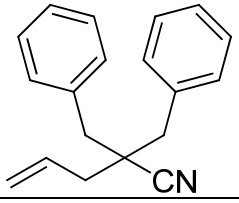
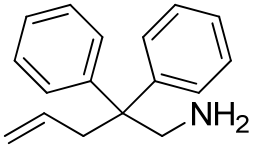
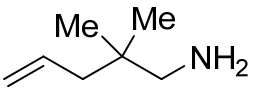
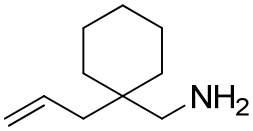
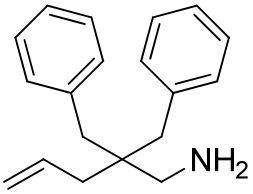
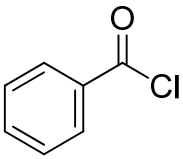
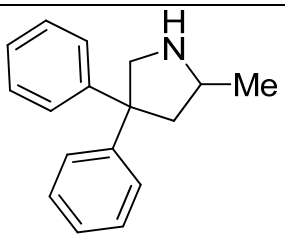
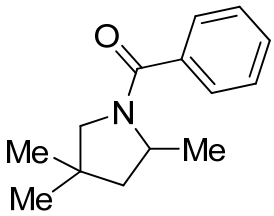
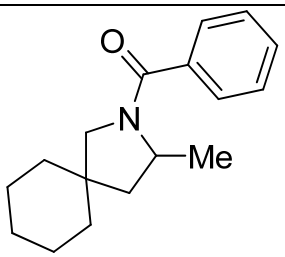
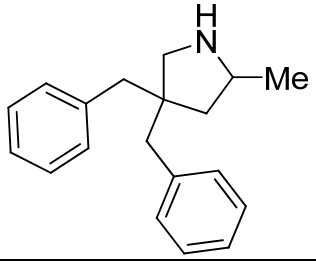
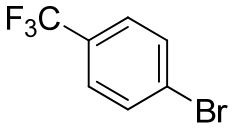
Identification code	R08060	
Empirical formula	C_{18} H_{17} N O_3	
Formula weight	295.33	
Temperature	153(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	Pbca	
Unit cell dimensions	a = 13.9893(4) Å	α = 90°.
	b = 8.3037(3) Å	β = 90°.
	c = 26.2780(9) Å	γ = 90°.
Volume	3052.53(18) $Å^3$	
Z	8	
Density (calculated)	1.285 Mg/m^3	
Absorption coefficient	0.088 mm^{-1}	
F(000)	1248	
Crystal size	0.80 x 0.47 x 0.37 mm^3	
Theta range for data collection	2.13 to 26.16°.	
Index ranges	-17<=h<=17, -10<=k<=10, -32<=l<=32	
Reflections collected	24978	
Independent reflections	3021 [R(int) = 0.0428]	
Observed reflections	2366 [I>2sigma(I)]	
Completeness to theta = 26.16°	99.0 %	
Absorption correction	None	
Max. and min. transmission	0.9683 and 0.9331	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3021 / 0 / 250	
Goodness-of-fit on F^2	1.027	
Final R indices [I>2sigma(I)]	R1 = 0.0299, wR2 = 0.0799	
R indices (all data)	R1 = 0.0398, wR2 = 0.0828	
Largest diff. peak and hole	0.224 and -0.144 $e.Å^{-3}$	

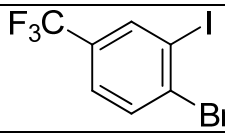
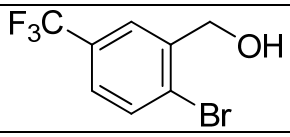
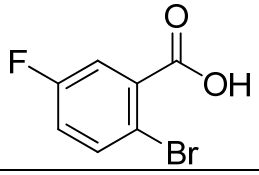
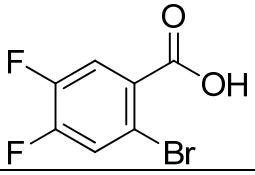
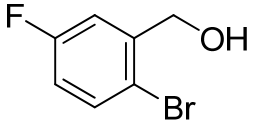
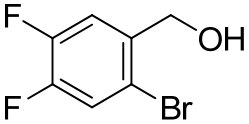
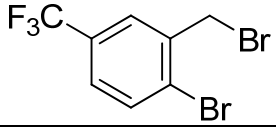
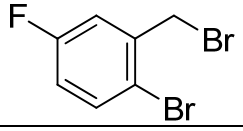
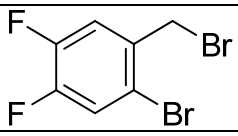
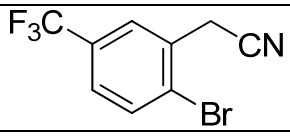
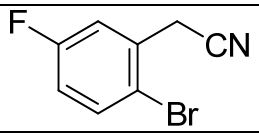
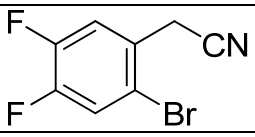
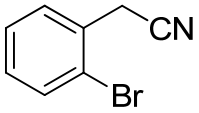
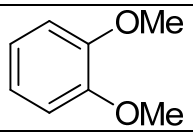
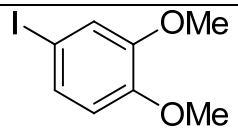
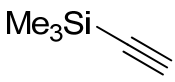
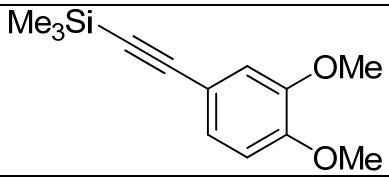
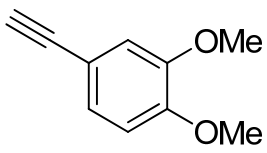
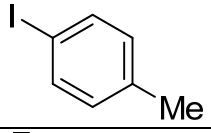
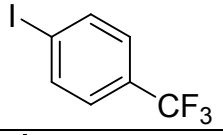
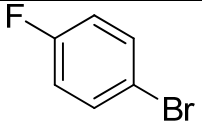
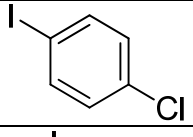
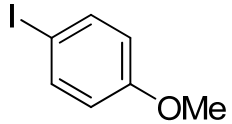
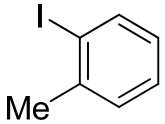
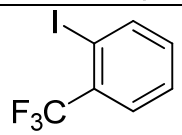
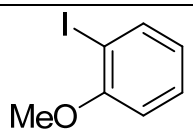
7. Legende nummerierter Verbindungen

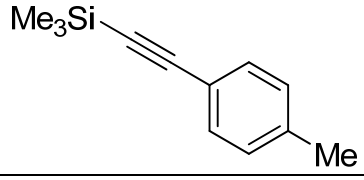
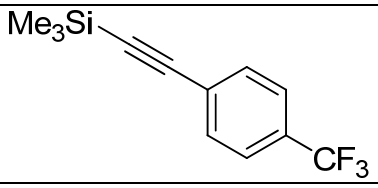
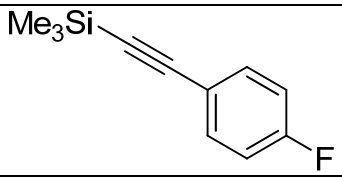
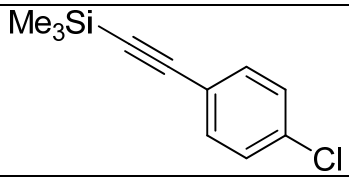
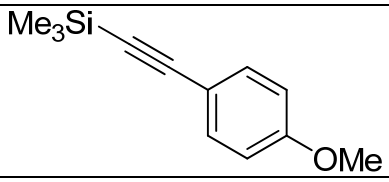
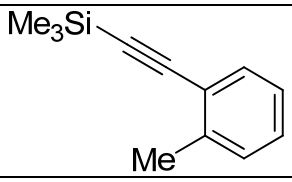
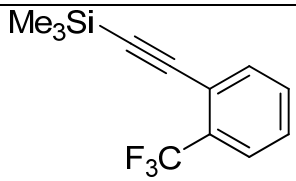
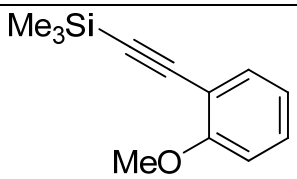
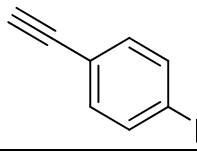
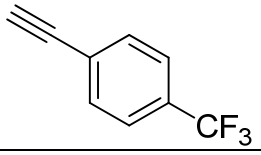
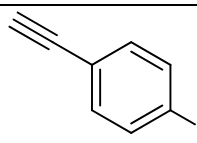
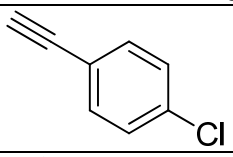
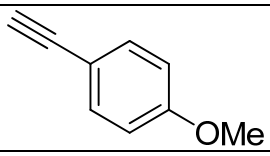
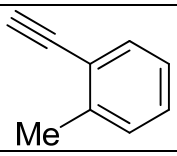
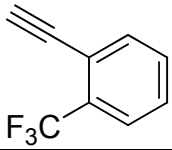
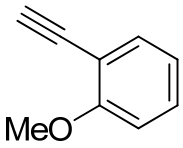
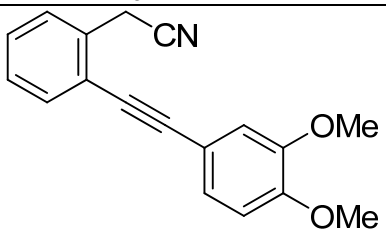
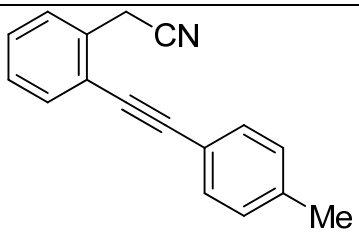
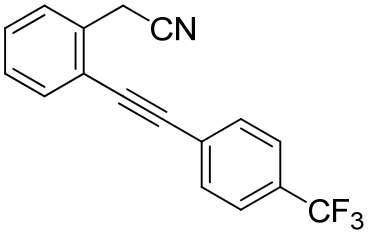
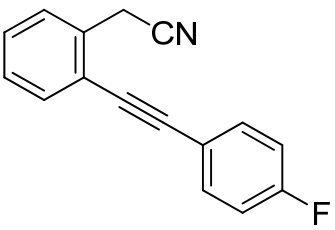
Nr.	Verbindung	Nr.	Verbindung
I		**II**	
III		**IV**	
V		**VI**	
VII		**VIII**	
1		**2**	
3		**4**	

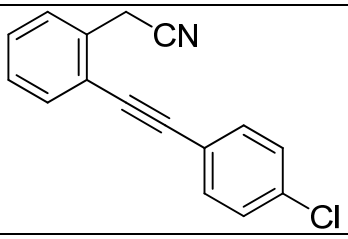
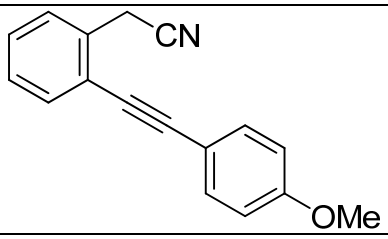
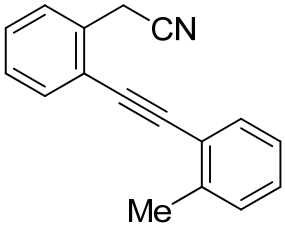
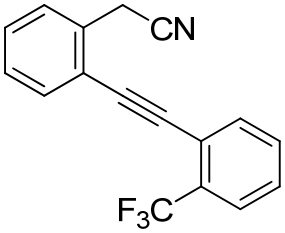
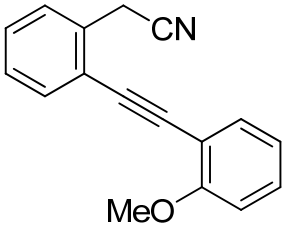
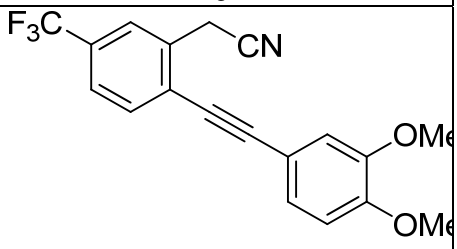
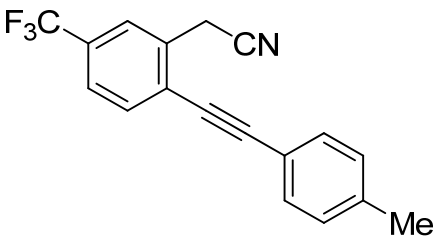
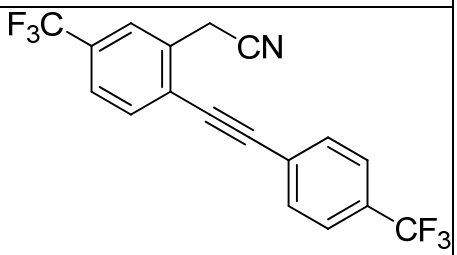
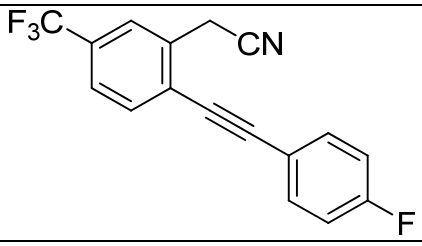
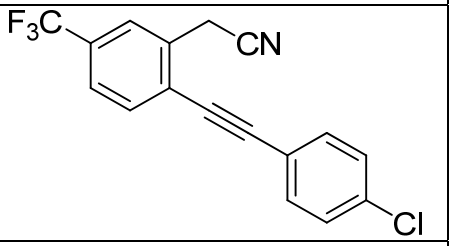
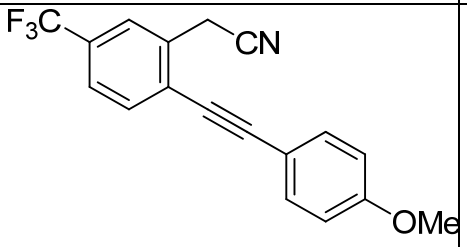
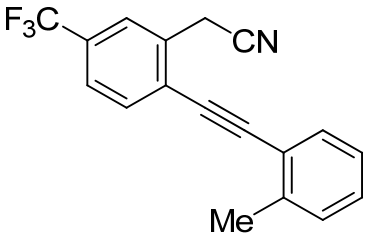
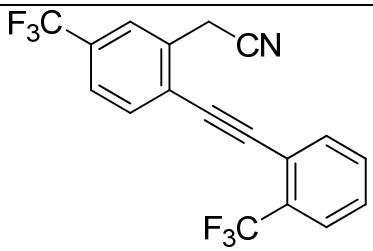
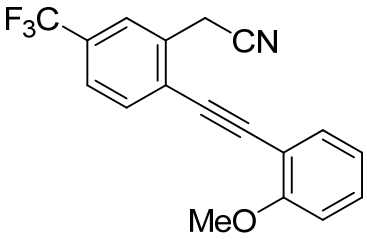
5		**6**	
7		**8**	
9		**10**	
11		**12**	
13		**14**	
15		**16**	
17		**18**	

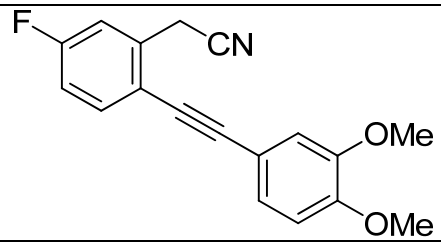
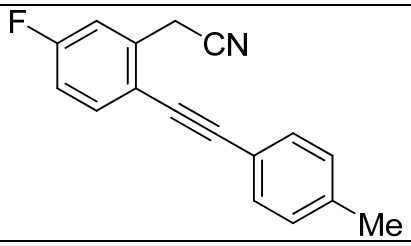
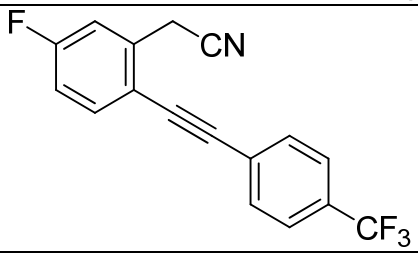
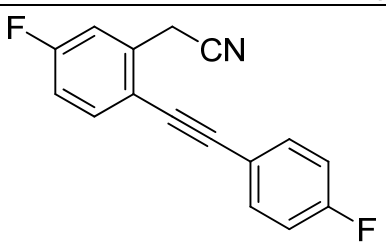
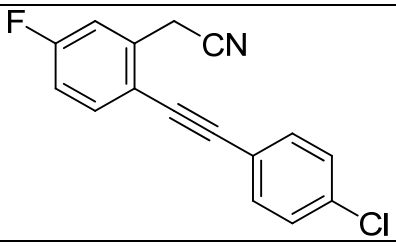
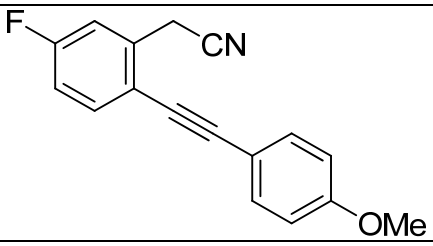
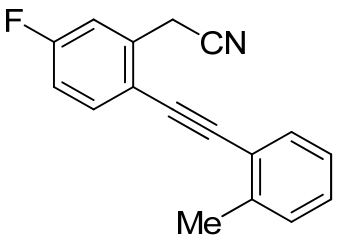
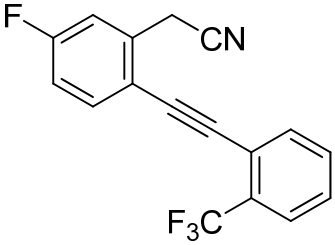
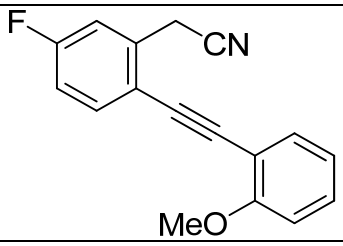
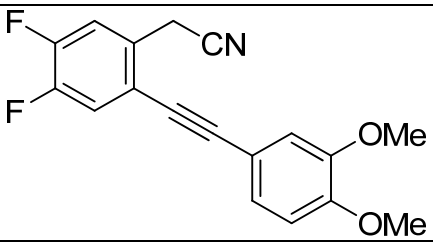
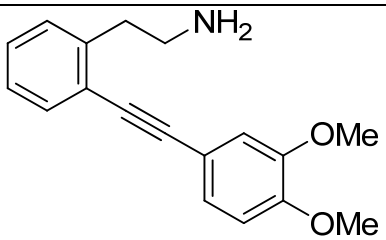
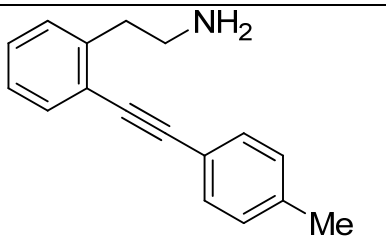
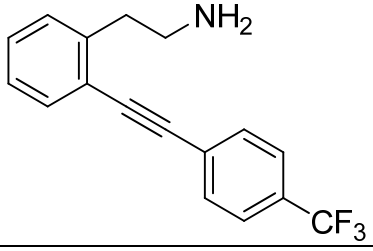
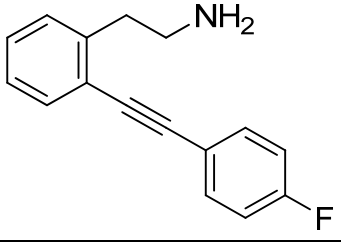
19		**20**	
21		**22**	
23		**24**	
25		**26**	
27		**28**	
29		**30**	

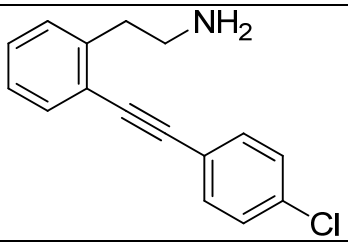
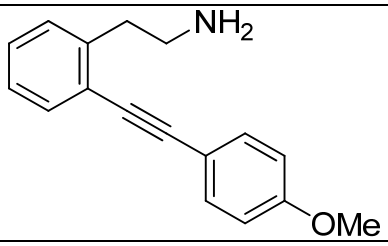
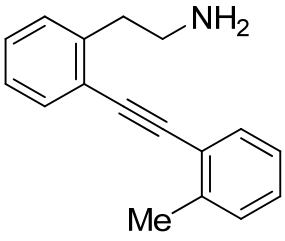
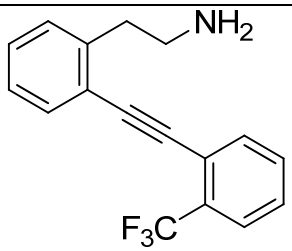
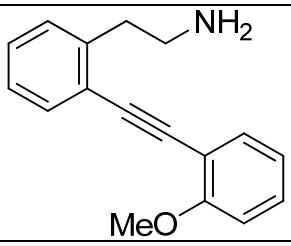
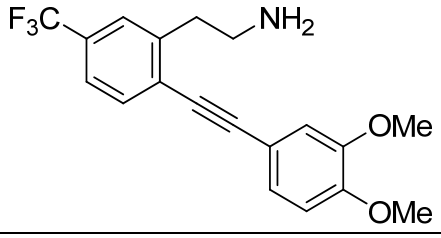
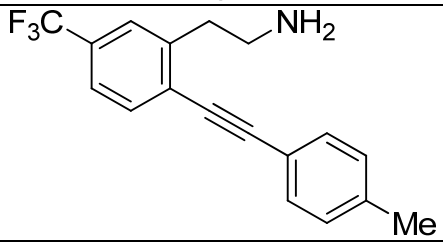
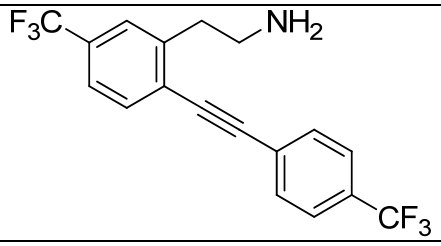
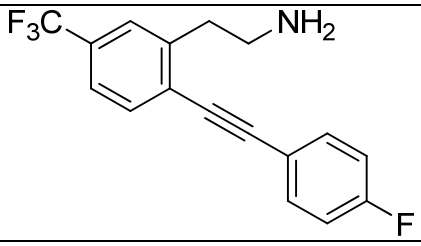
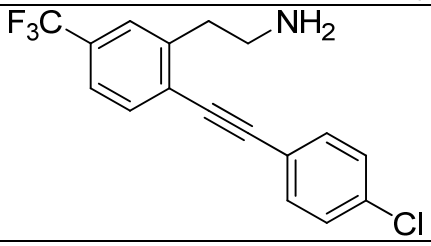
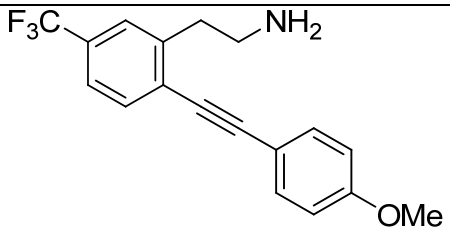
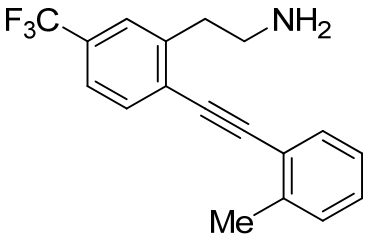
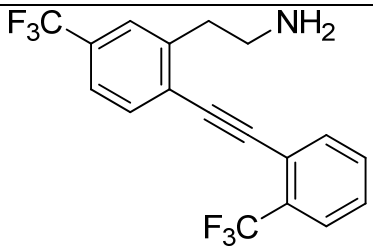
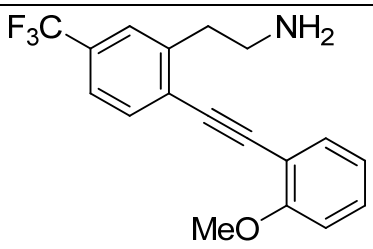
31		**32**	
33		**34**	
35		**36**	
37		**38**	
39		**40**	
41		**42**	
43		**44**	
45		**46**	
47		**48**	

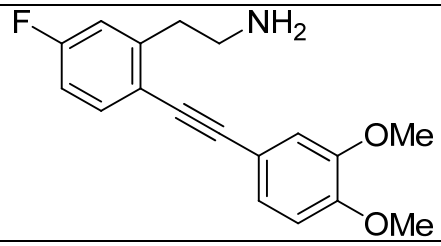
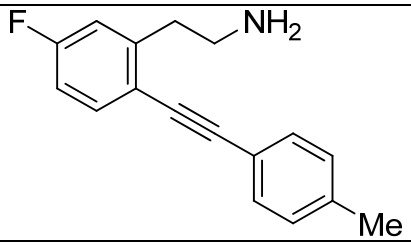
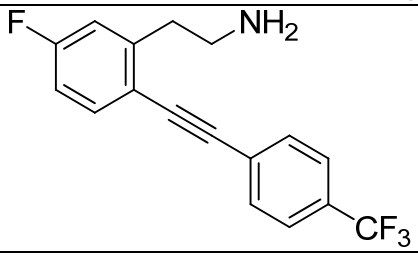
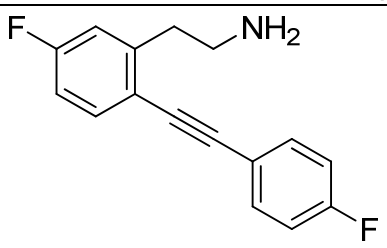
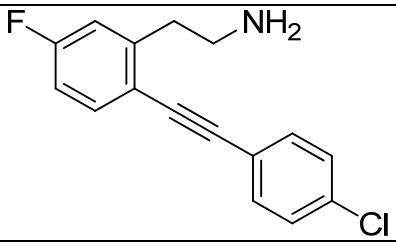
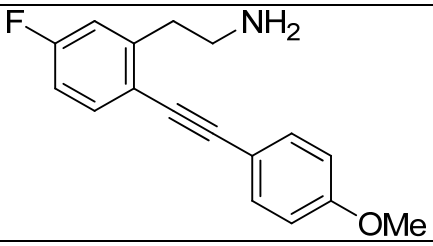
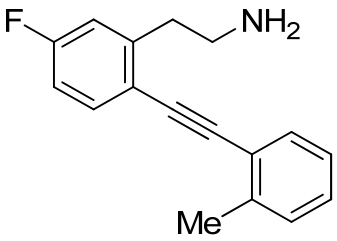
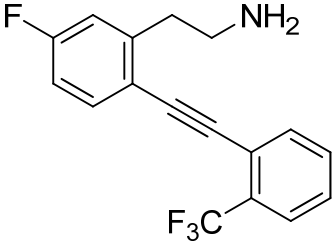
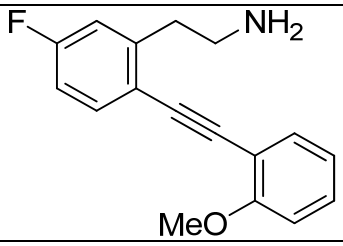
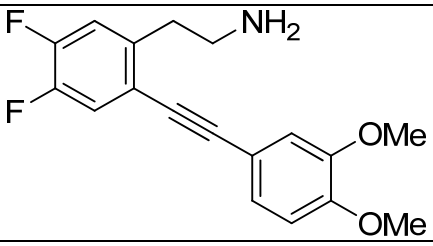
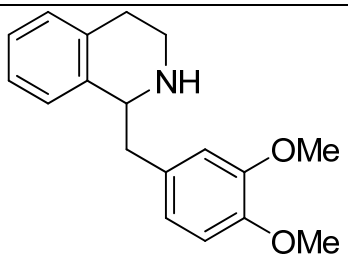
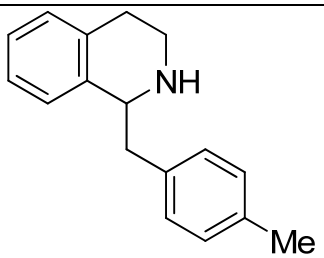
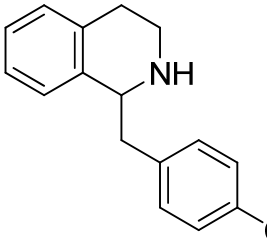
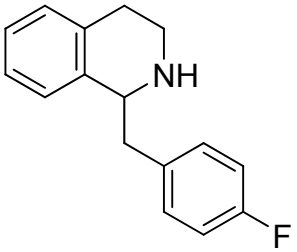
49		**50**	
51		**52**	
53		**54**	
55		**56**	
57		**58**	
59		**60**	
61		**62**	
63		**64**	
65		**66**	
67		**68**	
69		**70**	
71		**72**	
73		**74**	

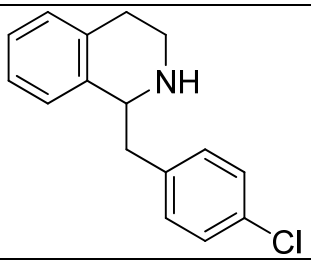
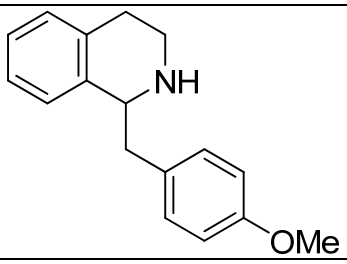
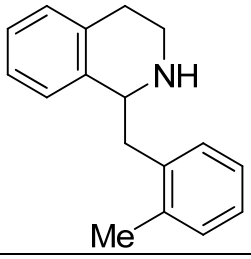
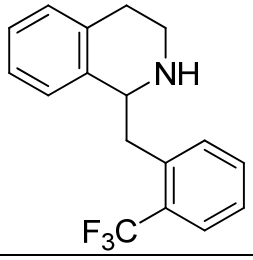
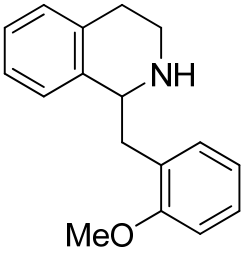
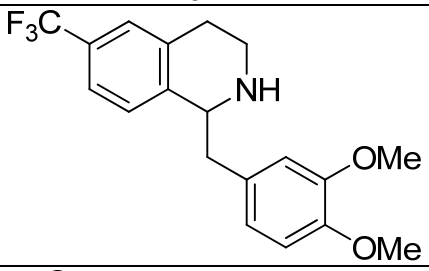
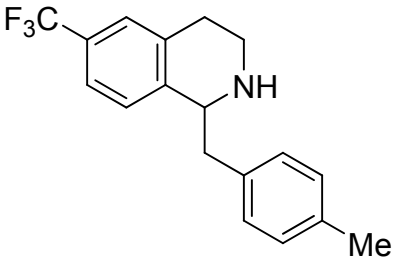
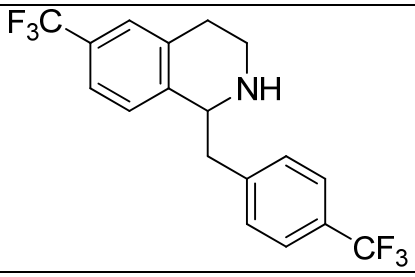
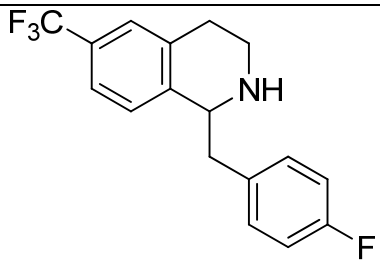
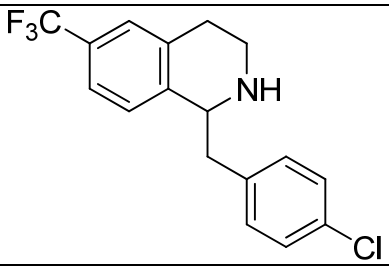
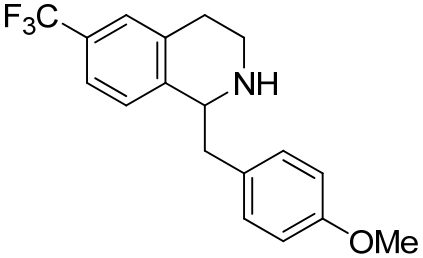
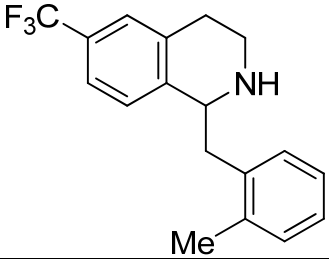
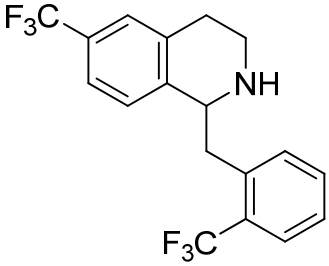
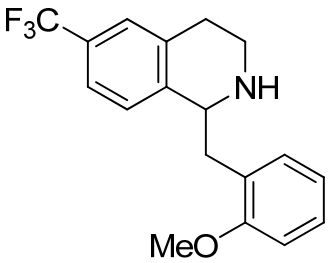
75		**76**	
77		**78**	
79		**80**	
81		**82**	
83		**84**	
85		**86**	
87		**88**	
89		**90**	
91		**92**	
93		**94**	

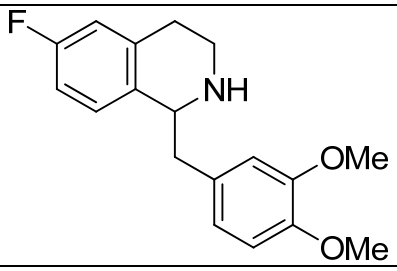
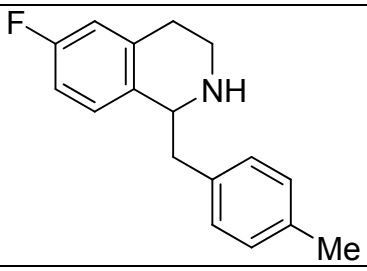
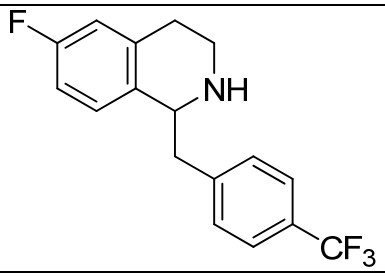
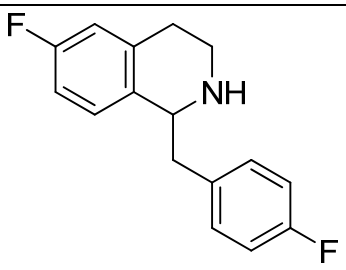
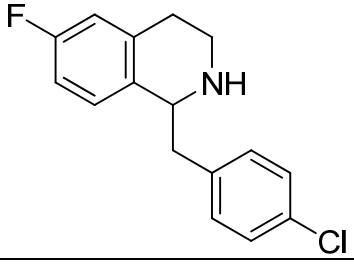
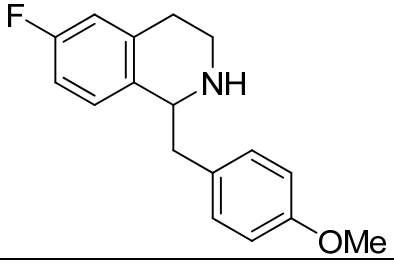
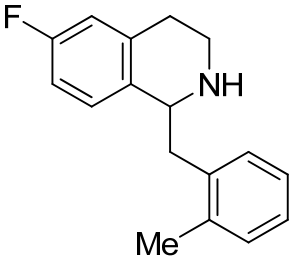
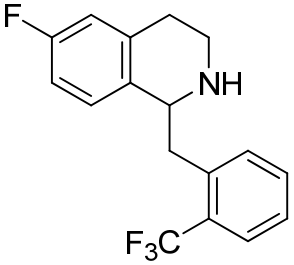
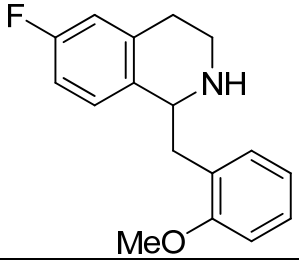
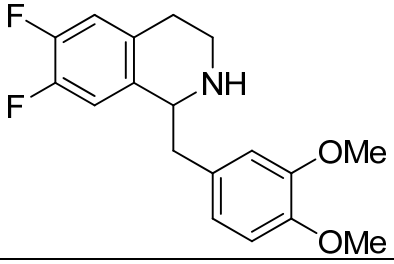
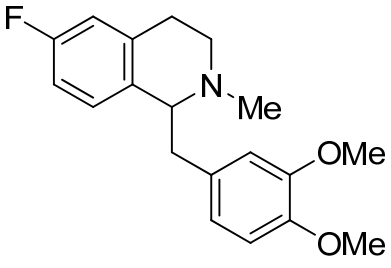
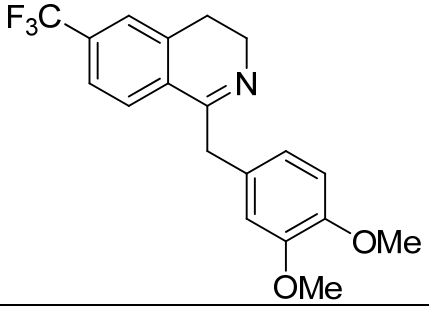
95		**96**	
97		**98**	
99		**100**	
101		**102**	
103		**104**	
105		**106**	
107		**108**	

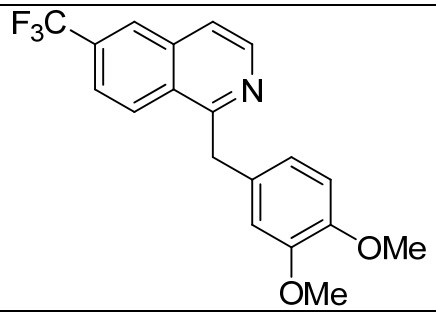
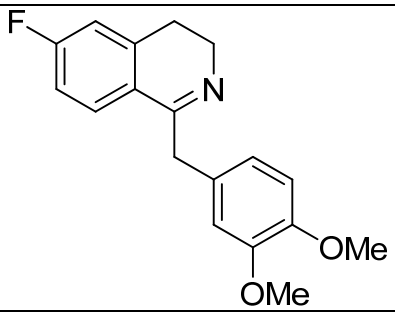
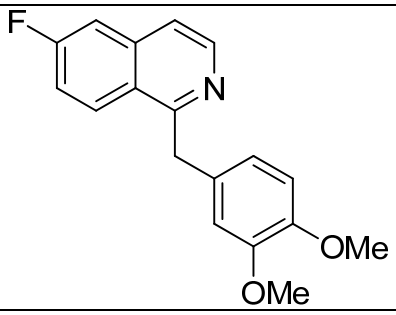
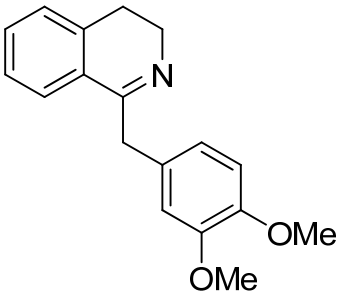
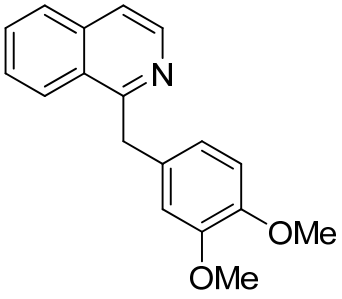
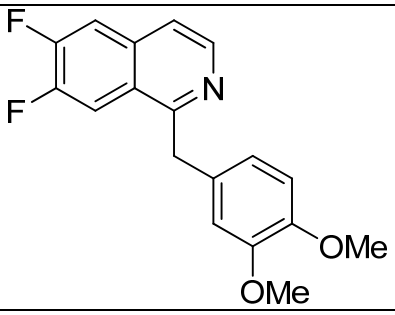
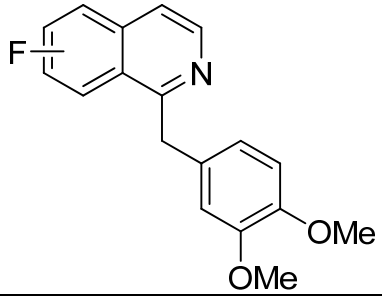
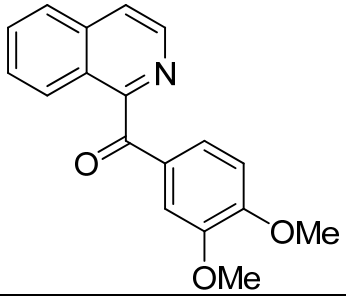
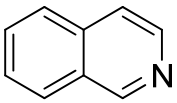
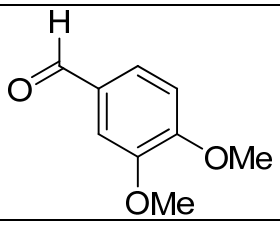
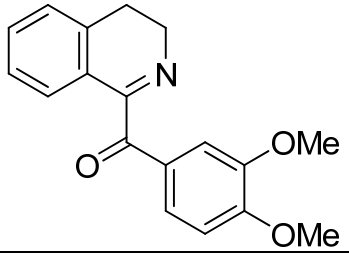
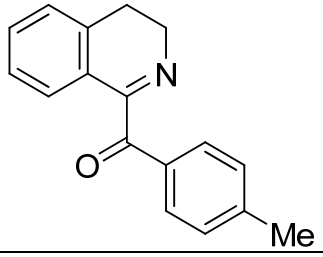
109		**110**	
111		**112**	
113		**114**	
115		**116**	
117		**118**	
119		**120**	
121		**122**	

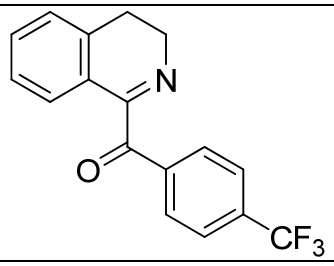
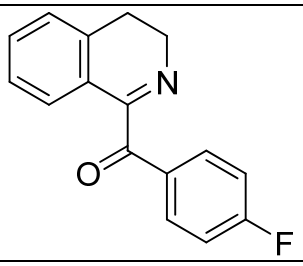
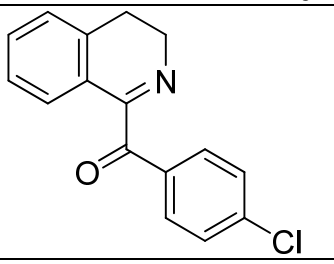
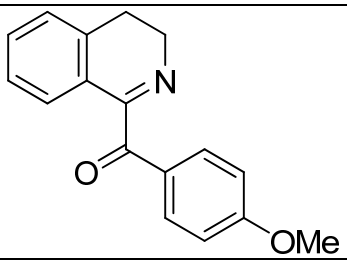
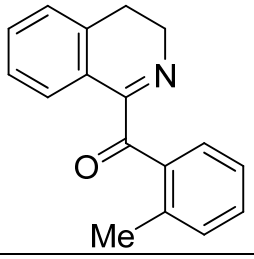
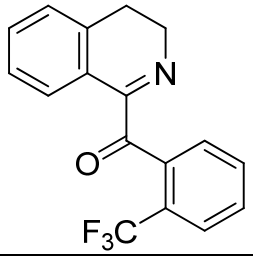
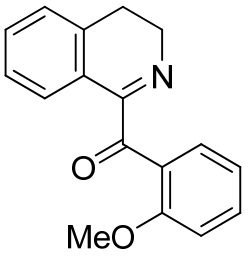
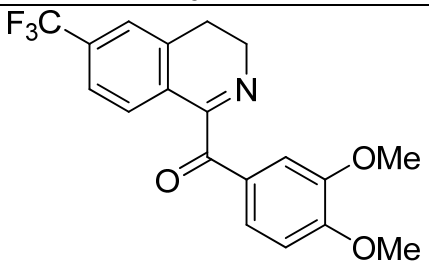
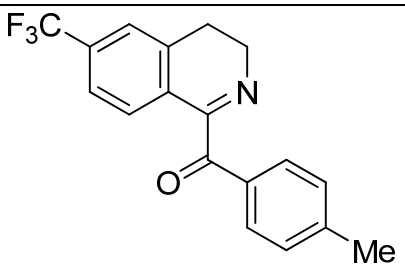
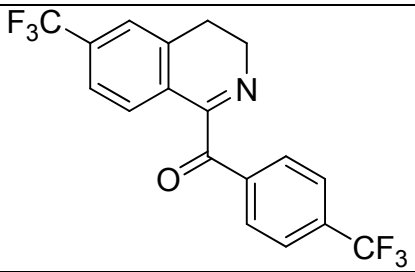
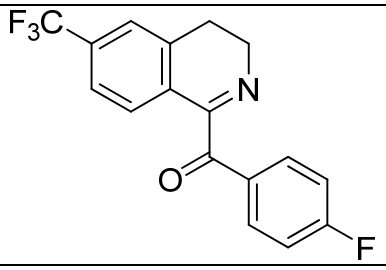
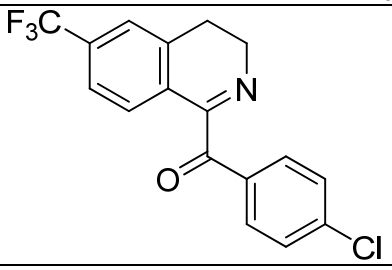
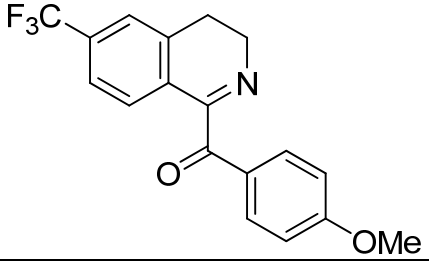
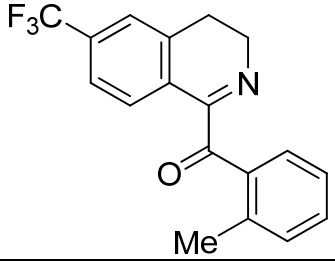
123		**124**	
125		**126**	
127		**128**	
129		**130**	
131		**132**	
133		**134**	
135		**136**	

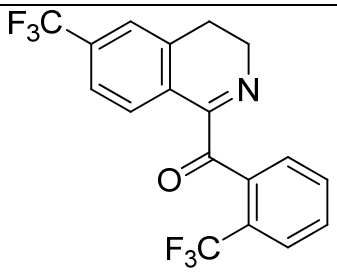
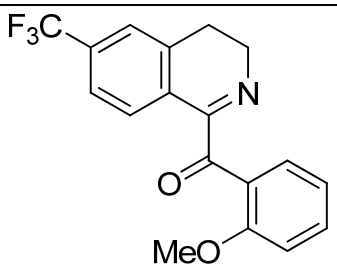
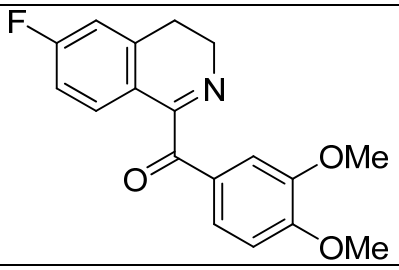
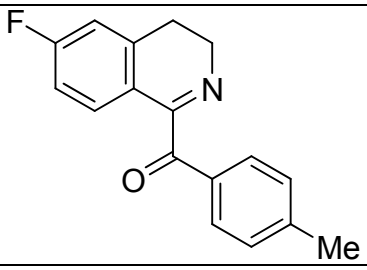
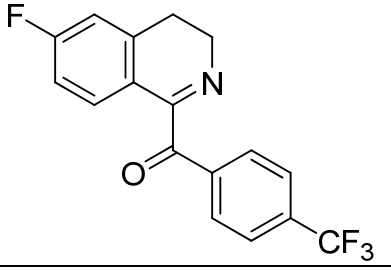
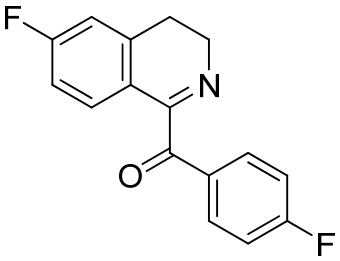
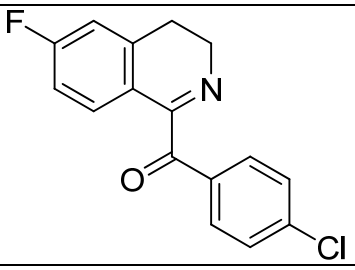
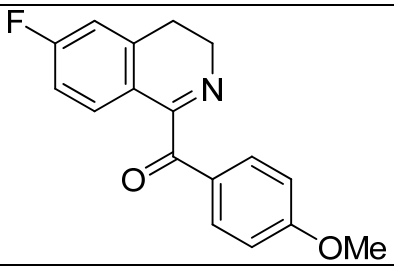
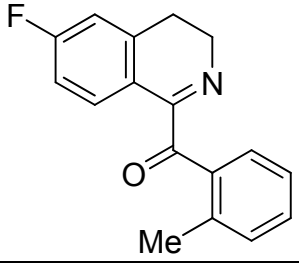
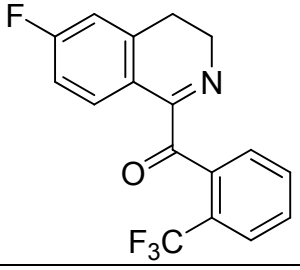
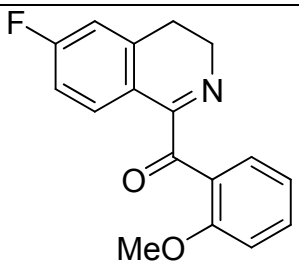
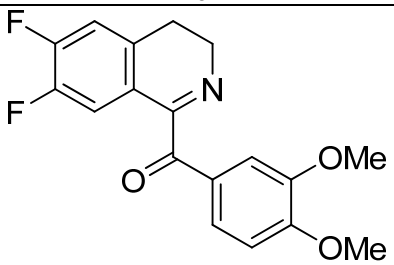
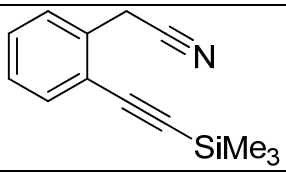
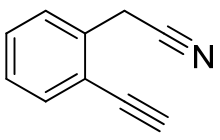
137		**138**	
139		**140**	
141		**142**	
143		**144**	
145		**146**	
***rac*-147**		***rac*-148**	
***rac*-149**		***rac*-150**	

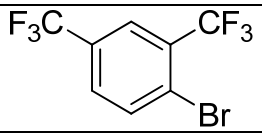
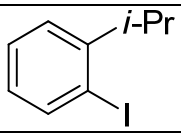
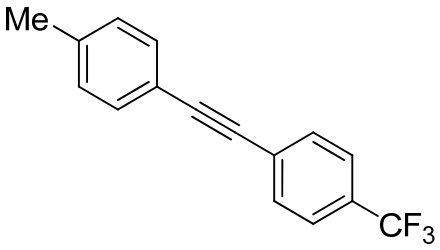
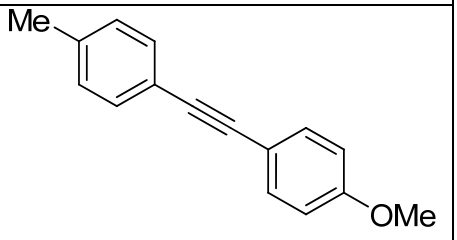
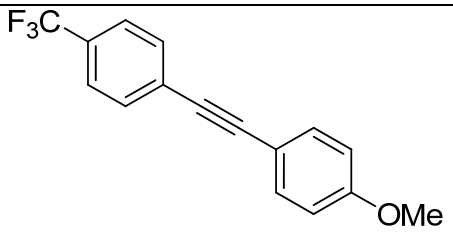
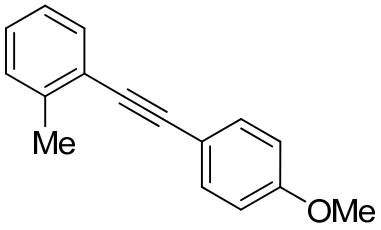
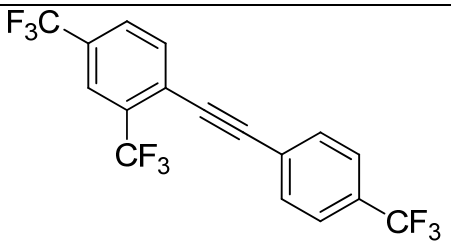
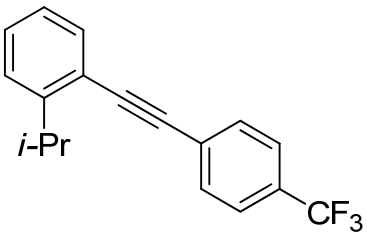
***rac*-151**		***rac*-152**	
***rac*-153**		***rac*-154**	
***rac*-155**		***rac*-156**	
***rac*-157**		***rac*-158**	
***rac*-159**		***rac*-160**	
***rac*-161**		***rac*-162**	
***rac*-163**		***rac*-164**	

***rac*-165**		***rac*-166**	
***rac*-167**		***rac*-168**	
***rac*-169**		***rac*-170**	
***rac*-171**		***rac*-172**	
***rac*-173**		***rac*-174**	
***rac*-175**		**176**	

177		**178**	
179		**180**	
181		**182**	
183		**184**	
185		**186**	
187		**188**	

189		**190**	
191		**192**	
193		**194**	
195		**196**	
197		**198**	
199		**200**	
201		**202**	

203		**204**	
205		**206**	
207		**208**	
209		**210**	
211		**212**	
213		**214**	
215		**216**	

217		**218**	
219		**220**	
221		**222**	
223		**224**	

8. Abkürzungen und Symbole

AChE	Acetylcholinesterase
Bn	Benzyl
BTHIQ	engl.: Benzyltetrahydroisoquionoline
Bz	Benzoyl
c	Konzentration
CGC	engl.: Constrained Geometry Catalyst
CI	Chemische Ionisation
CoMFA	eng.: Comparative Molecular Field Analysis
Cp	Cyclopentadienyl
d	Tag(e) oder Dublett (NMR)
dd	Dublett von Dublett (NMR)
DFT	Dichtefunktional-Theorie
DMF	Dimethylformamid
DMSO	Dimethylsulfoxid
ee	engl.: enantiomeric excess = Enantiomerenüberschuss
GC/MS	Masse [EI] gekoppelte Gaschromatgraphie
HRMS	eng.: High-Resolution Mass Spectrometer
Hz	Hertz
IC_{50}	mittlere inhibitorische Konzentration
Ind	Indenyl
i-Pr	iso-Propyl
IR	Infrarot
J	Kopplungskonstante zwischen zwei Kernen (NMR)
LDA	Lithiumdiisopropylamid
LM	Lösungsmittel
LS	Lewis-Säure
m	Multiplett (NMR)
m/z	Masse-zu-Ladungs-Verhältnis
MS	Massenspektrometrie
MW	engl.: Molecular Weight
NMR	engl.: Nuclear Magnetic Resonance = magnetische Kernresonanz
p	para
PPA	engl.: Polyphosphoric Acid
ppm	engl. :parts per million (NMR)
QSAR	engl. :Quantitative Structure-Activity Relationship
rac	Racemat
s	Singulett (NMR)
t	Tertiär,Triplett oder Zeit
Tetralin	Tetrahydronaphthalin
Tf_2O	Trifluormethansulfonsäureanhydrid
TFAA	Trifluoressigsäureanhydrid
THF	Tetrahydrofuran
TMS	Tetramethylsilan
Z	Formeleinheit pro Elementarzelle
δ	Chemische Verschiebung
$\tilde{\nu}$	Wellenzahl

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Ich versichere hiermit, dass ich diese Arbeit selbständig verfasst und nur die angegebenen Quellen und Hilfsmittel benutzt habe. Aus der Dissertation hervorgegangene Veröffentlichungen sind vor dem Inhaltsverzeichnis aufgeführt. Die Dissertation hat weder zu Teilen noch in Gänze einer anderen wissenschaftlichen Hochschule zur Begutachtung in einem Promotionsverfahren vorgelegen .

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