DISSERTATION

TRANSITION METAL ASSISTED ALKYNYLATION AND DEUTERATION REACTIONS

AUSGEFÜHRT ZUM ZWECKE DER ERLANGUNG DES AKADEMISCHEN GRADES EINES DOKTORS DER TECHNISCHEN WISSENSCHAFTEN UNTER DER LEITUNG VON

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Key

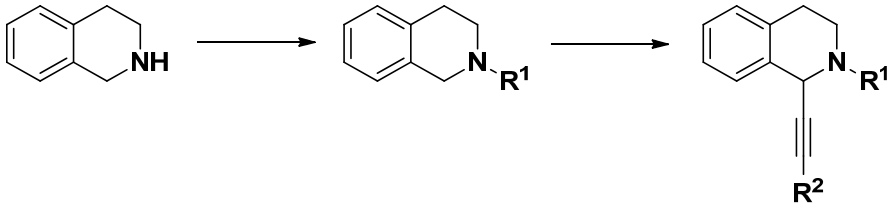
All Compounds prepared in this thesis are numbered in bold Arabic numbers. Compounds unknown to the literature are additionally underlined. General structures and compounds presented as literature examples are numbered in bold Roman numbers.

Literature citations are indicated by superscript Arabic numbers.

Abstract

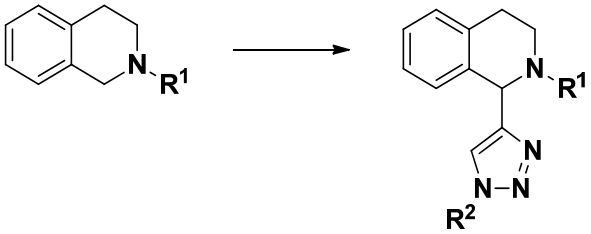
The aim of this PhD thesis was to develop a facile protocol for the synthesis of C-1 substituted 1,2,3,4-tetrahydroisoquinolines starting from N-protected 1,2,3,4-tetrahydroisoquinolines via direct functionalization of the C-1 C-H bond.

After protection of the N-H group, an alkyne functionality was inserted in the C-1 position of the 1,2,3,4-tetrahydroisoquinoline by copper-catalyzed dehydrogenative cross-coupling, using various alkyne sources.



For better handling, a one-pot protocol was investigated using alkynoic acids as alkyne sources, via a copper-catalyzed decarboxylation - alkynylation sequence at the C-1 position. Additionally, an alkynylation protocol in water and under air was developed.

In the second step, the alkyne functionality should be transformed into other functional groups. Therefore, triazole functionalities were generated via copper-catalyzed Click reaction. Furthermore, a one-pot protocol for the synthesis of C-1-triazolyl-1,2,3,4-tetrahydroisoquinolines was developed.

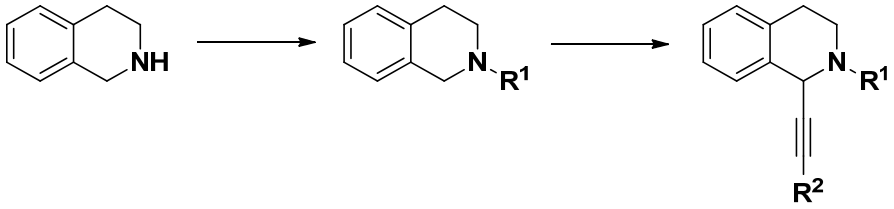


Moreover, two protocols for a ruthenium-catalyzed deuteration of both electron-rich and electron-poor N-heteroarenes with *t*-BuOD as deuterium source were developed. The batch protocol showed also to be applicable on 3 examples for the deuteration of sp^3-bonds.

Deutsche Kurzfassung

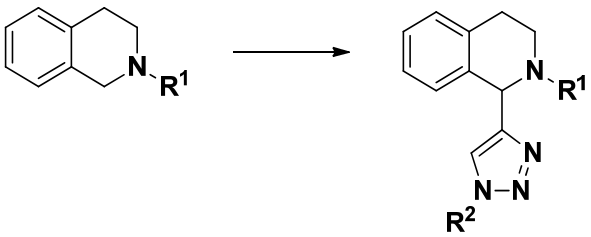
Das Ziel der vorliegenden Arbeit war es, eine einfache Methode zu entwickeln, um C-1 substituierte 1,2,3,4-Tetrahydroisochinoline, ausgehend von N-substituierten 1,2,3,4-Tetrhahydroisochinolinen, mittels direkter Funktionalisierung der C-H Bindung am C-1 herzustellen.

Nach erfolgreichem Schützen der N-H Gruppe, wurde mittels Kupfer-katalysierter oxidativer C-H Aktivierung eine Alkin-Funktionalität an der C-1 Position eingeführt.



Um eine einfachere Reaktionsführung, vor allem für kurzkettige Alkine, zu ermöglichen, wurden Alkinsäuren verwendet, welche nach Kupfer-katalysierter Decarboxylierung und anschließender Alkinilierung an der C-1 Position der 1,2,3,4-Tetrahydroisochinoline, die gewünschten substituierten Produkte bildeten. Weiters wurde eine Methode in Wasser und mit Luftsauerstoff als Oxidationsmittel entwickelt.

Das Alkin wurde anschließend mittels Kupfer-katalysierter Click-Reaktion in ein Triazol umgewandelt. Es gelang, eine One-pot Methode zur Synthese von C-1 substituierten Triazolyl-1,2,3,4-tetrahydroisochinolinen, ausgehend von N-substituierten 1,2,3,4-Tetrahydroisochinolinen, zu entwickeln.



Weiters wurden zwei Methoden zur Deuterierung von elektronenreichen und elektronenarmen N-Heteroaromaten mit *t*-BuOD als Deuterium-Quelle und Rutheniumcarbonyl als Katalysator entwickelt. Anhand von 3 Beispielen wurde auch die Möglichkeit der Deuterierung von sp^3-Bindungen gezeigt.

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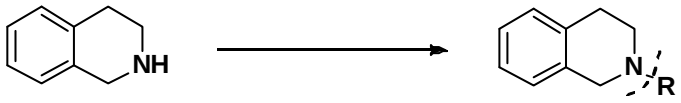
General Schemes

Synthesis of starting materials



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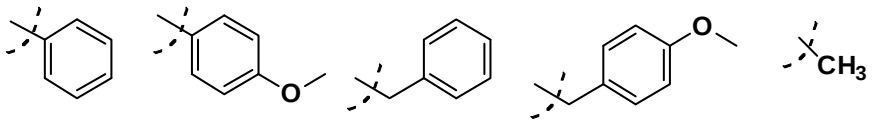

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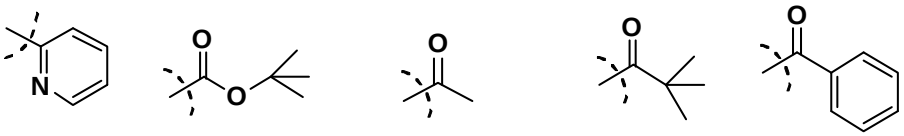
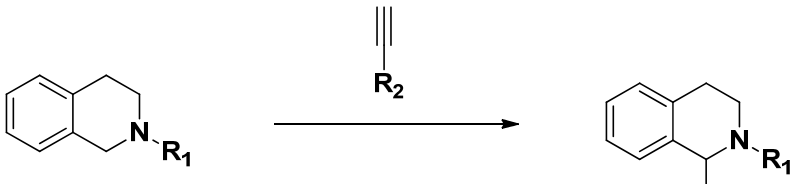
2b 79 %
2c 82 %
2d 86 %
2e 87 %



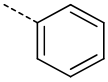
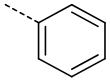
2f 64 %
2g 99 %
2h 75 %
2i 86 %
2j 98 %

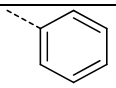
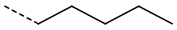
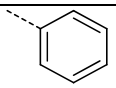
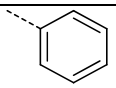
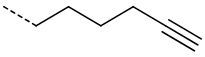
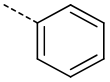
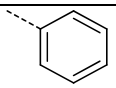
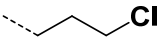
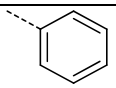
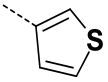
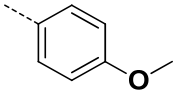
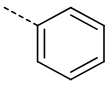
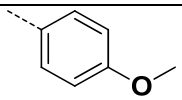
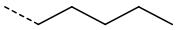
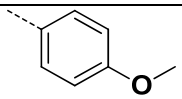
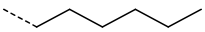
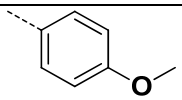
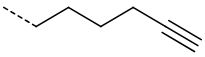
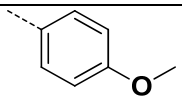
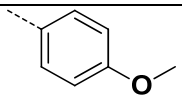
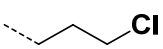
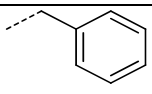
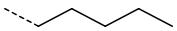
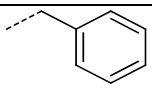
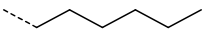
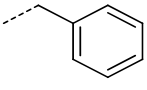
Alkynylation reactions

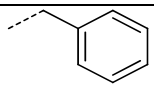
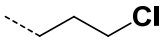


2a-c

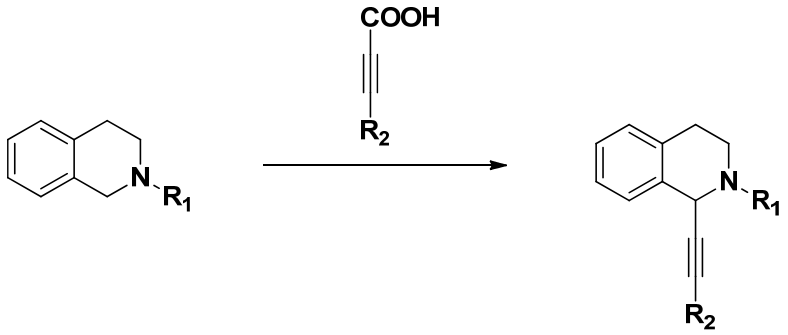
3a, 3b-g
4a, 4b-f
5a-d

Compound	R_1	R_2	Yield
3a			97%

3b			93%
3c			91%
3d			93%
3e			78%
3f			95%
3g			71%
4a			42%
4b			75%
4c			61%
4d			25%
4e			93%
4f			52%
5a			80%
5b			40%
5c			53%

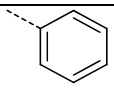
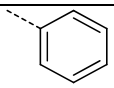
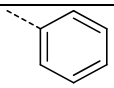
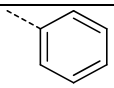
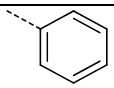
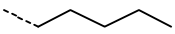
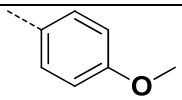
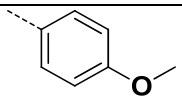
5d			48%

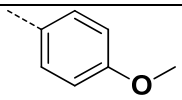
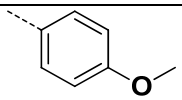
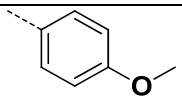
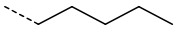
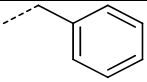
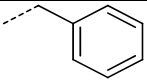
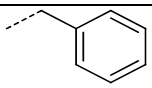
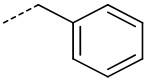
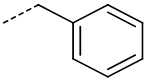
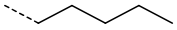
Decarboxylation-Alkynylation reactions



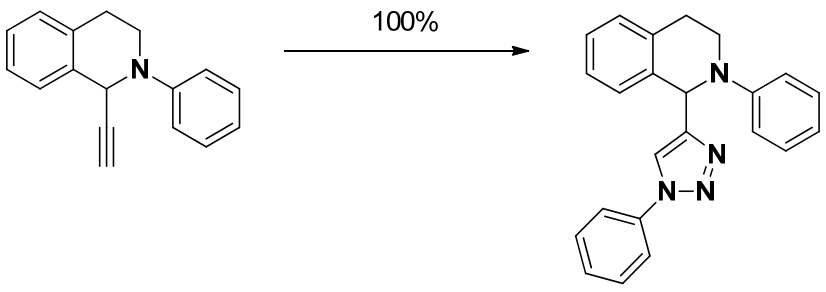
2a-c

3b, 3h-k
4b, 4g-j
5a, 5e-h

Compound	R_1	R_2	Yield
3h		-H	90%
3i			80%
3j			90%
3k			85%
3b			75%
4g		-H	53%
4h			47%

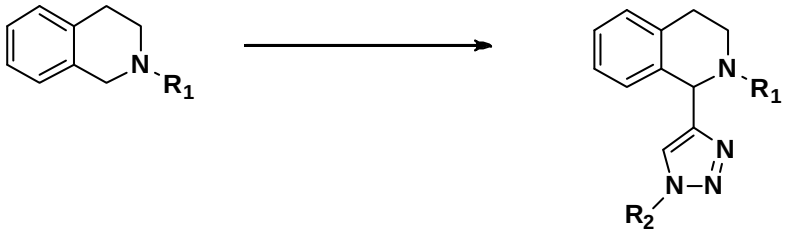
4i			67%
4j			57%
4b			71%
5e		-H	81%
5f			70%
5g			90%
5h			66%
5a			80%

Click reaction

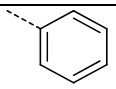
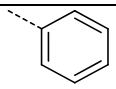
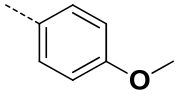
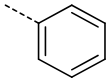


3h **6a**

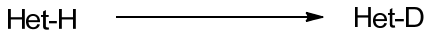
One-pot protocol

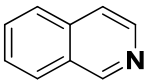
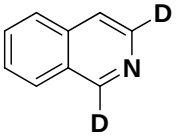
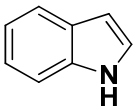
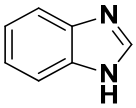
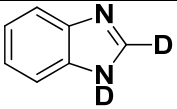
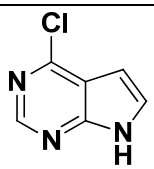
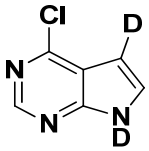


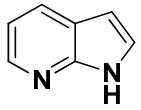
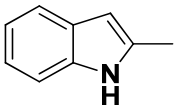
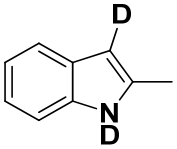
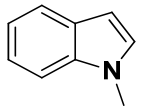
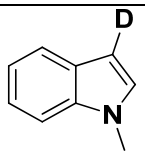
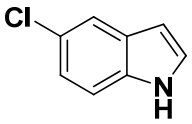
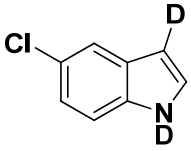
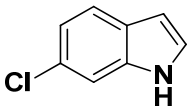
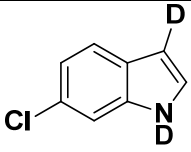
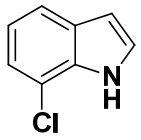
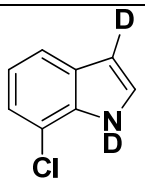
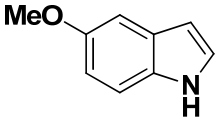
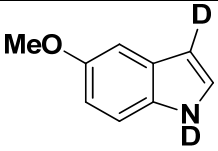
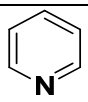
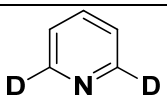
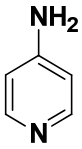
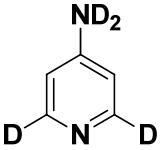
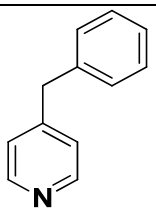
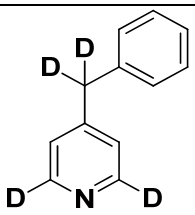
2a, 2b **6a, 6b**

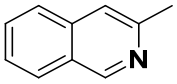
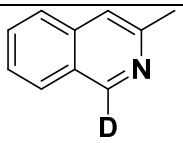
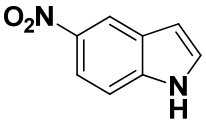
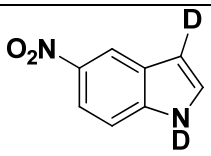
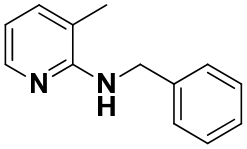
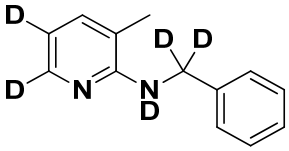
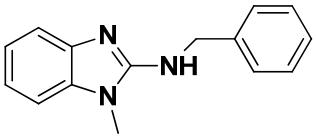
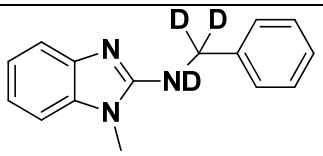
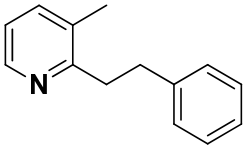
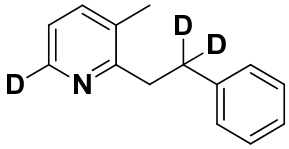
Compound	R_1	R_2	Yield
6a			90%
6b			50%

Deuteration reactions



Compound	Structure	Product	%D
7			93
8			90
9			71
10			78

11			80
12			70
13			85
14			85
15			87
16			86
17			84
18			79
19			50
20			50(Pyr) 87(Bn)

21			58
22			45
23			51 (Pyr-5) 22 (Pyr-6) 89 (Bn)
24			88
25			42 (Pyr) 87 (Bn)

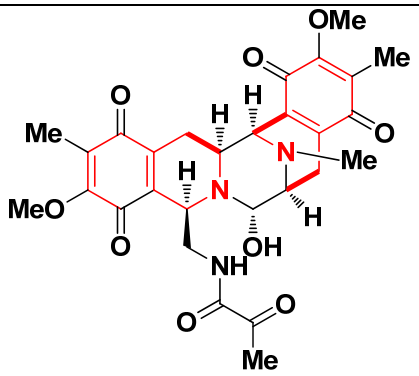
Introduction

1. 1,2,3,4-Tetrahydroisoquinoline (THIQ) derivatives

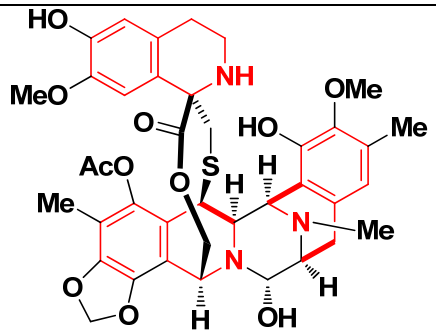
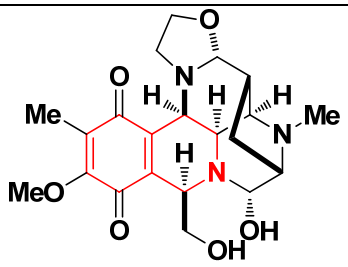
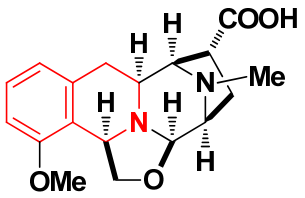
1.1 Biological activities

C1-substituted THIQ derivatives widely exist in nature and include potent cytotoxic agents displaying a range of antitumor or antimicrobial activities.[1] These substances are classified into saframycine, naphthyridinomycine/ bioxalomycine and quinocarcine/ tetrazomine families of natural products. They show activities against various bacteria, such as *Staphylococcus aureus* (causing skin infections, meningitis, pneumonia), *Streptococcus faecalis* (causing urinary tract infections, endocarditis, meningitis), *Corynebacterium diphtheriae* (causing diphtheria), and *Sarcina lutea* (causing minor skin infections), as well as against several tumor types including leukemia, lung cancer, colon cancer, and melanoma.[2,3,4,5] Table 1 shows examples of natural THIQ antitumor antibiotics, the THIQ core is indicated in red.

Table 1. Tetrahydroisoquinoline derivatives and their biological activities.

Name	Structure	Activities against
Saframycin S2		L1210 Leukemia, Ehrlich ascites tumors, Cornyebacterium diphtheriae

[1] Scott, J. D.; Williams, R. M.; *Chem. Rev.* **2002**, 102 (5), 1669
[2] Mikami, Y.; Yokoyama, K.; Tabeta, H.; Nakagaki, K.; Arai, T.; *J.Pharm. Dyn.* **1981**, 4, 282
[3] Mikami, Y.; Takahashi, K.; Yazawa, K.; Hour Young, C.; Arai, T.; *J.Antibiot.* **1988**, 41, 734
[4] Kluepfel, D.; Baker, H. A.; Piattoni, G.; Sehgal, S. N.; Sidorowicz, A.; Singh, K.; Vecina, C.; *J.Antibiot.* **1975**, 28, 497
[5] Tomita, F.; Takahashi, K.; Shimizu, K.; *J. Antibiot.* **1983**, 36, 463

Ecteinascidin 7433 (Et743)		B16 Melanoma, MEL-28 Melanoma, P388 Leukemia, L1210 Leukemia, A549 Lung cancer, HT-29 Colon cancer
Naphthyridinomycin4[6]		both Gram(-) and Gram(+) bacteria
Quinocarcin[5,7,8]		Staphylococcus aureus Bacillus subtilis Klebsiella pneumonia <u>Citrate salt:</u> St-4 Gastric carcinoma, Co-3 Human colon carcinoma, MX-1 Human mammary carcinoma, M5075 Sarcoma, B16 Melanoma, P388 Leukemia

[6] Singh, K.; Sun, S.; Kluepfel, D.; *Dev. Ind. Microbiol.* **1976**, 17, 209
[7] Tomita, F.; Takahashi, K.; Tamaoki, T.; *J. Antibiot.* **1984**, 37, 1268
[8] Fujimoto, K.; Oka, T.; Morimoto, M.; *Cancer Res.* **1987**, 47, 1516

Besides these antitumor and antibiotic activities, THIQ derivatives with less complex structures showed remarkable potential as N-methyl D-aspartate (NMDA) receptor antagonists.[9]

1.2 Long term potentiation and NMDA receptors

Long term potentiation (LTP) can be described as an activity-dependent form of synaptic plasticity proposed to underlie learning and memory formation in the brain, requiring calcium influx through NMDA (N-methyl D-aspartate) receptors.[10]

NMDA receptors play a key role in development of CNS as well as in learning and memory formation, due to modulation of neuronal activity and plasticity. Over activation of NMDA receptors by glutamate causes neuronal cell death, as found under pathological conditions of acute and chronic forms of neurodegeneration.[11] Both acute forms, such as caused by stroke and brain trauma, and chronic forms, for example like Alzheimer's disease, Parkinson's disease, amyotrophic laterial sklerosis (ALS), Huntington's disease or neurodegeneration caused by bacterial or viral infections, as well as schizophrenia, anxiety and depression can be triggered by NMDA receptor subtype specific blockers.[12]

In 2003, the following compounds have been found to be potent NMDA receptor antagonists:[9]

[9] Büttelmann, B.; Alanine, A.; Bourson, A.; Ramanjit, G.; Heitz, M.-P.; Mutel, V.; Pinard, E.; Trube, G.; Wyler, R.; *Bioorg. Med. Chem. Lett.* **2003**, 13, 1759
[10] Foster, K.A.; et al; *J. Neurosci.* **2010**, 30(7), 2676
[11] Choi, D. W.; *Neuron* **1988**, 1, 623
[12] Alanine, A.; Bourson, A.; Buettelmann, B.; Fischer, G.; Heitz, N. M.-P.; Mutel, V.; Pinard, E.; Roever, S.; Trube, G.; Wyler, R.; *Brit. UK Pat. Appl.*, **1997**, GB2309642A19970806

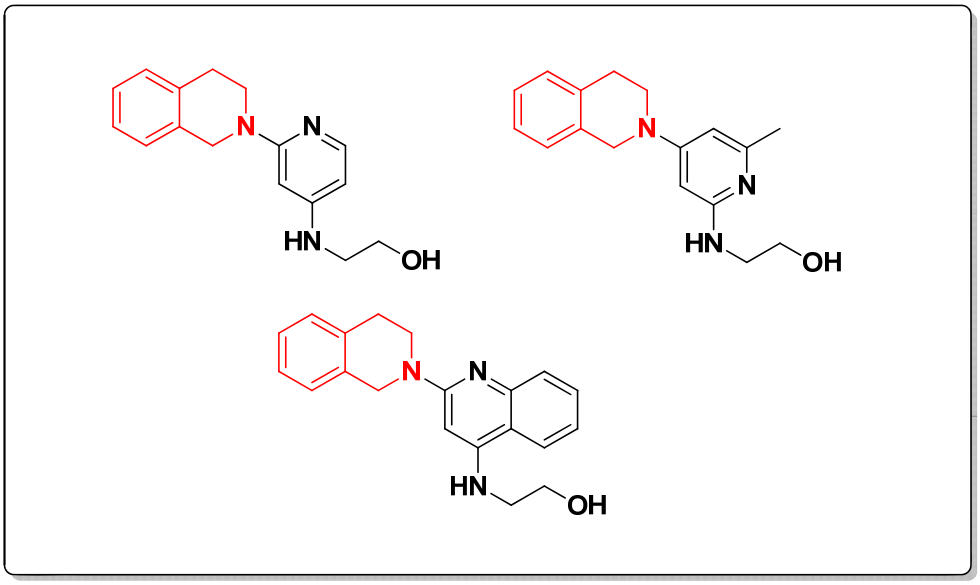


Figure 1. THIQ derivatives shown to be NMDA receptor antagonists.

More recently, C-1 substituted THIQ derivatives have been generally classified to be NMDA-receptor subtype selective blockers:[10]

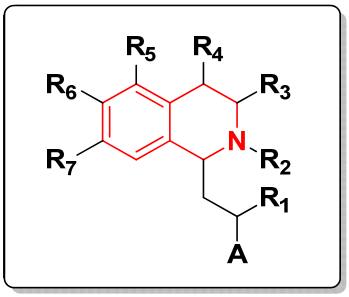


Figure 2. The THIQ core as promising structure for blocking NMDA receptors.

1-Benzyl-THIQ, which exists naturally in animal brain tissue, was found to induce Parkinson's disease in monkeys and mice.[13,14] Its concentration in the cerebro-spinal fluid of Parkinsonian patients is approximately three times higher than found in healthy individuals.

In contrast to these findings, 1-methyl-THIQ has been shown to prevent these induced abnormalities,[15,16,17] leading to the suggestion that substituents attached to the C1-position of THIQ may influence the pharmacological and biological properties of THIQ derivatives.

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[13] Kotake, Y.; Tasaki, Y.; Makino, Y.; Ohta, S.; Hirobe, M.; *J. Neurochem.* **1995**, 65(6), 2633
[14] Kotake, Y.; Yoshida, M.; Ogawa, M.; Tasaki, Y.; Hirobe, M.; Ohta, S.; *Neurosci. Lett.* **1996**, 217(1), 69
[15] Luszczki, J. J.; Antkiewicz-Michaluk, L.; Raszewski, G.; Czuczwar, S. J.; *Epilepsy Research* **2010**, 89, 207
[16] Tasaki, Y.; Makino, Y.; Ohta, S.; Hirobe, M.; *J. Neurochem.* **1991**, 57, 1940
[17] Abe, K.; Saitoh, T.; Horiguchi, Y.; Utsunomiya, I.; Taguchi, K.; *Biol. Pharm. Bull.* **2005**, 28(8), 1355

Introducing an N-propargyl functional group showed to play a crucial role in reducing cytotoxicity and to have preventative effects on MPP^+-treated cells.[18] MPP^+, 1-methyl-4-phenylpyridinium ion, is inducing cell death by fragmenting DNA. Several 1-alkyl- and 1-alkyl-N-propargyl-THIQ derivatives were tested on their cytotoxicity and inhibitory effects on MPP^+-induced cell death. Examples are shown in Figure 3.

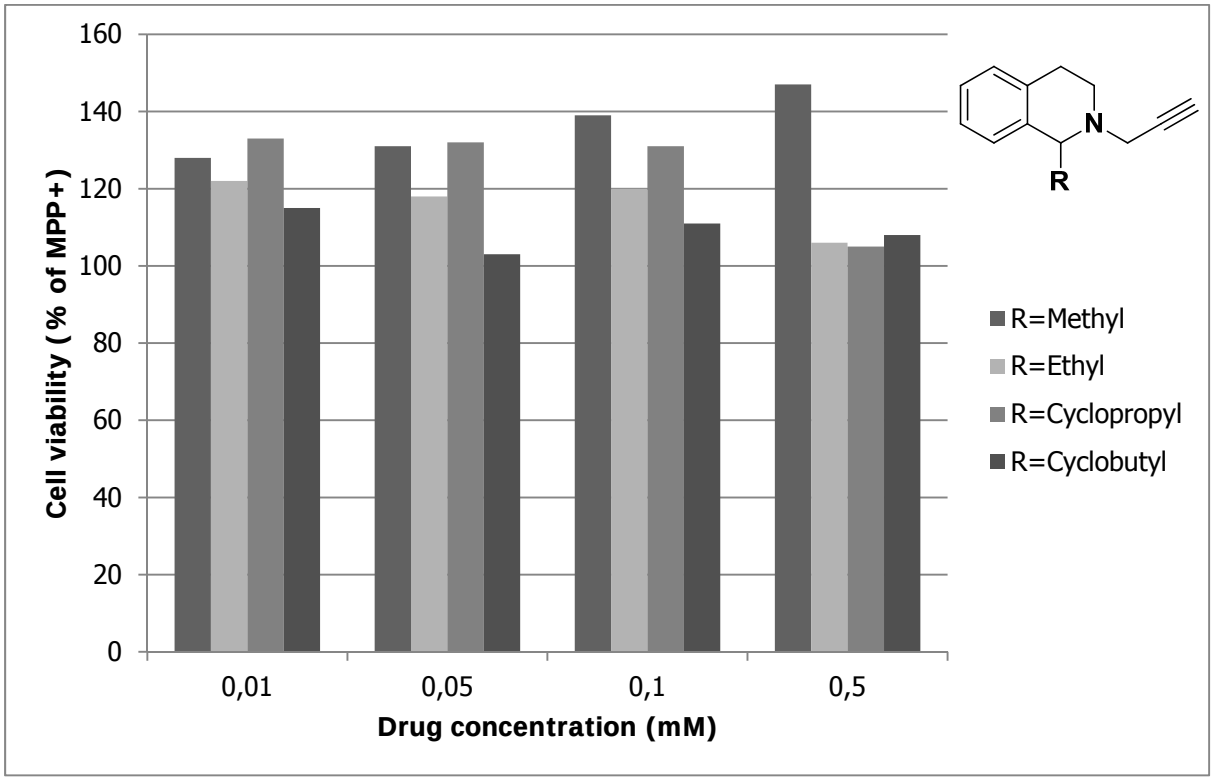


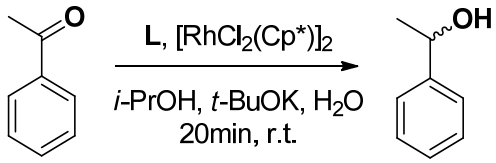
Figure 3. Inhibitory effect of 1-alkyl-N-propargyl-THIQ derivatives on MPP^+-induced cell death.[18]

1.3 Use in asymmetric catalysis

Amine- and diamine-based ligands can be used for various asymmetric catalytic reactions.[19, 20, 21] Tetrahydroisoquinoline ligands gave promising results for the addition of diethylzinc to benzaldehyde.[22] Peters et al. published a protocol for asymmetric transfer hydrogenation of prochiral ketones in 2010, using rhodium

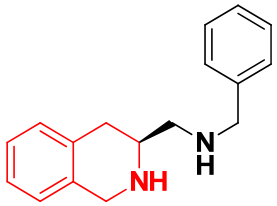
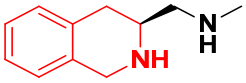
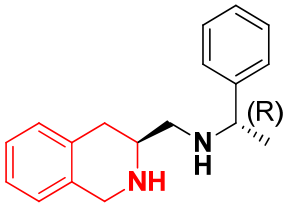
[18] Kitabatake, M.; Nagai, J.; Abe, K.; Tsuchiya, Y.; Ogawa, K.; Yokoyama, T.; Mohri, K.; Taguchi, K.; Horiguchi, Y.; *Eur. J. Med. Chem.* **2009**, 44, 4034
[19] Bianchi, M.; Matteoli, U.; Menchi, G.; Frediani, P.; Pratesi, S.; Piacenti, F.; Botteghi, C.; *J. Org. Chem.* **1980**, 198, 73
[20] Botteghi, C.; Chelucci, G.; Chessa, G.; Delogu, G.; Gladiali, S.; Soccolini, F.; *J. Org. Chem.* **1986**, 304, 217
[21] Kvintovics, P.; Heil, B.; *J. Org. Chem.* **1989**, 361, 117
[22] Hari, Y.; Sakuma, M.; Miyakawa, A.; Hatano, K.; Aoyama, T.; *Heterocycles* **2008**, 76, 305

catalysts with THIQ ligands.[23] They obtained yields from 5 to 81% and enantiomeric excesses from 11 to 77%. Reaction conditions and examples are shown in Scheme 1 and **Fehler! Verweisquelle konnte nicht gefunden werden.**.



Scheme 1. Rh-catalyzed asymmetric hydrogenation of acetophenone.[23]

Table 2. Ligands for Rh-catalyzed asymmetric hydrogenation of acetophenone.[23]

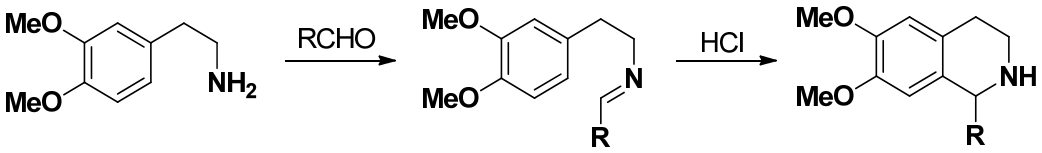
Ligand	Conversion [%]	ee [%]	Isomer
	81	70	S
	67	71	S
	24	77	R

[23] Peters, B. K.; Chakka, S. K.; Naicker, T.; Maguire, G. E. M.; Kruger, H. G.; Andersson, P. G.; Govender, T.; *Tetrahedron Asymm.* **2010**, 21, 679

1.4 Synthesis of THIQ derivatives

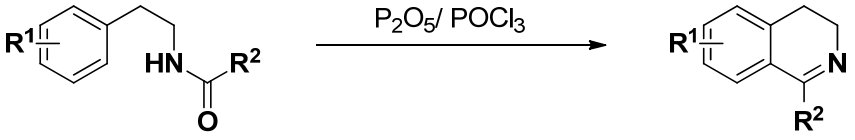
Classical methods to synthesize the isoquinoline ring system are:

The **Pictet-Spengler** reaction[24], where the THIQ product is formed via condensation of a β-arylethylamine with an aldehyde (Scheme 2).



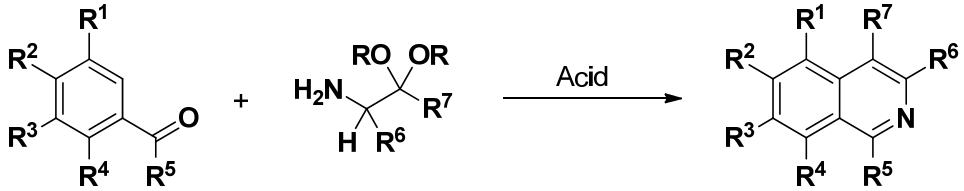
Scheme 2. Pictet-Spengler reaction.

The **Bischler-Napieralski** reaction,[25,26] involving the cyclization of phenethyl amides in the presence of dehydrating agents, such as P_2O_5 or $POCl_3$, resulting in 3,4-dihydroisoquinoline products (Scheme 3).



Scheme 3. Bischler-Napieralski reaction.

The **Pommeranz-Fritsch** reaction ,[27,28] resulting in isoquinoline derivatives (Scheme 4).



Scheme 4. Pommeranz-Fritsch reaction.

Figure 4 shows a summary of the different pathways towards the synthesis of C1-substituted THIQs.

[24] Pictet, A.; Spengler, T.; *Ber. Deutsch. Chem. Ges.* **1911**, 44, 2030
[25] Bischler, A.; Napieralski, B; *Ber. Deutsch. Chem. Ges.* **1893**, 26(2), 1903
[26] Li, J. J., *Name reactions in heterocyclic chemistry*, Wiley
[27] Pomeranz, P.; *Monatsh. Chem.* **1893**, 14, 116
[28] Fritsch, P.; *Ber. Deutsch. Chem. Ges.* **1893**, 26, 419

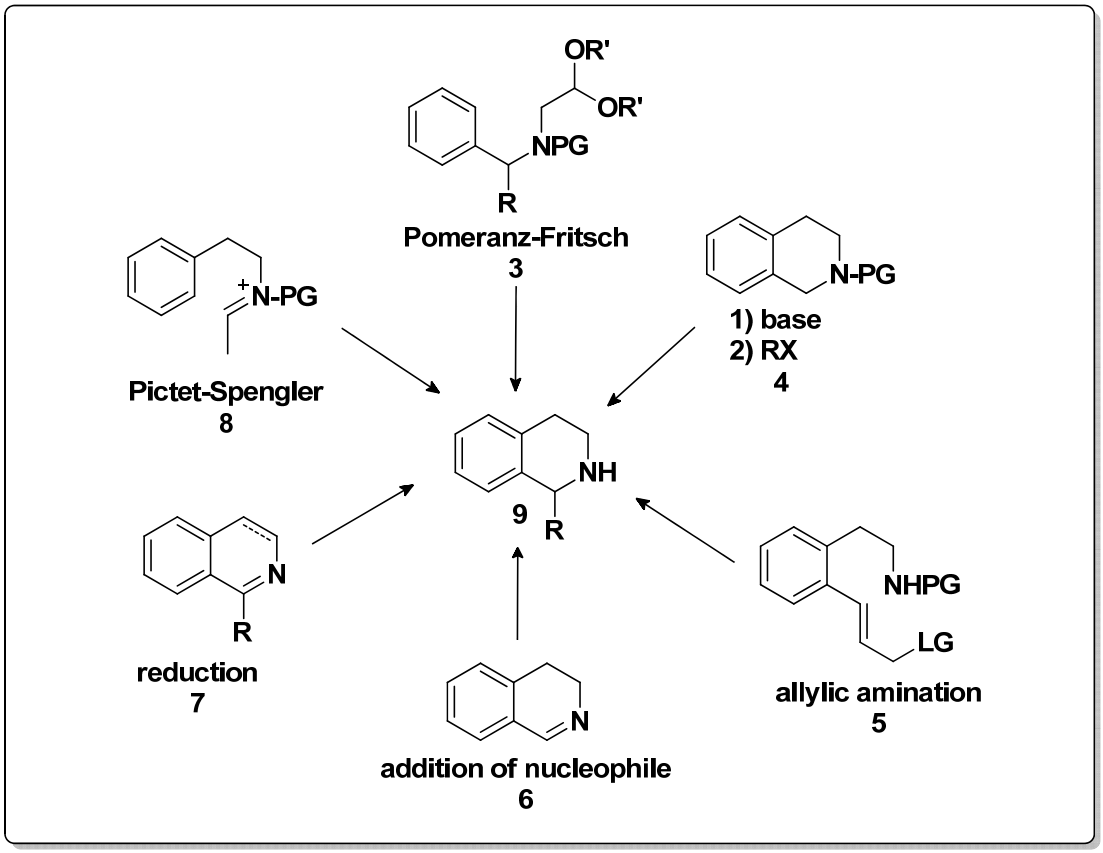


Figure 4. Pathways towards C-1 substituted THIQ's.

However, the trend goes into the direction of functionalizing simple scaffolds via different methods to get to the desired THIQ derivatives rather than building up the desired ring system for each compound separately. In this regard, metal catalyzed cross-coupling reactions have been very successful in synthetic chemistry over the past decades.

2. Transition metal catalyzed C-C bond formation

2.1 C-C cross coupling

The term "cross coupling reaction" is universal for reactions where two different organic compounds are connected with the aid of a metal catalyst. Originally, cross coupling reactions created C-C bonds but in the past decades different cross coupling reactions have been established, where also C-heteroatom bonds are formed.[29,30]

[29] a) Herrmann, P.; Bach, T. *Chem. Soc. Rev.* **2011**, *40*, 2022. b) Yeung, C. S.; Dong, V. M. *Chem. Rev.* **2011**, *111*, 1215.
[30] Hartwig, J.; *Organotransistion Metal Chemistry – From Bonding to Catalysis*, **2010**, 877

One of the first examples of cross coupling reactions was done by Wurtz and Fittig 19th century.[31] Until the 1960's the scope of cross-coupling reactions was rather limited to those involving Mg- and Li-organyls.

In 1972, Kumada and co-workers[32] proposed a three-stage catalytic cycle, which describes the principles of a cross-coupling reaction, involving the following main steps: Oxidative Addition, Transmetallation and Reductive Elimination. Normally, a catalyst precursor is first converted to an active catalyst and then enters the catalytic cycle. Basically, this pattern can also be used to describe C-H activation reactions, but the order of steps can vary. The catalytic cycle is shown in Figure 5.

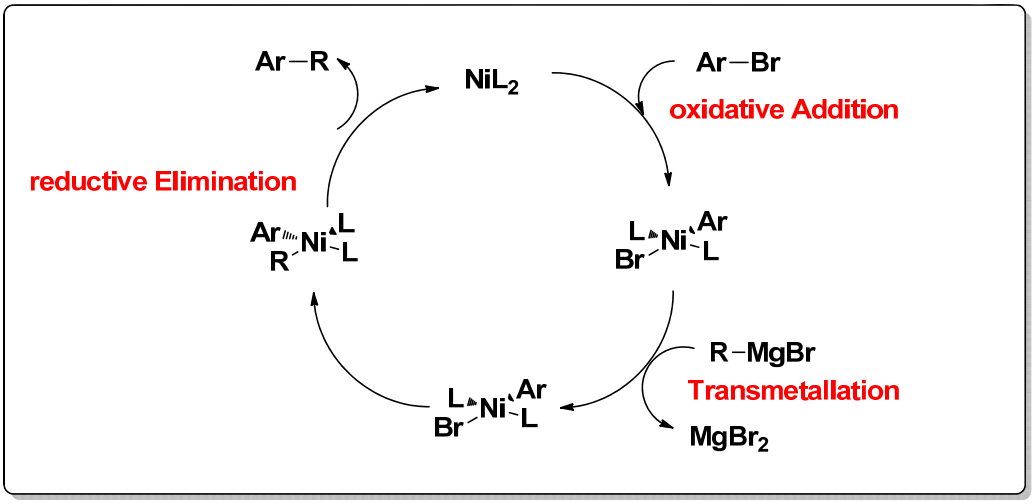


Figure 5. Proposed catalytic cycle for cross coupling reactions.[32]

In 2010 Richard Heck, Akira Suzuki and Ei-ichi Negishi were awarded with the Nobel Prize in chemistry for their contributions to the development of metal catalyzed cross coupling reactions.[33,34,35] However, many coupling reactions including those of Heck, Suzuki and Negishi require organohalides or organometallic reagents, which are often not commercially available or relatively expensive,[36] are air- and moisture sensitive, and produce a stoichiometric amount of metal salts.[37] In light of the ongoing trend towards a more sustainable, less waste producing, "greener" chemistry, it was only a matter of time until researchers started to address these limitations of the classical cross coupling reactions.

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[31] a) Tollens, B.; Fittig, R.; *Annalen der Chemie und Pharmacie*. **1864**, 131(3), 303. b) Fittig, R.; König, J.; *Annalen der Chemie und Pharmacie.* **1867**, 144(3), 277
[32] Tamao, K.; Sumitani, K.; Kumada, M.; *J. Am. Chem. Soc.* **1972**, *94*, 4374
[33] Heck, R.F.; Nolley, J. P.; *J. Org. Chem.*, **1972**, 37(14), 2320
[34] a) Miyaura, N.; Suzuki, A.; *J. Chem. Soc.*, **1979**, 19, 866. b) Miyaura, N.; Yamada, K.; Suzuki, A.; *Tetrahedron Lett.* **1979**, 20(36), 3437
[35] King, A. O.; Okukado, N.; Negishi, E.-I.; *Chem. Comm.* **1977**, 683
[36] Ackermann, L.; Vicente, R.; Kapdi A. R.; *Angew. Chem. Int. Ed.* **2009**, 48, 9792
[37] Scheuermann, C. J.; *Chem. Asian J.* **2010**,5,436

2.2 C-H activation

What is C-H activation?

C-H activation is a method to introduce a new functionality or a C-C bond via direct C-H bond transformation. The expression itself was primarily used for alkanes, where a more "active" C-H bond was generated via transition metal reagents. Nowadays, the substrate range is starting from lower alkanes, arenes and polyarenes up to more complex organic compounds, as well as synthetic and biological polymers. Furthermore, the term "C-H bond transformation" was introduced, describing C-H cleaving processes of several compound classes, especially hydrocarbons. Later, this term was generally used and led uncertainty about its definition. There is still no accurate definition of "C-H activation" respectively "C-H bond transformation", but within this contribution the term is used to describe reactions, which involve organometallic reagents, also known as "organometallic definition".[38]

Figure 6 shows the differences between classical cross coupling reactions, and C-H activation reaction types, such as "one-site" activation or cross-dehydrogenative coupling, which is an oxidative method.

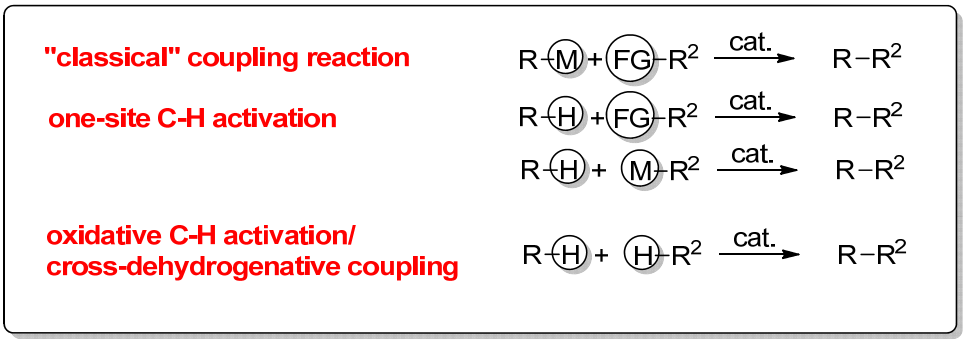


Figure 6. Classical coupling versus C-H activation reactions (M=metal, FG=functional group).

[38] For reviews on various aspects of C-H activation see: a) Engle, K. M.; Mei, T.-S.; Wasa, M.; Yu J.-Q.; *Acc. Chem. Res.,* **2012**, *45*, 788. b) Joucla, L.; Djakovitch, L. *Adv. Synth. Catal*. **2009**, *351*, 673. c) Catellani, M.; Motti, E.; Della Ca, N. *Acc. Chem. Res*. **2008**, *41*, 1512. d) Shen, H. *Chemtracts* **2005**, *18*, 44. e) Du Bois, J. *Chemtracts* **2005**, *18*, 1. f) Davies, H. M. L.; Loe, O. *Synthesis* **2004**, *16*, 2595. g) Balskus, E. P.; Ley, S. V. *Chemtracts* **2003**, 16, 443. h) Ishiyama, T.; Miyaura, N. *J. Organomet. Chem*. **2003**, *680*, 3. j) Davies, H. M. L.; Beckwith, R. E. J. *Chem. Rev.* **2003**, *103*, 2861. i) Jones, W. D. *Acc. Chem. Res.* **2003**, *36*, 140. j) Crabtree, R. H. *J. Chem. Soc., Dalton Trans*. **2001**, 2437. k) Godula, K, Sames, D. *Science*, **2006**, *312*, 67. l) Shilov, A. E.; Shul'pin, G. B. *Chem. Rev*. **1997**, *97*, 2879. m) Zhang, C.; Tang, T.; Jiao, N. *Chem. Soc. Rev*. **2012**, *41*, 3464. n) Wencel-Delord, J.; Dröge, T.; Liu, F.; Glorius, F. *Chem. Soc. Rev*. **2011**, *40*, 4740. o) Ackermann L.; *Chem. Rev*. **2011**, *111*, 1315. p) Jazzar, R.; Hitce, J.; Renaudat, A.; Sofack-Kreitzer, J.; Baudoin, O. *Chem. Eur. J*. **2010**, *16*, 2654.

While classical cross-coupling reactions require two functional groups, such as an organo metal compound and an organo halide to form a C-C bond, C-H activation reactions can be performed with only one or even without a functional group on one of the reaction partners.

2.3 Cross-dehydrogenative Coupling (CDC) and Green Chemistry

Being aware of the disadvantages of cross couplings, Li et al. pioneered a new type of cross coupling using "low-energy" starting materials featuring unfunctionalized C-H bonds for the formation of a new C-C bond. These reactions were termed cross dehydrogenative coupling (CDC) and require only oxidative conditions, which can be obtained by the use of for example *tert*-butylhydroperoxide (*t*BuOOH), and first row metal catalysts. Advantages of CDC reactions are maximization of resource utilization, reaction schemes become shorter and thus more efficient, decreasing of overall waste, cost and working time. In some cases, CDC reactions can be performed under green chemistry conditions. [39] Green chemistry has gained prominence in the past decades and is a term for a chemical process, which avoids the use and production of chemicals with negative environmental impacts.[40,41] Its 12 principles are:[42]

- It is better to prevent waste than to treat or clean up waste after it is formed.
- Synthetic methods should be designed to maximize the incorporation of all materials used in the process into the final product.
- Wherever practicable, synthetic methodologies should be designed to use and generate substances that possess little or no toxicity to human health and the environment.
- Chemical products should be designed to preserve efficacy of function while reducing toxicity.
- The use of auxiliary substances (e.g. solvents, separation agents, etc.) should be made unnecessary wherever possible and innocuous when used.
- Energy requirements should be recognized for their environmental and economic impacts and should be minimized. Synthetic methods should be conducted at ambient temperature and pressure.
- A raw material or feedstock should be renewable rather than depleting wherever technically and economically practicable.
- Reduce derivatives - Unnecessary derivatization (blocking group, protection/ deprotection, temporary modification) should be avoided whenever possible.

[39] Li, C.-J.; *Acc. of Chem. Res.* **2009**, 42(2), 335
[40] Noyori, R.; Chem.Comm. **2005**, (14), 1807
[41] *United States Environmental Protection Agency.* "Green Chemistry". 2006-06-28. Retrieved 2011-03-23
[42] *United States Environmental Protection Agency*. "The 12 Principles of Green Chemistry". Retrieved 2006-07-3

- Catalytic reagents (as selective as possible) are superior to stoichiometric reagents.
- Chemical products should be designed so that at the end of their function they do not persist in the environment and break down into innocuous degradation products.
- Analytical methodologies need to be further developed to allow for real-time, in-process monitoring and control prior to the formation of hazardous substances.
- Substances and the form of a substance used in a chemical process should be chosen to minimize potential for chemical accidents, including releases, explosions, and fires.

3. C-H transformations at terminal alkynes[43]

3.1 The Sonogashira reaction

The Sonogashira-coupling, also known as Sonogashira-Hagihara-coupling, was first reported in 1975 by Kenkichi Sonogashira and Nobue Hagihara and is a modification of the Stephens-Castro-coupling.[44] With this palladium catalyzed method an alkyne functionality can be introduced to aryl groups by using terminal alkynes and aryl halides.[45,46]

Figure 7 shows the proposed catalytic cycle by Chinchilla and Najera.[47]

[43] Dyker, G.; *Handbook of C-H Transformations*, Wiley-VCH, **2005**, 31
[44] Stephens, R. D.; Castro, C. E.; *J. Org. Chem.*; **1963**, 28, 3313
[45] Sonogashira, K.; Tohda, Y.;, Hagihara, N.; *Tetrahedron Lett.*. **1975**, 4467
[46] Sonogashira, K.; *Journal of Organometallic Chemistry.* **2002**, 46
[47] Chinchilla, R.: Najera, C.; Chem. Soc. Rev., **2011**, 40, 5084

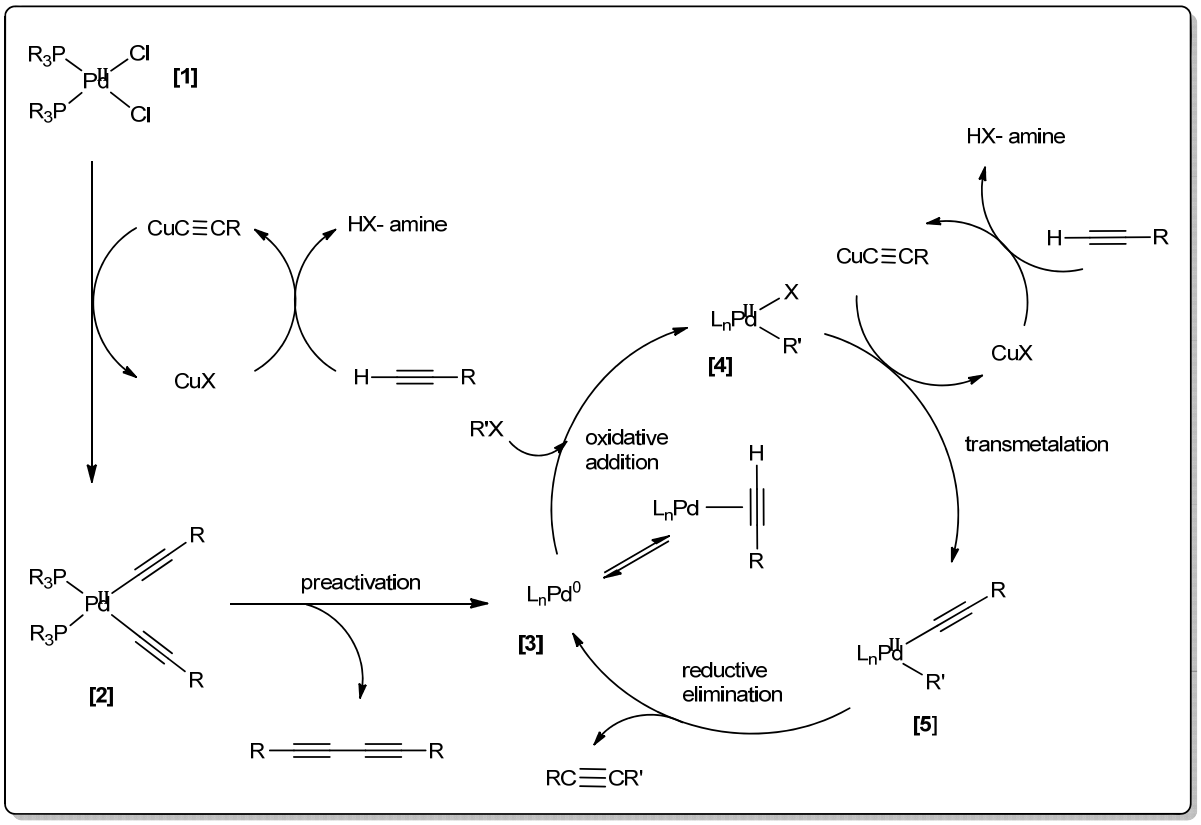


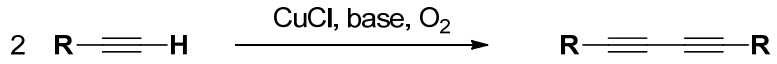
Figure 7. Proposed catalytic cycle of the Sonogashira reaction.[47]

The catalytic cycle can be divided into a palladium and a copper cycle. First, an inactive Pd^{II} compound **[1]** is reduced to an active Pd^0L_2 species **[3]**, followed by oxidative addition of an aryl or vinyl halide, leading to compound **[4]**. The oxidative addition is proposed to be the rate-limiting step.[48] In the meanwhile a π-alkyne complex is formed by a copper halide and a terminal alkyne, leading to the formation of a copper acetylide. Via transmetalation between the copper acetylide and the palladium complex **[4]** compound **[5]**, whereas the copper halide is released. After trans-cis isomeration, the alkyne is formed via reductive elimination. Both the copper halide and the palladium catalyst are regenerated within this reaction.

3.2 The Glaser Coupling – Oxidative Homocoupling

The first description of homocoupling of terminal alkynes came by Glaser in 1869, reporting a protocol using a base, a copper(I) salt and oxygen (Scheme 5).[49,50]

[48] Gottardo, C.; Kraft, T. M.; Hossain, M. S.; Zawada, P. V.; Muchall, H. M.; *Can. J. Chem.*, **2008**, 86, 410
[49] Glaser, C.; *Ber. Dtsch. Chem. Ges.*, **1869**, 2, 422
[50] Glaser, C.; *Ann. Chem. Pharm.*, **1870**, 154, 137



Scheme 5. Glaser Homocoupling.

The mechanism of the oxidative homocoupling is not clear, due to the complexity of connectivities depending on experimental settings. Figure 8 shows a mechanistic proposal of Bohlmann and colleagues.[51]

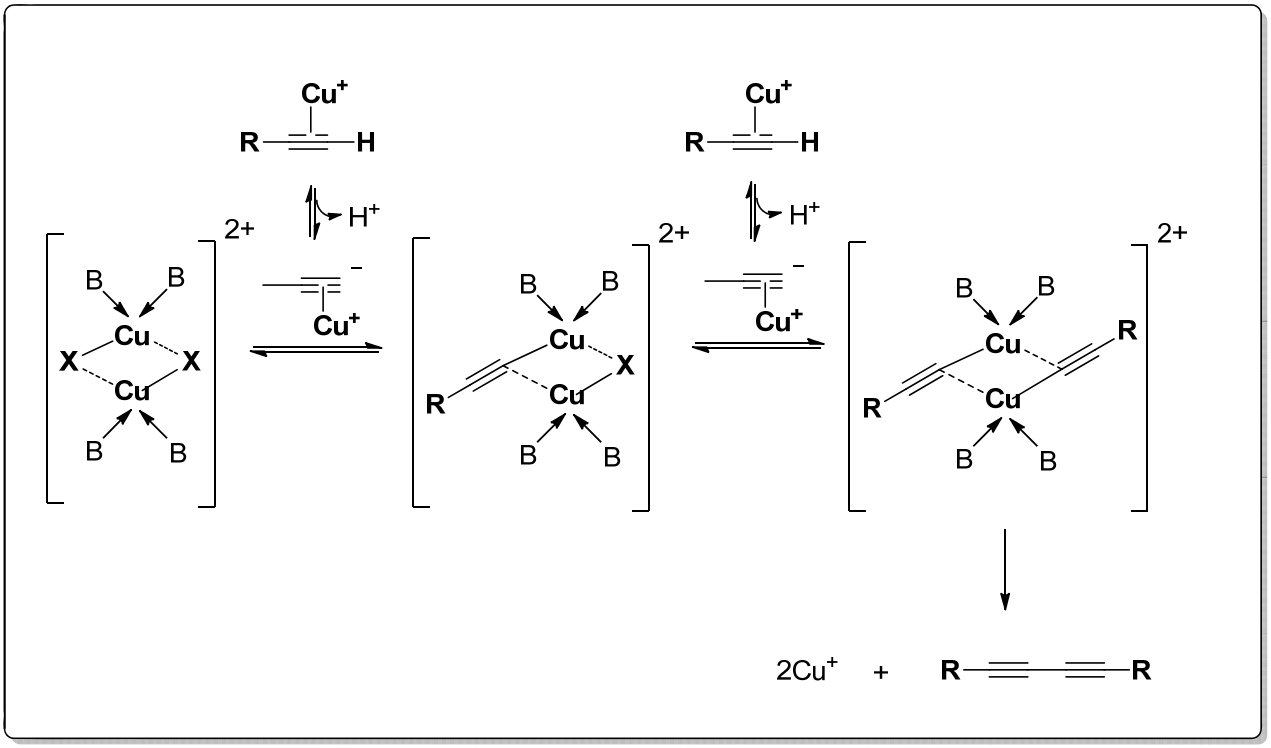


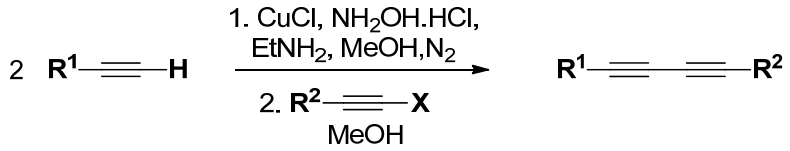
Figure 8. Mechanistic proposal of the Glaser coupling by Bohlmann et. al (B=N-ligand, X=Cl⁻, OAc⁻).

First, the corresponding alkynes undergo deprotonation by coordination of the copper ions . This step is followed by replacement of the anions of the copper(II) salt dimers, resulting in a dinuclear copper(II) acetylide complex. Then the diacetylene is formed via reductive elimination of the copper(I).

3.3 The Cadiot-Chodkiewicz Reaction – Non-oxidative Heterocoupling

In 1957, Chadiot and Chodkiewicz reported a non-oxidative protocol for heterocoupling of terminal alkynes with 1-haloalkynes in the presence of copper salts and amines (Scheme 6).[52]

[51] Bohlmann, F.; Schönowsky, H.; Inhoffen, E.; Grau, G.; *Chem. Ber.*, **1964**, 97, 794
[52] Chodkiewicz, W.; Cadiot, P.; *Ann. Chim. (Paris)*, **1957**, 2, 819



Scheme 6. Cadiot-Chodkiewicz Reaction.

For the non-oxidative coupling two proposed mechanistic pathways exist (see Figure 9):

1) Oxidative addition of the copper(I) acetylide to the alkynyl halide, followed by formation of a copper(III) intermediate and subsequent reductive elimination, resulting in the diacetylene[53]
2) Nucleophilic addition without change of the oxidation state[54]

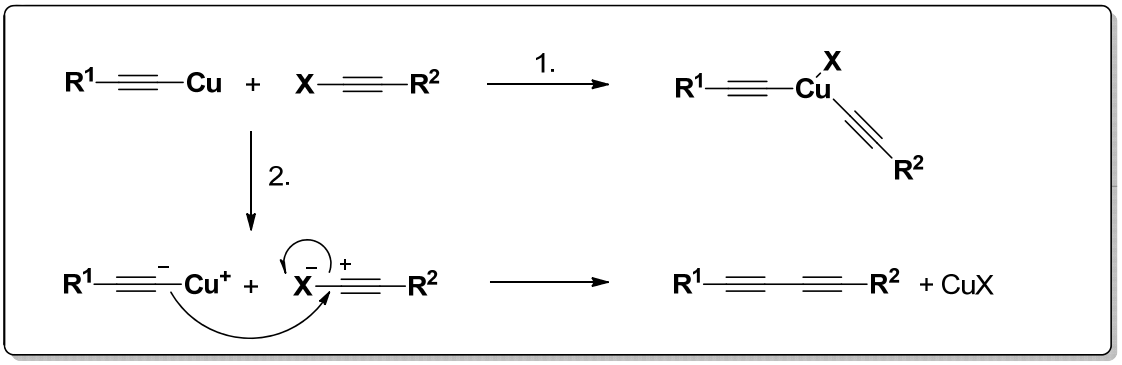


Figure 9. Proposed mechanisms for the Cadiot-Chodkiewicz Reaction.[53, 54]

3.4 Dimerization of terminal alkynes

The direct coupling of two acetylene units can be performed by using palladium,[55,56] mononuclear ruthenium complexes,[57,58] rhodium-trimethylphosphine systems,[59,60] or lanthanide metallocene compounds [61] as catalysts, with good regio- and stereochemical control, leading to linear or branched enyne isomers (see Scheme 7).

[53] Cadiot, P.; Chodkiewicz, W.; *Chemistry of Acetylenes (Ed.: H. G. Viehe), Dekker, New York*, **1969**, chap. 9, 597
[54] Viehe, H. G.; *Chem. Ber.*, **1959**, 92, 3064
[55] Trost, B. M.; Chan, C.; Rühter, G.; *J. Am. Chem. Soc.*, **1987**, 109, 3486
[56] Trost, B. M.; Sorum, M. T.; Chan, C.; Harms, A. E.; Rühter, G.; *J. Am. Chem. Soc.*, **1997**, 119, 698
[57] Bianchini, C.; Frediani, P.; Masi, D.; Peruzzini, M.; Zanobini, F.; *Organometallics*, **1994**, 13, 4616
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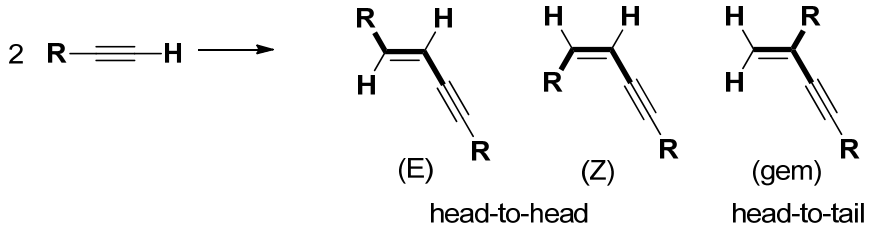
[60] Ohmura, T.; Yorozuya, S.; Yamamoto, Y.; Miyaura, N.; *Organometallics*, **2000**, 19, 365
[61] Heeres, H. J.; Teuben, J. H.; *Organometallics*, **1991**, 10, 1980



Scheme 7. Dimerization of alkynes to linear and branched enyne isomers.

3.5 Enantioselective addition of terminal alkynes to aldehydes

The first addition of acetylene to aldehydes and ketones was reported in 1900 by Favorski, using KOH to form a 1:1 complex with acetylene.[62] Over the years, more methods were introduced, such as a protocol by Corey, using CsF/CsOH salts and trimethylsilylalkynes.[63] In 1999, Carreira reported a protocol using Zn(II) salts to metalate terminal acetylenes under mild conditions, followed by deprotonation in presence of a strong base, and introduction of the electrophilic aldehyde.[64] The proposed metalation mechanism is shown in Figure 10.

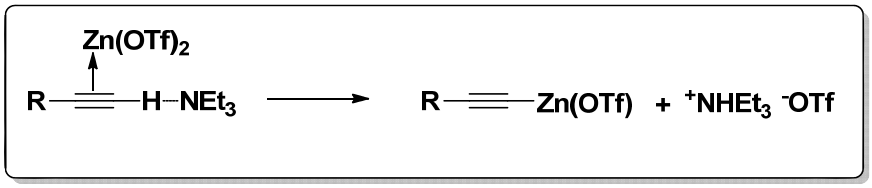


Figure 10. Metalation of terminal alkynes by Zn(II) triflate and triethylamine.

Reactions can either be performed by stoichiometric, preformed metalated acetylenes [65] or via in-situ formation of metal alkynylides in substoichiometric amount.

3.6 *Anti*-Markovnikov Addition to terminal alkynes

Via direct formation of catalytic metal vinylidene complexes, an *anti*-Markovnikov addition to acetylenes can be performed, leading to the formation of vinylcarbamates,[66, 67] enol esters,[68, 69] vinylic ethers,[70] unsaturated ketones,[71,72] cyclic

[62] Favorski, A. E.; Skossarewsky, M.; *Russ. J. Phys. Chem. Soc.*, **1900**, 32, 652
[63] Busch-Petersen, J.; Bo, X. Y.; Corey, E. J.; *Tetrahedron Lett.*, **1999**, 40, 2065
[64] Frantz, D. E.; Fässler, R.; Carreira, E. M.; *J. Am. Chem. Soc.*, **1999**, 121, 11245
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[66] Sasaki, Y.; Dixneuf, P. H.; *J. Chem. Soc., Chem. Commun.,* **1986**, 790
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[68] Ipaktschi, J.; Mohsseni-Ala, J.; Uhlig, S.; *Eur. J. Inorg. Chem.*, **2003**, 4313;
[69] Doucet, H.; Derrien, N.; Kabouche, Z., Bruneau, C.; Dixneuf, P. H.; *J. Organomet. Chem.*, **1997**, 551, 151
[70] Gemel, C.; Trimmel, G.; Slugovc, C.; Kremel, S.; Mereiter, K.; Schmid, R.; Kirchner, K.; *Organometallics*, **1996**, 15, 3998

enol ethers and lactones,[73,74] aldehydes,[75] or conjugated enals.[76,77] Ruthenium catalysts showed excellent activities for these reactions. A general mechanism is displayed in Figure 11.

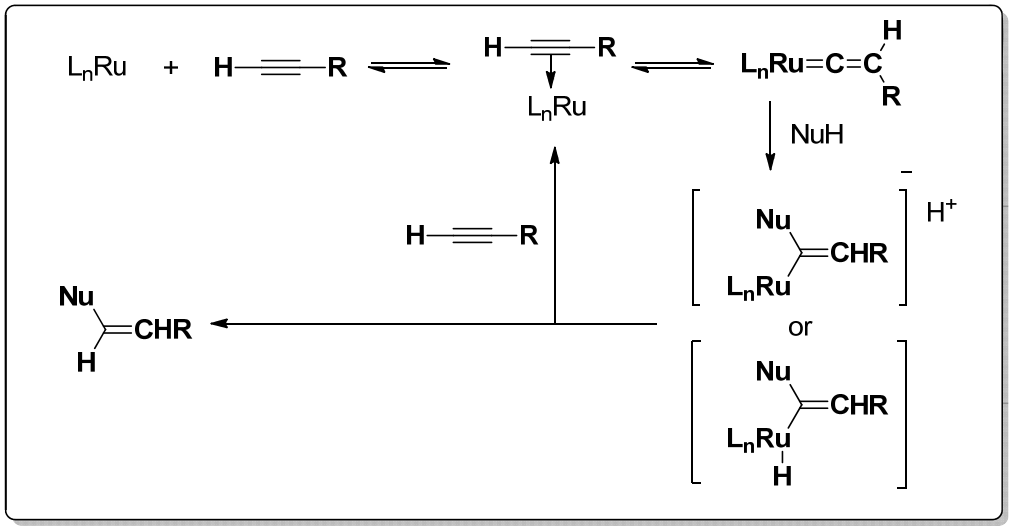

Figure 11. General mechanism for the ruthenium catalyzed anti-Markovnikov addition to terminal alkynes.

4. Synthesis of THIQ derivatives via transition metal catalyzed C-C bond formation

Various methods have been established, such as arylation,[78] alkenylation,[79] alkynylation,[80,81,82,83] indolation,[84] methoxylation,[85] phosphonation,[86,87] cyanation,[88,89]

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[71] Trost, B. M.; Dyker, G.; Kulaviec, R. J.; *J. Am. Chem. Soc.*, **1990**, 112, 7809
[72] Trost, B. M.; Kulaviec, R. J.; *J. Am. Chem. Soc.*, **1992**, 114, 5579
[73] Trost, B. M.; Rhee, Y. H.; *J. Am. Chem. Soc.*, **2002**, 124, 2528
[74] Trost, B. M.; Rhee, Y. H.; *J. Am. Chem. Soc.*, **1999**, 121, 11680
[75] Suzuki, T.; Tokunoga, M.; Wakatsuki, Y.; *Org. Lett.*, **2001**, 3, 735
[76] Piquet, M.; Bruneau, C.; Dixneuf, P. H.; *J. Chem. Soc., Chem. Commun.*, **1997**, 1201
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[78] Li, C.-J.; Basle, O.; *Org. Lett*, **2008**, 10, 3661
[79] Li, Z.; Bohle, S.; Li, C.-J.; *PNAS*, **2006**, 103, 8928
[80] Li, Z.; Li, C.-J.; *J. Am. Chem. Soc.*, **2004**, 126, 11810
[81] Li, Z.; Li, C.-J.; *Org. Lett.*, **2004**, 6 (26), 4997
[82] Li, Z.; MacLeod, P. D.; Li, C.-J.; *Tetrahedron: Asymmetry*, **2006**, 17, 590
[83] Jovel, I.; Prateeptongkum, S.; Jackstell, R.; Vogl, N.; Weckbecker, C.; Beller, M.; *Chem. Commun. (Cambridge, U.K.)*, **2010**, 46, 1956
[84] Li, Z.; Li, C.-J.; *J. Am. Chem. Soc.*, **2005**, 127, 6968
[85] Murahashi, S.; Naota, T.; Miyaguchi, N.; Nakato, T.; *Tetrahedron Lett.*, **1992**, 33, 6991
[86] Basle, O.; Li, C.-J.; *Chem. Commun. (Cambridge, U.K.)*, **2009**, 4124
[87] Hari, D. P.; König, B.; *Org. Lett.* **2011**, 13(15), 3852
[88] Murahashi, S.-I.; Komiya, N.; Terai, H.; *Angew. Chem. Int. Ed.*, **2005**, 44, 6931
[89] Murahashi, S.-I.; Nakae, T.; Terai, H.; Komiya, N.; *J. Am. Chem. Soc.*, **2008**, 130, 11005

and introduction of nitroalkanes,[90] 2-naphthols,[79] or malonic esters[91] to the C-1 position of N-substitued THIQs.

An overview of the various reactions on THIQ derivatives is given in Figure 12.

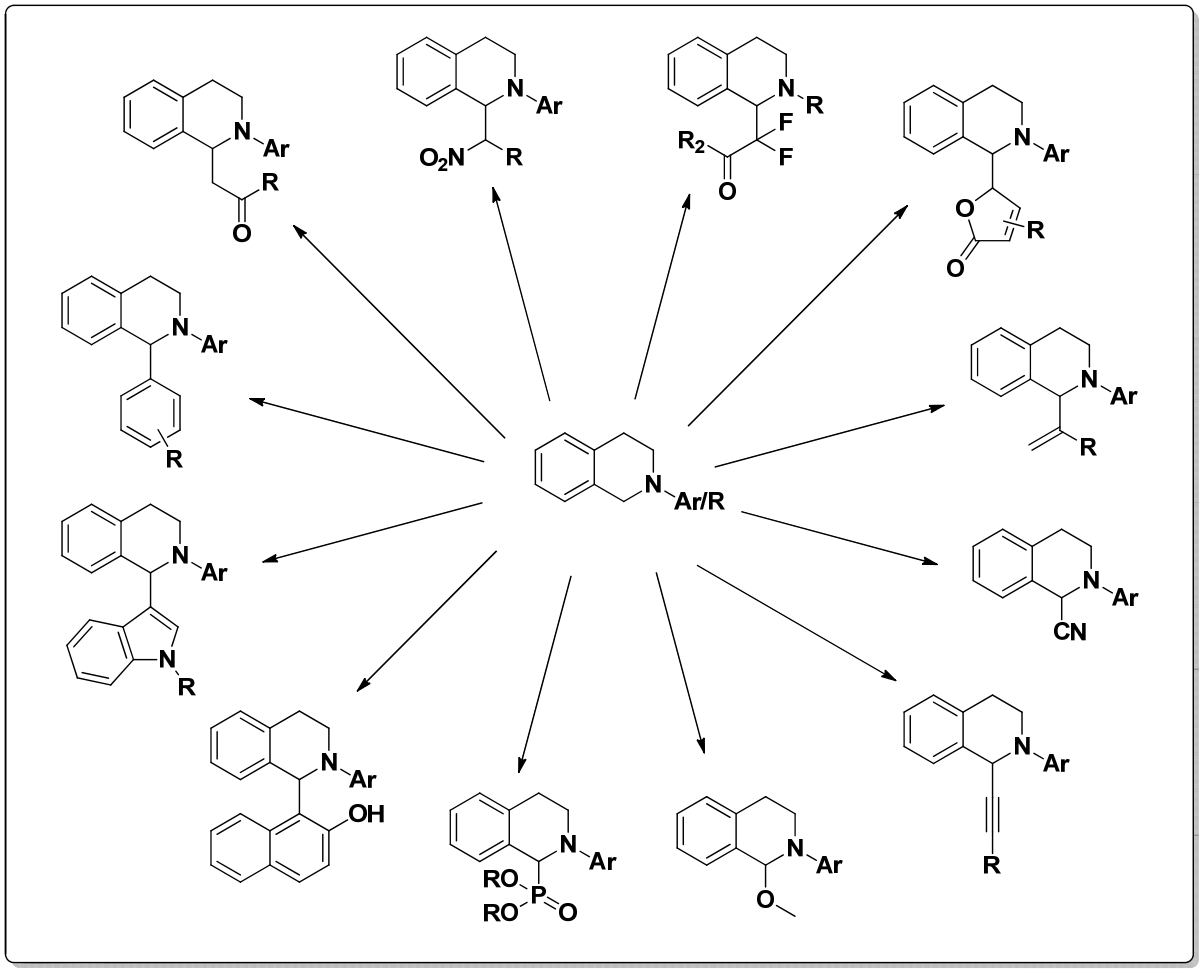


Figure 12. Direct functionalization of the C1-position of THIQs.

Among these examples, there is also a Sonogashira-type method, which allows introducing alkyne functionalities to the C1 position and shall be discussed in more detail.

In 2004, Z. Li and coworkers[84] reported a novel catalytic method to synthesize asymmetric 1-alkynylated 1,2,3,4-tetrahydroisoquinoline derivatives (see Figure 13, Scheme 8).

Various combinations of copper catalysts, ligands, solvents and reaction temperatures were applied, showing highest ee's (63%) with CuOTf/Pybox in THF at 50°C. Ligands used are shown in Figure 13, various reaction conditions are listed in Table 3.

[90] Li, Z.; Li, C.-J.; *J. Am. Chem. Soc.* **2005**, 127, 3672
[91] Li, Z.; Li, C.-J.; *Eur. J. Org. Chem.* **2005**, 3173

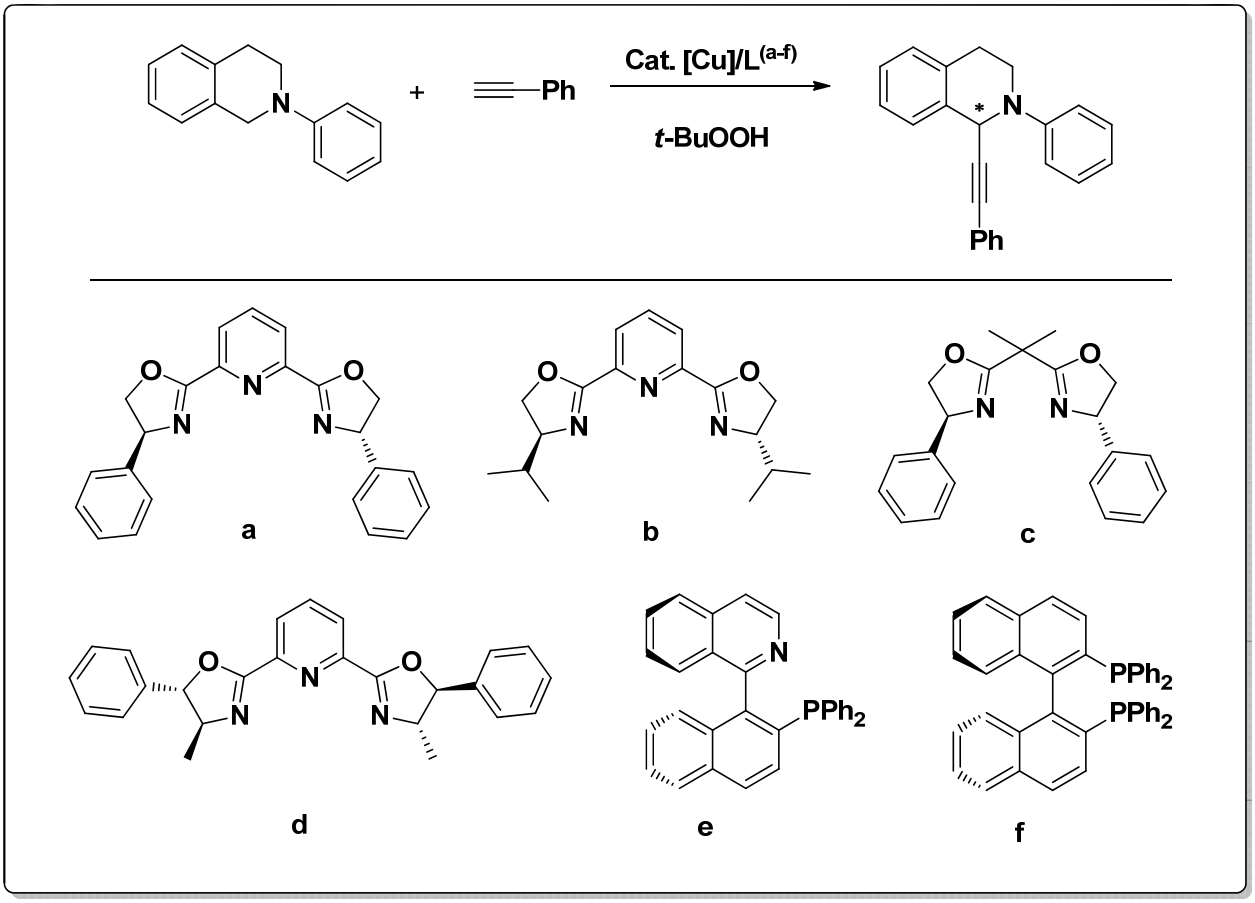


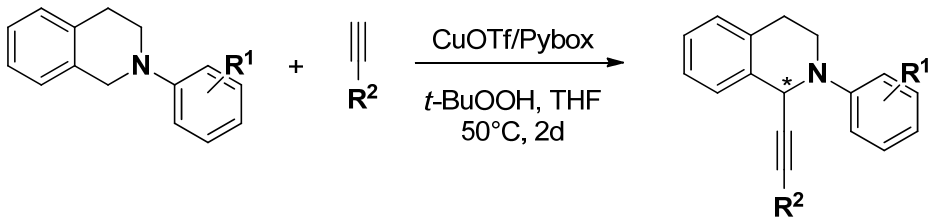
Figure 13. Ligands used for alkynylation reactions on N-substituted THIQ's.

Table 3. Effects of conditions on the enantioselectivity of alkynylation reactions on THIQ's.

Entry	catalyst	ligand	Temperature [°C]	solvent	ee [%]
1	CuOTf	a	80	no	19
2	CuOTf	a	80	toluene	21
3	CuOTf	a	50	toluene	42
4	CuOTf	a	50	1,2-dichloroethane	20
5	CuOTf	a	50	H_2O	18
6	CuOTf	a	50	1,4-dioxane	50
7	CuOTf	a	50	THF	56
8	CuBr	a	50	1,4-dioxane	18
9	$CuBr_2$	a	50	1,4-dioxane	12

10	$Cu(OTf)_2$	a	50	1,4-dioxane	40
11	CuOTf	b	50	dichloromethane	9
12	CuOTf	c	50	THF	14
13	CuOTf	d	50	THF	13
14	CuOTf	e	50	THF	20
15	CuBr	e	50	THF	4
16	CuOTf	f	50	THF	8
17	CuOTf	a	50	THF	63

Using CuOTf/Pybox as chiral catalyst and *t*-BuOOH as oxidant, various alkynylated products were obtained in moderate to good yields and moderate ee's (see Scheme 8, Table 4).



Scheme 8. Catalytic enantioselective Alkynylation on 1,2,3,4-Tetrahydroisoquinolines.

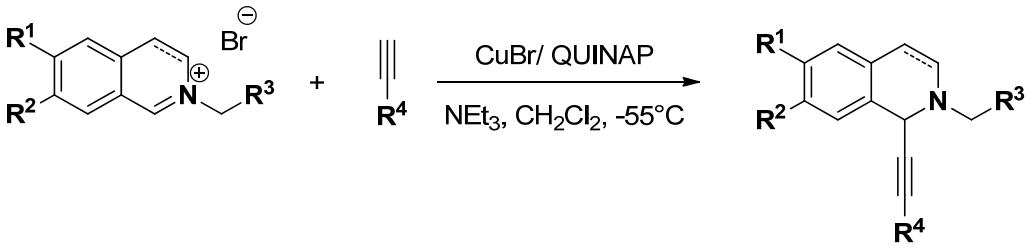
Table 4. Yields and enantioselectivity of coupling of 1,2,3,4-Tetrahydroisoquinolines with various terminal alkynes.

Entry	R^1	R^2	Yield [%]	ee [%]
1	H	Ph	67	63
2	H	4-MeOPh	65	41
3	H	4-BrPh	72	64
4	H	Hex	65	26
5	H	TMS	11	30
6	4-MeO	Ph	59	60

7	4-MeO	Hex	48	5
8	2-MeO	Ph	54	73
9	2-MeO	4-MeOPh	56	69
10	2-MeO	4-BrPh	61	74
11	2-MeO	Py	57	36

The substrate scope is limited to *N*-Phenyl-, *N*-p-methoxyphenyl- and *N*-o-methoxyphenyl-THIQs, yet referring to the removability of methoxy-substituted aryls.[92] Introduction of an o- or p- substituent to the aryl resulted in slightly lower yields (from 65-72% to 48-61%). Alkynylations were carried out with alkynes carrying larger substituents, such as aromatic groups (Table 4, examples 1-3, 6, 8-11) or long alkyl chains (Table 4, examples 4, 7). Regarding the yields no remarkable dependency on the structure of the alkyne substituent is observed, except in the case of TMS as substituent (Table 4, example 5), where the yield was very low (11%) compared to all other experiments.
Best enantioselectivities were observed with o-methoxyphenyl and alkynes with aromatic residues. In the case of aliphatic substituted alkynes ee's were rather low (5-26%, see Table 4, examples 4, 7).

In 2006, Schreiber and Taylor [93] published an asymmetric, copper-catalyzed addition of terminal alkynes to alkylisoquinolinium salts at -55°C, using 10 equivalents of alkyne (Scheme 9). In the presence of 5mol% CuBr, 5.5mol% QUINAP and 1 equivalent triethylamine, various propargylic amines were obtained in good to excellent yields up to 95%, with good ee's up to 99%. Examples are listed below in Table 5.



Scheme 9. Catalytic enantioselective addition of terminal alkynes to isoquinoline iminium salts.

[92] Porter, J. R.; Traverse, J. F.; Hoveyda, A. H.; Snapper, M. L.; *J. Am. Chem. Soc.*, **2001**, 123, 10409
[93] Taylor, A. M.; Schreiber, S. L.; *Org. Lett.*, **2006**, 8(1), 143

Table 5. Yields and enantioselectivity of nucleophilic addition of various terminal alkynes to alkylisoquinoline iminums.

Entry	R^1	R^2	R^3	R^4	Yield [%]	ee [%]
1	MeO	MeO	(2-Br-5-OMe-)Ph	Ph	85	95
2	MeO	MeO	(2-Br-5-OMe-)Ph	$Si(Me)_3$	91	99
3	MeO	MeO	(2-Br-5-OMe-)Ph	OEt	95	70
4	MeO	MeO	(2-Br-5-OMe-)Ph	CH_2OMe	78	98
5	MeO	MeO	H	CH_2OMe	71	94
6	H	MeO	(2-Br-5-OMe-)Ph	$Si(Me)_3$	67	83

Interestingly, reaction scope is limited to benzylic N-substituents or N-methyl-THIQs. In contrast to the observations in Li's CDC reactions[84], the structure of the alkyne substituent slightly influences yields and enantioselectivity, with best results (91% isolated yield and 99%ee) using TMS-acetylene (Table 5, entry 3). Absence of the second methoxy-group on the isoquinoline resulted in a remarkably lower yield of 67% and ee of 83% (Table 5, entry 6). Furthermore, one complete reduction of the alkyne group was carried out with Pd/C in 75% yield, using N-Methyl-THIQ and 3,4-methoxyphenylacetylene as alkynylation substrates.

In 2011, a solvent-free mechanically activated cross-dehydrogenative coupling method between THIQs, and indoles, nitroalkanes and terminal alkynes, was reported by Su and colleagues[94], using a high-speed ball milling technique. With 2,3-dichloro-5,6-dicyanoquinone (DDQ), which has showed to be a powerful oxidation agent for oxidative C-C couplings,[95,96,97,98,99] and copper balls, indoles and terminal alkynes (see Scheme 10) could be introduced to the C-1 position of N-arylated THIQs. In the case of nitroalkanes as pronucleophiles, stainless steel balls could be used to achieve yields from 70 up to 85%.

[94] Su, W.; Yu, J.; Li, Z.; Jiang, Z.; *J. Org. Chem.*, **2011**, 76, 9144
[95] Zhang, Y. H.; Li, C. J.; *Angew. Chem. Int. Ed.*, **2006**, 118, 1983
[96] Cheng, D. P.; Bao, W. L.; *Adv. Synth. Catal.*, **2008**, 350, 1263
[97] Cheng, D. P.; Bao, W. L.; *J. Org. Chem.*, **2008**, 73, 6881
[98] Li, Y.; Bao, W. L.; *Adv. Synth. Catal.*, **2009**, 351,865
[99] Correia, C. A.; Li, C.; *J. Adv. Synth. Catal.*, **2010**, 352, 1446

Scheme 10. Coupling Reaction of THIQ's with terminal alkynes via ball milling.

Table 6. Coupling Reaction of THIQs with alkynes via ball milling.

Entry	Ar	R	Time [min]	Yield [%]
1	Ph	Ph	20	78
2	Ph	4-MeC_6H_4	20	74
3	Ph	4-FC_6H_4	20	87
4	Ph	2-Py	40	69
5	Ph	Pr	30	67
6	Ph	CH_3OCO	30	73
7	4-$MeOC_6H_4$	Ph	30	75
8	4-$MeOC_6H_4$	4-MeC_6H_4	30	70
9	4-$MeOC_6H_4$	4-FC_6H_4	20	84
10	4-$MeOC_6H_4$	CH_3OCO	30	72

Compared to other alkynylation methods, this protocol appeals with short reaction times from 20-40 minutes, but is limited to phenyl- and p-methoxyphenyl-THIQs. No enantioselective experiments were carried out so far with this method. Using aromatic alkynes, electron-rich aryl groups resulted in slightly lower yields than electron-poor substituents (Table 6, entries 1-3 and 7-9). With aliphatic alkynes and propiolate good yields of 67-73% were achieved (Table 6, entries 5, 9, 10).

5. Click Chemistry

The term "click reaction" was first mentioned by Sharpless and colleagues in 2001, describing various reactions, characterized by high efficiency and joining small units together.[100] Reactions include [3+2] cycloadditions, especially between azides and terminal alkynes,[101,102] thiol-ene click reactions,[103] Diels-Alder and Inverse-Electron-Demand-Diels-Alder reaction, [104] [4+1] cycloadditions between isonitriles and tetrazines, nucleophilic substitution to epoxy and aziridine compounds.

Click reactions are known for their very simple experimental conditions, requiring no solvents or easily removable solvents such as water, high yields, readily available reagents, easy product isolation and their multiple applications, and have been broadly reviewed.[105, 106, 107, 108, 109]

5.1 The Copper-catalyzed Azide-Alkyne Cycloaddition

In 2005, Sharpless and colleagues reported a copper-catalyzed [3+2] cycloaddition between azides and terminal alkynes, with high acceleration rates of 10^7 to 10^8, tolerating a broad temperature range, pH values from 4 to 12 and various functional groups. It is insensitive to aqueous conditions products can be isolated by simple filtration or extraction without the need for chromatography or recrystallization.[110]

Figure 14 shows the mechanism of the [3+2] cycloaddition:

[100] Kolb, H.C.; Finn, M. G.; Sharpless, K. B.; *Angew. Chem. Int. Ed.*, **2001**, 40(11), 2004
[101] Evans, R. A.; *Australian Journal of Chemistry*, **2007**, 60(6), 384
[102] Spiteri, C.; Moses, J. E.; *Angew. Chem.Int. Ed.,* **2010**, 49(1), 31
[103] Hoyle, C. E.; Bowman, C. N.; *Angew. Chem. Int. Ed.*, **2010**, 49(9), 1540
[104] Blackman, M. L.; Royzen, M.; Fox, J. M.; *J. Am. Chem. Soc.,* **2008**, 130(41), 13518
[105] Moses, J.E.; Moorhouse, A. D.; *Chem. Soc. Rev.,* **2007**, 36(36), 1249
[106] Weixian, X.; Scott, T. F.; Kloxin, C. J.; Bowman, C. N.; *Adv. Funct. Mat.*, **2014**, 24(18), 2572
[107] Aizpura, J. M.; Fratila, R. M.; Monasterio, Z.; Perez-Esnaola, N.; Andreieff, E.; Irastorza, A.; Sagartzazu-Aitzpurua, M.; *New J. of Chem.*, **2014**, 38(2), 474
[108] Bunz, U. H. F.; *Synlett.*, **2013**, 24(15), 1899
[109] Xiong, X.; Chen, H.; *Youji Huaxue*, **2013**, 33(7), 1437
[110] Himo, F.; Lovell, T.; Hilgraf, R.; Rostovtsev, V. V.; Noodleman, L.; Sharpless, K. B.; Fokin, V. V. ; *J. Am. Chem. Soc.*, **2005**, 127, 210

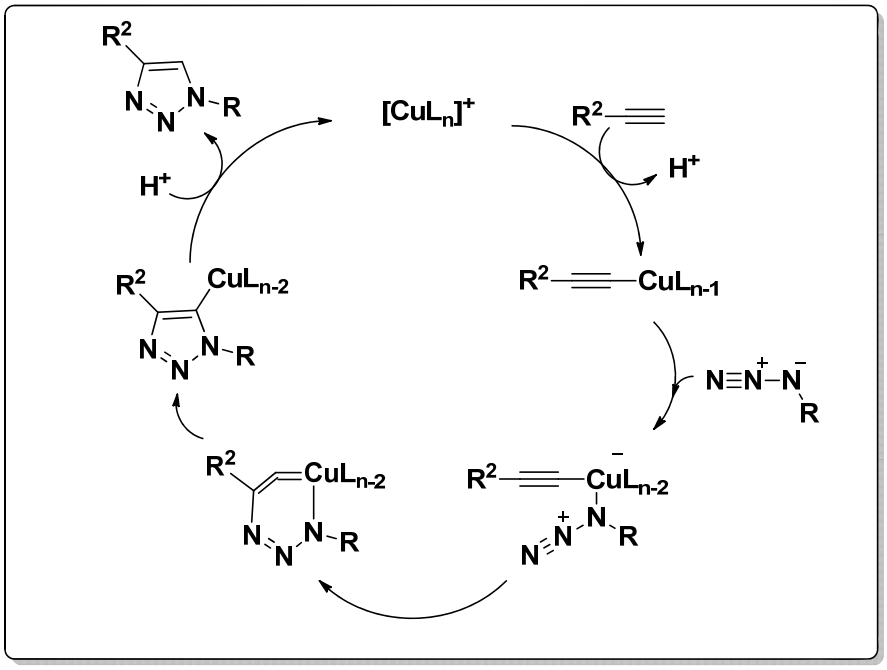


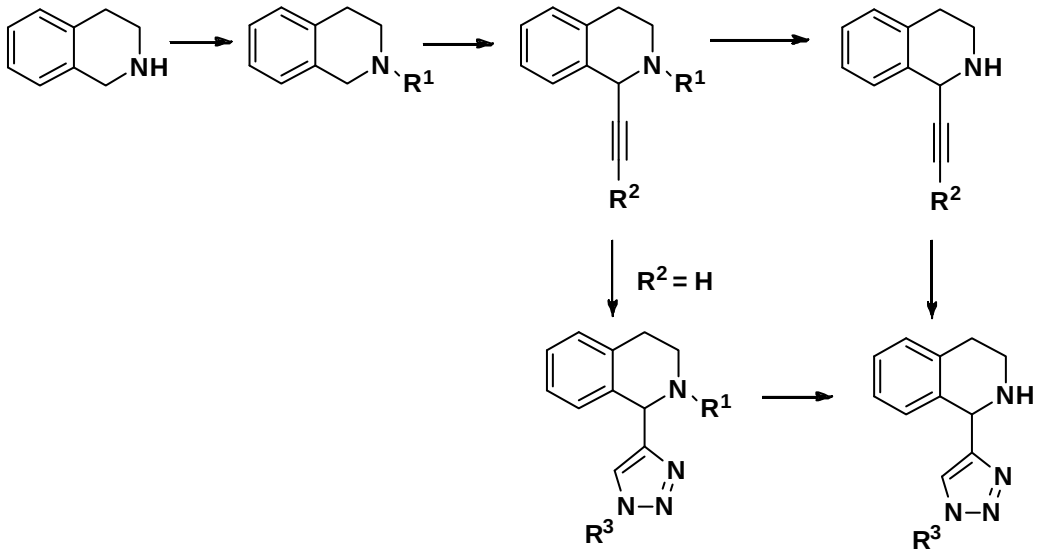
Figure 14. Copper-catalyzed azide-alkyne cycloaddition.

Over the past decade, the protocol has been extended using vinyl acetates[111] or different alkyne sources, such as acetylene gas,[112] calcium carbide,[113] or alkynoic acids,[114,115] in situ generation of azides leading to one-pot synthesis, [115, 116, 117, 118] using acidic or basic additives,[119,120] or phase transfer catalysts,[121] heterogeneous catalysts,[122,123,124] or solid-phase catalysts.[125,126]

[111] Hansen, S. G.; Jensen, H. H.; *Synlett*, **2009**, 3275
[112] Wu, L.-Y.; Xie, Y.-X.; Chen, Z.-S.; Niu, Y.-N.; Liang, Y.-M.; *Synlett*, **2009**, 1453
[113] Jiang, Y.; Kuang, C.; Yang, Q.; *Synlett*, **2009**, 3163
[114] Kolarovič, A.; Schnürch, M.; Mihovilovic, M.D.; *J. Org. Chem.*, **2011**, *76*, 2613
[115] Xu, M.; Kuang, C.; Wang, Z.; Yang, Q.; Jiang, Y.; *Synthesis*, **2011**, 223
[116] Barral, K.; Moorhouse, A. D.; Moses, J. E.; *Org. Lett.*, **2007**, *9*, 1809
[117] Friscourt, F.; Boons, G.-J.; *Org. Lett.*, **2010**, *12*, 4936
[118] Grimes, K. D.; Gupte, A.; Aldrich, C. C.; *Synthesis*, **2010**, 1441
[119] Shao, C.; Wang, X.; Zhang, Q.; Luo, S.; Zhao, J.; Hu, Y.; *J. Org. Chem.*, **2011**, *76*, 6832
[120] Shao, C.; Wang, X.; Xu, J.; Zhao, J.; Zhang, Q.; Hu, Y.; *J. Org. Chem.*, **2010**, *75*, 7002
[121] Shin, J.-A.; Lim, Y.-G.; Lee, K.-H.; *J. Org. Chem.*, **2012**, *77*, 4117
[122] Liu, M.; Reiser, O.; *Org. Lett.*, **2011**, *13*, 1102
[123] Park, I. S.; Kwon, M. S.; Kim, Y.; Lee, J. S.; Park, J.; *Org. Lett.*, **2008**, *10*, 497
[124] Lipshutz, B. H.; Taft, B. R.; *Angew. Chem. Int. Ed.*, **2006**, *45*, 8235
[125] Yamada, Y. M. A.; Sarkar, S. M.; Uozumi, Y.; *J. Am. Chem. Soc.*, **2012**, *134*, 9285
[126] Miaoa, T.; Wang, L.; *Synthesis*, **2008**, 363

Objective

The subject of the presented PhD-thesis was the preparation of various C1-alkynylated 1,2,3,4-tetrahydroisoquinolines, since introduction of an alkyne functionality in the C1-position allows a broad variety of further transformations, such as synthesis of triazolyl-derivatives, hydratisation to the ketones or reduction to the alkenes.



Results and Discussion

1. Copper-catalyzed C-H activation reactions on 1,2,3,4-Tetrahydroisoquinolines

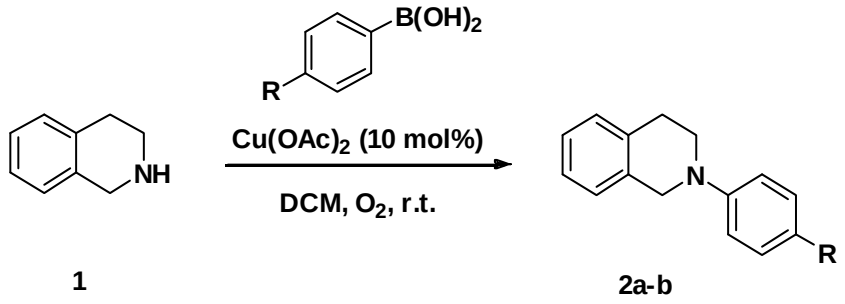
As previously discussed, Cu-catalyzed alkynylations of sp^3 C-H bonds adjacent to a nitrogen, especially on N-arylated 1,2,3,4-THIQ's, were reported by Zhiping Li and Chao-Jun Li.[80,81]

They established in their studies that CuBr was the most effective catalyst for alkynylation reactions according to the yield. Yet, they reported that Cu(OTf) provided better enantioselectivities than CuBr. Lowering the reaction temperature from 100°C to 50°C was also found to be beneficial to the enantioselectivities.
Experiments described below were carried out under literature conditions to verify if the published yields and ee's can be reproduced.

1.1 Synthesis of Substrates

1.1.1 Synthesis of N-phenyl- and N-pmp-1,2,3,4-Tetrahydroisoquinoline

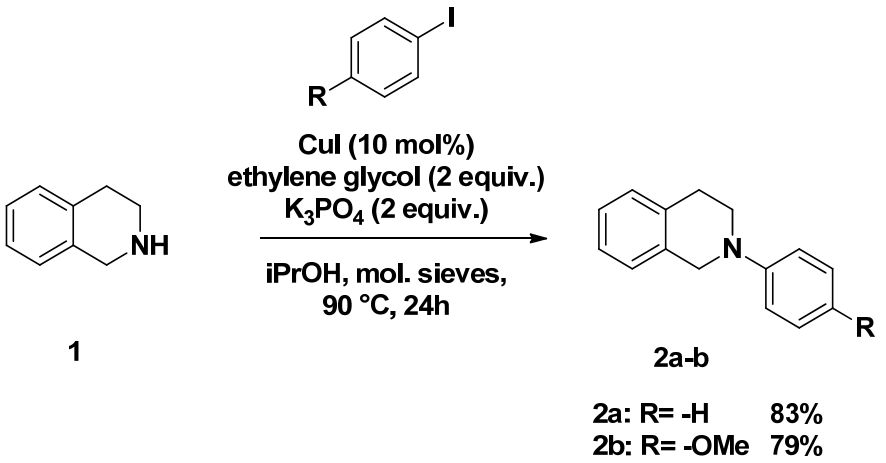
Both products **2a** and **2b** were prepared via a copper-catalyzed method by Quach and colleages,[127] starting from THIQ and the corresponding arylboronic acid (see Scheme 11).



Scheme 11. Synthesis of N-arylated 1,2,3,4-THIQ's via arylboronic acids.

Since both reactions resulted in low yields of 26% and 36%, a different protocol, reported by Buchwald and colleagues,[128] was applied (Scheme 12):

[127] Quach, T.D.; Batey, R. A.; *Org. Lett.*, **2003**, 5, 4397

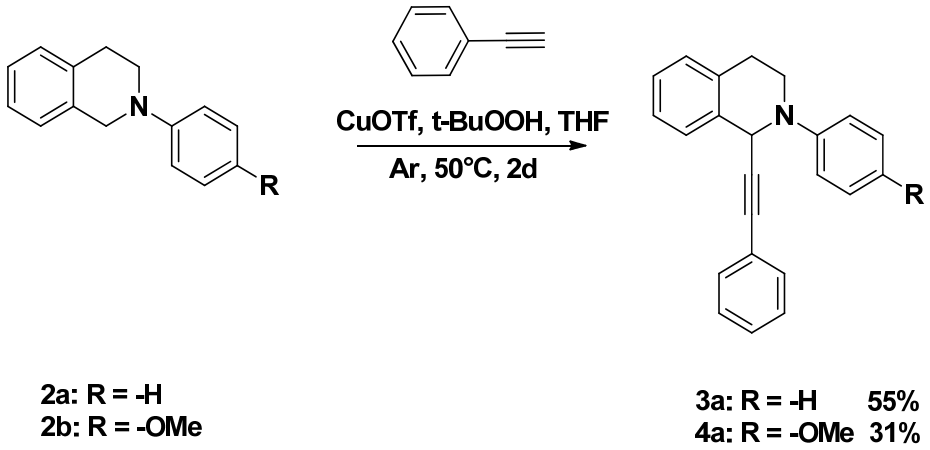


Scheme 12. Synthesis of N-arylated 1,2,3,4-THIQ's via aryl iodides.

Using iodobenzene or 4-iodoanisole, CuI as catalyst and ethylene glycol as ligand, resulted in high yields of both **2a** (83%) and **2b** (79%, Lit: 80%[128]).

1.2 Alkynylation of N-Ph- and N-pmp-THIQ

Based on the published experiments of Zhiping Li et al.[81] the following C-H activation experiment was carried out (Scheme 13).



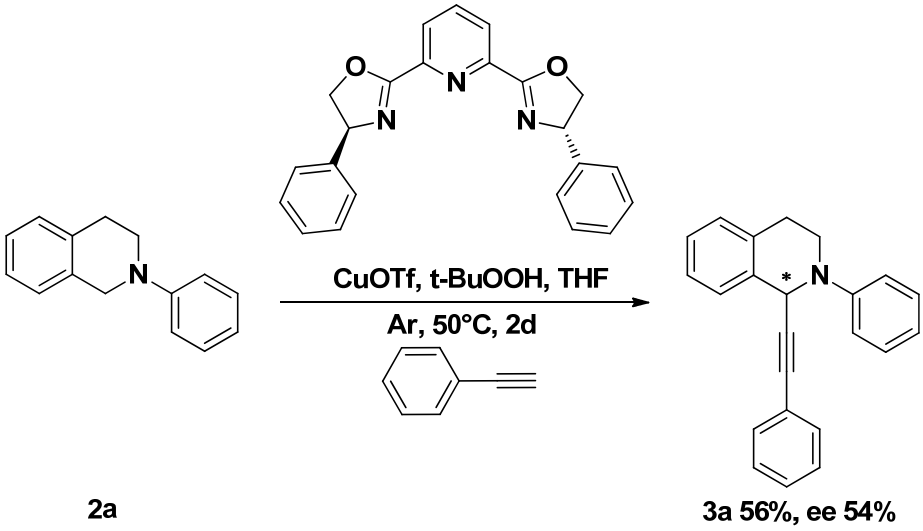
Scheme 13. Cu-catalyzed alkynylation of N-arylated 1,2,3,4-THIQ's.

With $CuOTf_2$ toluene complex as catalyst and *t*-BuOOH as oxidant, both substrates could be successfully alkynylated in the C1-position, yielding in 55 % for **3a** (Lit: 67 %) and 31 % for **4a** (Lit: 65%).

[128] Kwong, F. Y.; Klapars, A.; Buchwald, S. L.; *Org. Lett.*, **2002**, 4, 581

1.2.1 Enantioselective reaction

After successful isolation of products **3a** and **4a**, the reaction from Scheme 13 was repeated, adding Pybox (see Scheme 14) to the reaction mixture as chiral ligand. After isolation of the product, ee was determined via chiral HPLC.



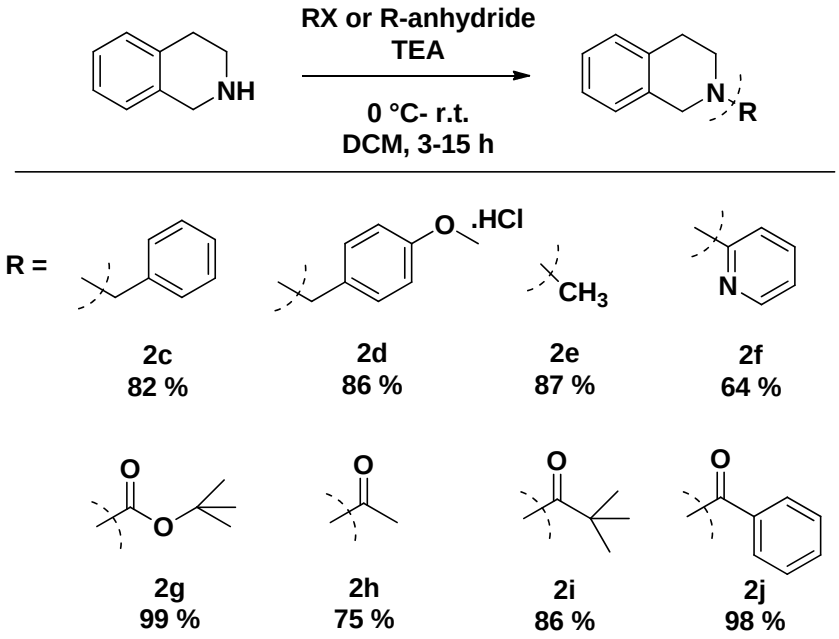
Scheme 14. Enantioselective alkynylation of N-Phenyl-1,2,3,4-THIQ.

Summarizing, literature experiments could be successfully reproduced. Hence, for additional reactions and applications there lies an interest in alkynylated 1,2,3,4-tetrahydroisoquinolines without substitution on the nitrogen atom. Zhiping Li and colleagues only published alkynylation experiments on 1,2,3,4-tetrahydroisoquinoline substrates with phenyl-, o- and p-methoxyphenyl- substituents in 2-position. Yet, they never tried to cleave these groups and since the cleavage of aryls is impossible and of o- or p-methoxy substituted aryls very difficult, investigations were made towards a broader substrate scope. In our case deprotection of the pmp group was unsuccessful and led to decomposition of the alkynylated THIQ (see Chapter 1.11.1).

1.3 Substrate screening

1.3.1 Preparation of 1,2,3,4-Tetrahydroisoquinolines

Various N-substituted 1,2,3,4-Tetrahydroisoquinolines were prepared according to literature protocols. Products were obtained in good to high yields.



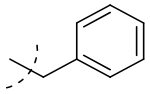
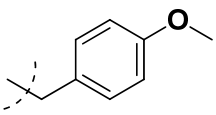
Scheme 15. Synthesis of N-substituted 1,2,3,4-THIQ's

All protecting groups, except of substrate **2e** were chosen because of their cleavability. Use of Pyridine as removable directing group – as in Substrate **2f -** , was reported by Schnürch et al. in 2010.[129] The methyl group in **2e** is hard to cleave, but was of interest because of the structural similarity to the products of high cell viability in Figure 3.

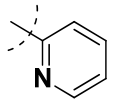
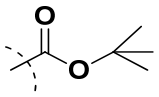
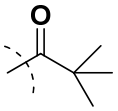
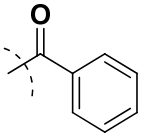
1.3.2 Alkynylation reactions

Alkynylation experiments were carried out under the same conditions as in Scheme 13.

Table 7. N-substituents on 1,2,3,4-tetrahydroisoquinoline for alkynylation reactions.

Entry	R^1	Yield [%]
1		n.c.
2		traces
3		traces

[129] Dastbaravardeh, N.; Schnürch, M.; Mihovilovic, M. D.; *Org. Lett.* **2012**, 14 (7), 1930

4		n.c.
5		n.c.
6		traces
7		n.c.
8		n.c.
9	-H	n.c.

Except in the cases of methyl-, 4-methoxybenzyl- and acetyl- substituted 1,2,3,4-tetrahydroisoquinolines, where traces of alkynylated product were detected via GC-MS, no product was found to be formed in the experiments under literature reaction conditions. However, the formation of the alkynylated product by using the acetyl, methyl and 4-methoxy-benzyl protecting groups could not be reproduced in further experiments.

Alkynylation experiments were also carried out on other N-containing systems with a benzylic sp^2 center adjacent to the nitrogen atom (see Figure 15). The substrates used were available from other projects.[130] Unfortunately, no conversion to the desired alkynylated products was observed.

[130] Dastbaravardeh, N.; Vienna UT, *PhD Thesis*, **2012**

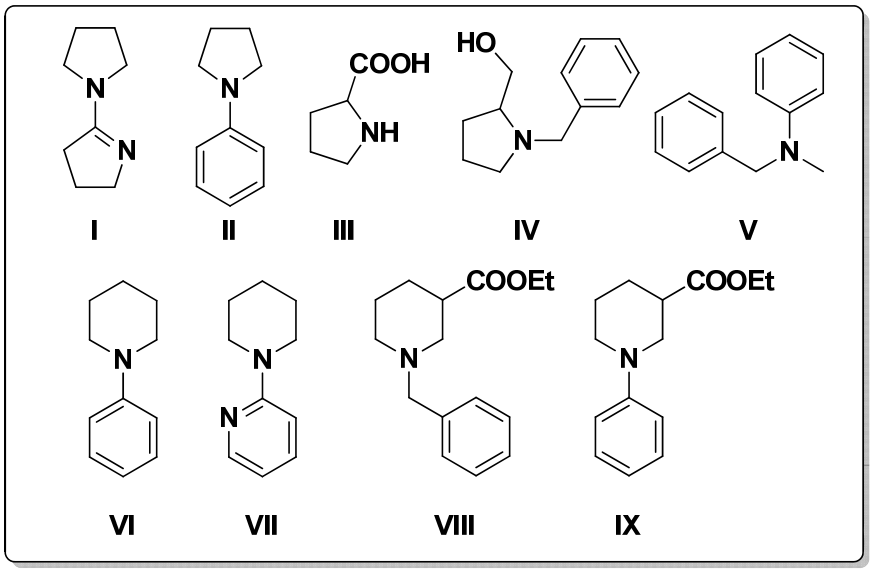


Figure 15. Systems screened for the alkynylation reaction.

So far, N-Phenyl- and N-pmp-THIQs proved to be the only substrates suitable for these alkynylation conditions. Since the maximum achieved yield was 55 % (Lit: 67 %[81]), further efforts were made in improving the yield.

1.4 Parameter screening

To improve the published yield of only 67%, various reaction parameters were screened for the alkynylation of 2-phenyl-1,2,3,4-tetrahydroisoquinoline with phenylacetylene.

Reactions were carried out with CuBr, CuCl, CuCN, $Cu(NO_3)_2.3H_2O$, $(CuOTf)_2$ toluene complex, CuÖÖ1 (see Figure 16) and $Fe(NO_3)_2.9H_2O$ as catalysts, at room temperature, 50°C and 100°C, and in THF, acetonitrile, dichloromethane or neat for **2d**. Parameters and yields of successful experiments are listed in Table 8.

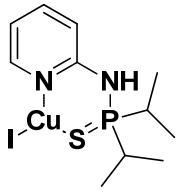


Figure 16. Structure of CuÖÖ1.

CuÖÖ1 was provided by the group of Karl Kirchner as racemic mixture.[131] The compound was of interest because of its potential as chiral catalyst. Yet, enantiomers were not available and no further investigations were made using CuÖÖ1 as catalyst.

Since indolation reactions on THIQ's could be successfully carried out with $Fe(NO_3)_2.9H_2O$ as catalyst,[132] it was also used for alkynylation reactions.

Table 8. variation on catalysts and reaction conditions for the alkynylation on 2-phenyl-THIQ's.

Entry	Catalyst	T [°C]	solvent	yield [%][a]
1	$(CuOTf)_2$ toluene complex	50	THF	55
2	$(CuOTf)_2$ toluene complex	50	MeCN	75
3	$(CuOTf)_2$ toluene complex	50	neat	26
4	$(CuOTf)_2$ toluene complex	50	DCM	33
5	$(CuOTf)_2$ toluene complex	100	neat	n.c.
6	$(CuOTf)_2$ toluene complex	100	MeCN	n.c.
7	CuBr	50	neat	66
8	CuBr	50	DCM	53
9	CuBr	50	MeCN	55
10	CuBr	50	THF	51
11	CuBr	100	neat	100
12	CuBr	100	MeCN	59
13	$Cu(NO_3)_2.3H_2O$	50	neat	80
14	$Cu(NO_3)_2.3H_2O$	50	MeCN	61
15	$Cu(NO_3)_2.3H_2O$	50	DCM	67
16	$Cu(NO_3)_2.3H_2O$	50	THF	48
17	$Cu(NO_3)_2.3H_2O$	100	neat	72
18	$Cu(NO_3)_2.3H_2O$	100	MeCN	37
19	CuCl	50	THF	70
20	CuCl	50	MeCN	86
21	CuCl	50	neat	67
22	CuCl	50	DCM	65
23	CuCl	100	neat	58
24	CuCl	100	MeCN	60
25	CuCN	50	MeCN	45
26	CuÖÖ1	50	MeCN	60
27	$Fe(NO_3)_2.9H_2O$	50	MeCN	n.c.
28	$Fe(NO_3)_2.9H_2O$	100	neat	n.c.

a) Isolated yields

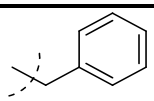
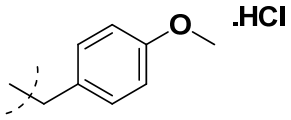
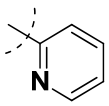
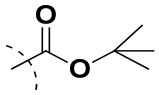
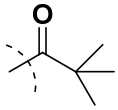
[131] Öztopcu, Ö; Mereiter, K.; Puchberger, M.; Kirchner, K.; *Dalton Transactions*, **2011**, 40, 7008
[132] Ghobrial, M.; Harhammer, K.; Mihovilovic, M. D.; Schnürch, M.; *Chem. Comm.,* **2010**, 46, 8836

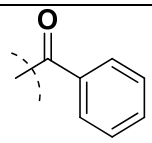
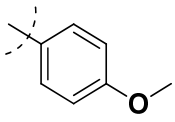
In most cases moderate to high yields could be achieved, except with copper triflate at 100°C (entries 5 and 6) and with iron nitrate (entries 27 and 28), where no product formation was observed. The highest yield was achieved with CuBr at 100°C, neat (entry 11), and with CuCl at 50°C in acetonitrile (entry 20).

1.5 Substrate screening

With these improved reaction conditions at hand, the screening of substrates with different N-protecting groups was revisited. Reactions were carried out at 100°C with CuBr as catalyst, as well as at 50°C with CuCl as catalyst, the conditions that previously led to highest alkynylation yields (see Table 8, entries 11 and 20). The results are listed below in tables

Table 9. CuBr-catalyzed alkynylation reactions on various THIQ's (100°C, neat).

Entry	R^1	Conversion [%][a]
1		n.c.
2	 .HCl	n.c.
3		~50
4		n.c.
5		<10
6		n.c.
7		n.c.

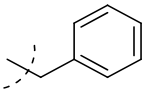
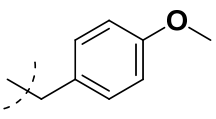
8		n.c.
9	-H	n.c.
10		21

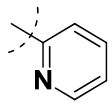
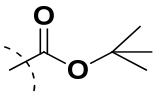
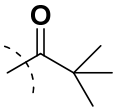
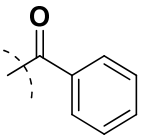
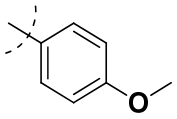
a) GC yield with internal standard

In the case of CuBr as catalyst, at 100°C and neat, product formation was observed for the pmp-, methyl- and Boc-protecting groups (see Table 9, entries 3, 5 and 10). Although conversion was around 50% according to GC-MS for 2-methyl-1,2,3,4-tetrahydroisoquinoline, the alkynylation product could not be isolated due to purification difficulties. In the case of the Boc-protected substrates, product formation was very low – beyond 10% – according to GC-MS and crude ^{1}H-NMR. However, since a methyl-group is not a desirable protecting group because of bad cleavability, and since the product conversion of the Boc-protected substrate could not be improved, no further investigations were made into isolating the methyl- and Boc-substituted alkynylation products.

Unfortunately, the protocol using CuCl did not lead to more promising results:

Table 10. CuCl-catalyzed alkynylation reactions on various THIQ's (50°C, MeCN).

Entry	R^1	Conversion [%][a]
1		traces
2	 .HCl	n.c.
3		n.c.

4		n.c.
5		n.c.
6		n.c.
7		n.c.
8		n.c.
9	-H	n.c.
10		42

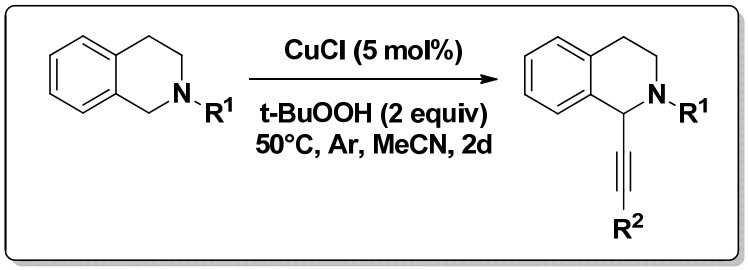
a) GC yield with internal standard

Since the alkynylation reaction could not be applied to other substrates than N-Ph- and N-pmp-THIQs, investigations towards a broader product range were made using different alkynes.

1.6 Variation of alkynes

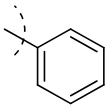
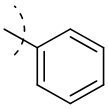
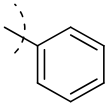
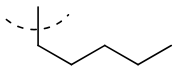
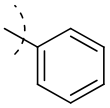
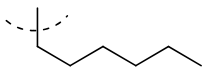
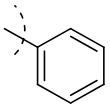
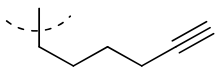
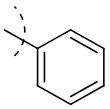
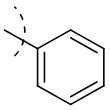
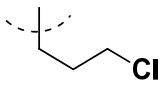
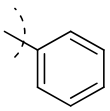
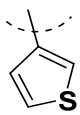
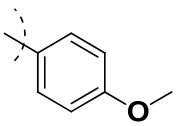
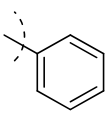
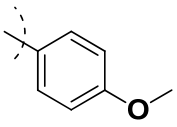
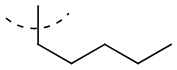
Zhiping Li and colleagues published successful experiments with phenylacetylene, 1-octyne and some other alkynes,[81] which could be reproduced in similar yields. Yet, the scope was limited to terminal alkynes with long alkyl chains, TMS or aromatic substituents.

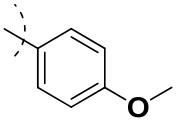
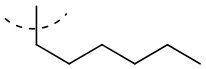
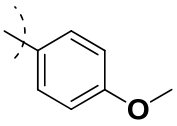
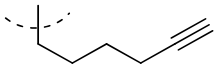
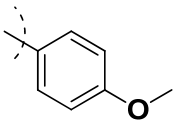
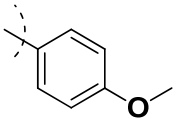
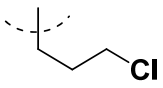
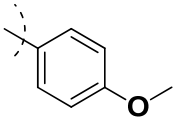
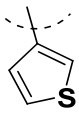
Alkynylation reactions were carried out with various alkynes under the conditions shown in Scheme 16.



Scheme 16. Reaction conditions for alkynylation with various alkynes.

Table 11. Alkynylation of Phenyl- and pmp-THIQ's with various alkynes

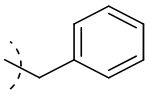
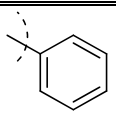
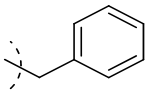
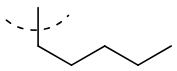
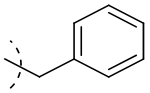
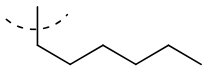
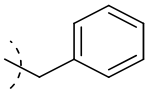
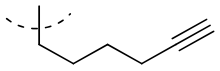
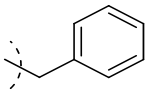
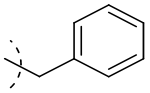
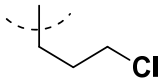
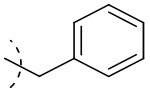
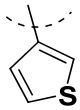
Entry	Substance	R^1	R^2	Yield [%]
1	3a			86
2	3b			67
3	3c			49
4	3d			93
5	3e			42
6	3f			77
7	3g			57
8	4a			42
9	4b			71

10	4c			61
11	4d			25
12	4e			93
13	4f			52
14				n.c.

Compared to Li's results[84] on phenyl- and pmp-THIQ's (see Figure 4), this modified protocol delivers similar yields for compounds 3c (Li: 65%), 4a (Li: 48%) and 4c (Li: 54%), but shows a big difference form product 3a with 86% (Li: 67%). With only 4 examples of phenyl-THIQ's and 2 examples of pmp-THIQ's in Li's protocol, product scope could be enlarged for the alkynylation reaction. The reaction showed to tolerate other alkyl chains bearing functional groups (3d, 3f, 4b, 4d, 4f), cyclic alkanes (3e, 4e), and electron rich heterocycles, such as thiophene (3g).
With N-phenyl-THIQ as substrate, moderate to high yields were achieved in all cases, tolerating various functional groups. On pmp-THIQ, the yields were lower with unsaturated substituents (entries 8, 11 and 14) and higher with aliphatic substituents (entries 9, 10 and 12). With the thiophenyl-substituent no product was formed (entry 14). Interestingly, using 1,7-octadiyne, only formation of the single-alkynylated product was observed (entries 4 and 11).

Since Benzyl-THIQ or Boc-THIQ would have been desirable substrates due to their easy cleavability, two further experiments were carried out with octyne, to see if reactions may be successful if not using aromatic substituents, such as phenylacetylene. In the case of benzyl-THIQ, product formation was observed and reactions with other alkynes were carried out, showing moderate yields for alkyl-alkynes. Results are listed below in Table 12.

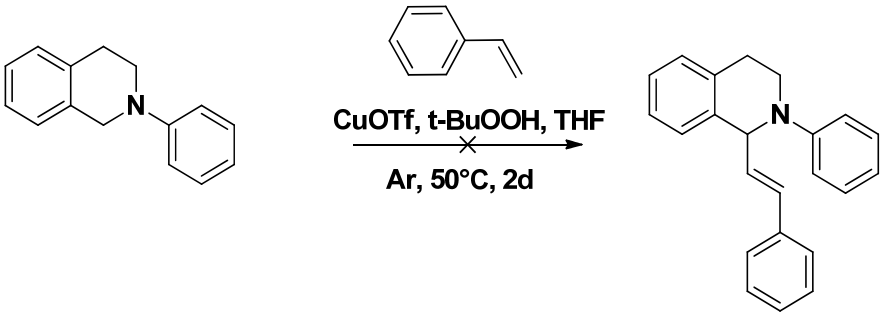
Table 12. Alkynylation reactions on Benzyl-THIQ.

Entry	Substance	R^1	R^2	Yield [%]
1				n.c.
4	5a			30
5	5b			40
6				n.c.
2	5c			53
3	5d			48
7				n.c.

Interestingly, reactions with unsaturated alkyne substituents (entries 1, 6 and 7) were not successful. This might be due to a possible π-complexation of the catalyst, resulting in significantly lower activity.

1.7 Alkenylation attempts

Since an alkene functionality in the C1-position of THIQ's would also be of interest, an alkenylation experiment under alkynylation conditions, using styrene instead of phenylacetylene, was carried out (see Scheme 17).



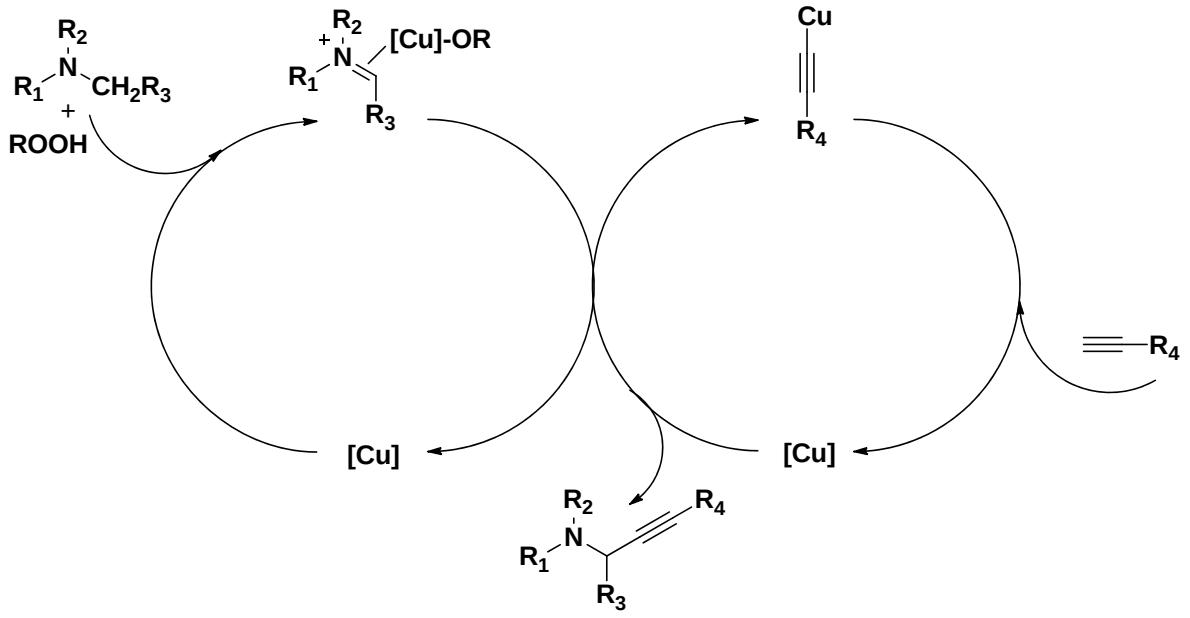
Scheme 17. Alkenylation attempt.

No product formation was observed. Since alkynes can be converted to alkenes and alkanes via reduction, no further investigations were made towards C1-alkenylation on THIQ's.

1.8 Alkynylation reactions in water

1.8.1 Mechanistic questions

Zhiping Li and colleagues proposed a tentative mechanism for the alkynylation reaction, based on their studies on systems with sp^3 C-H bonds adjacent to a nitrogen atom.[81]

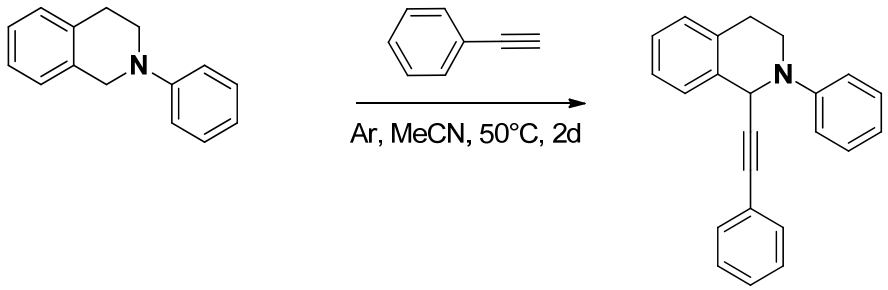


Scheme 18. Tentative mechanism for the direct oxidative coupling of amines with alkynes by Li et al.

The copper compound activates the terminal alkyne and catalyzes the formation of an imine-type intermediate by activation of the sp^3 bond, followed by coupling of the two intermediates and regeneration of the catalyst.

Nevertheless, the mechanism of the reaction and the specific roles of the reactants were not clear.

To find out, which oxidation state of the catalyst is needed for the alkynylation reaction and if it is reduced during the reaction several experiments were carried out on N-phenyl-THIQ, with phenylacetylene, and with different copper sources and catalyst amounts (see Scheme 19 and Table 13). Furthermore, experiments were carried out with and without *t*-BuOOH.



Scheme 19. Alkynylation reaction for mechanistic studies.

Table 13. Variation of parameters.

Entry	Catalyst	Loading	t-BuOOH	Yield [%][a]
1	CuCl	5 mol%	Yes	90
2	CuCl	5 mol%	No	-
3	$CuCl_2$	5 mol%	Yes	78
4	$CuCl_2$	5 mol%	No	traces
5	CuCl	1 equiv.	No	-
6	$CuCl_2$	1 equiv.	No	35

a) Isolated yields

Traces of alkynylation product were detected via GC-MS in the presence of 5mol% of copper(II) source (Table 13, entry 4) without *t*-BuOOH. When carrying out the reaction with 1 equivalent of copper(II) source (Table 13, entry 6), 35% of product were detected after 2d. No product was found to be formed with 5mol% of copper(I) source and without *t*-BuOOH (Table 13, entry 2). In the presence of *t*-BuOOH, reactions worked both with catalytic amounts (5mol%) of copper(I) or copper(II) sources (Table 13, entries 1 and 3).

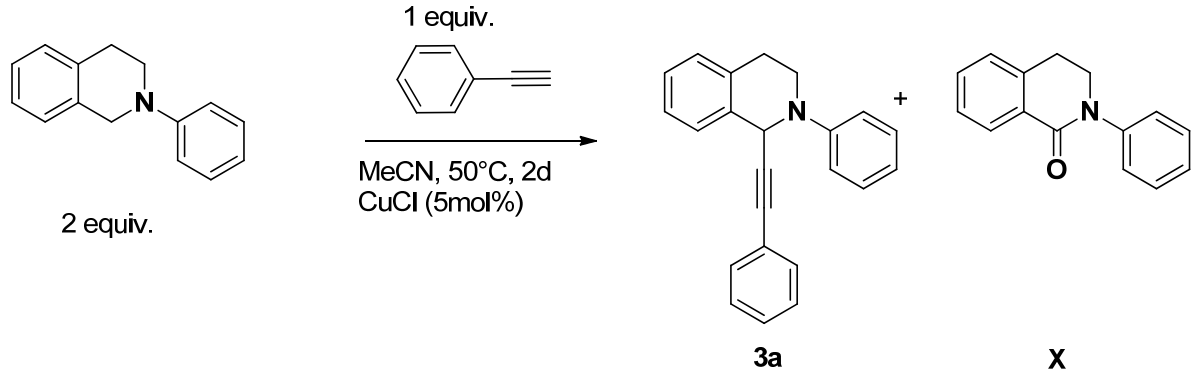
These findings indicate that Cu(II) is needed for the alkynylation process, and is reduced during the alkynylation reaction. Since the reaction is working without *t*-BuOOH but with quantitative amount of Cu(II), the only role of *t*-BuOOH is to oxidize the copper source back to oxidation state II after the alkynylation step.

1.8.2 Variation of oxidants

Since the only role of *t*-butylhydroperoxide in the alkynylation reaction is to oxidize the copper catalyst back to oxidation state II, other possible oxidants were examined (see Table 14, Scheme 20).

Table 14. Variation of oxidants. (CuCl = 5mol%, MeCN, 50°C, 2d)

Entry	oxidant	p [bar]	Yield [%]	Side product X [equiv.]
1	t-BuOOH	1	90	traces
2	H_2O_2	1	-	-
3	O_2	1	95	0.3 equiv.
4	air	1	20	traces
5	air	5	93	traces



Scheme 20. Alkynylation reaction with variation of oxidants.

Use of hydrogen peroxide did not lead to product formation, but decomposition of the substrate to several unidentifiable side products was observed (Table 14, entry 2). Performing the reactions under oxygen atmosphere led to almost quantitative formation of the desired alkynylation product (**3a**) and formation of approximately 30% of oxidized product (**X**), due to the excess of starting material (Table 14, entry

3). When carrying out the reactions under air atmosphere, only 20% of relative product formation was observed (Table 14, entry 4), either due to bad circulation in a closed vial with an air balloon or due to evaporation of the solvent and alkyne source when carrying out the reaction in an open vial. When performing the reactions under pressure (5bar), almost quantitative conversion was observed (Table 14, entry 5).

1.8.3 Reaction in water

Since the reaction tolerated traces of water when using $Cu(NO_3)_2.3H_2O$ and air as atmosphere, reactions were also carried out in water under pressure (5bar). This led to quantitative conversion to the desired product **3a**, but also formation of oxidized side product **X** of about 0.2 equiv. was observed.

1.8.4 Reaction time

A time screening was done for conditions as in Scheme 20, but in water and under air, with 5 and 10 mol% of CuCl. Results are shown in Figure 17 and Figure 18.

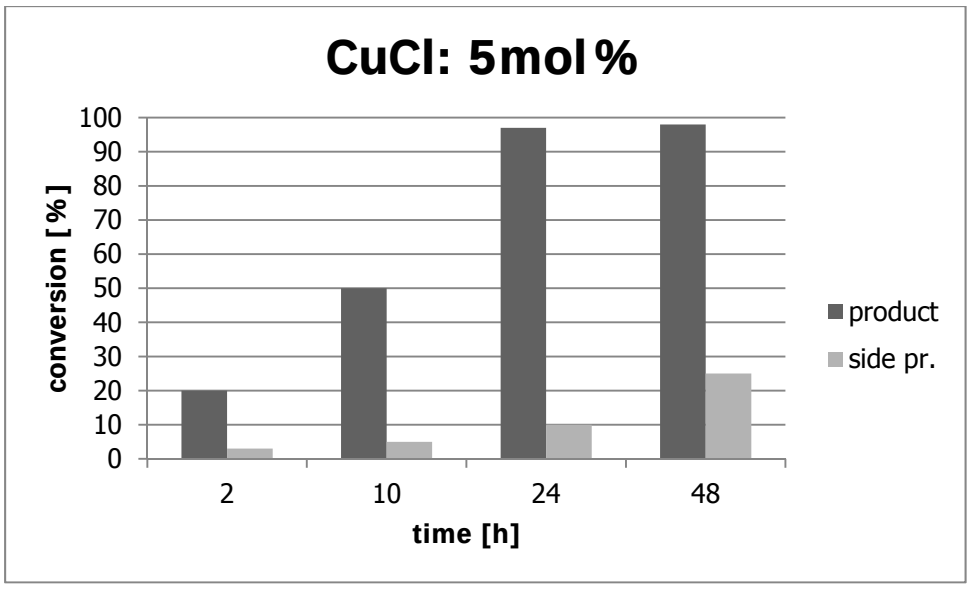


Figure 17. Time Screening for the alkynylation reaction in water with 5mol% of CuCl.

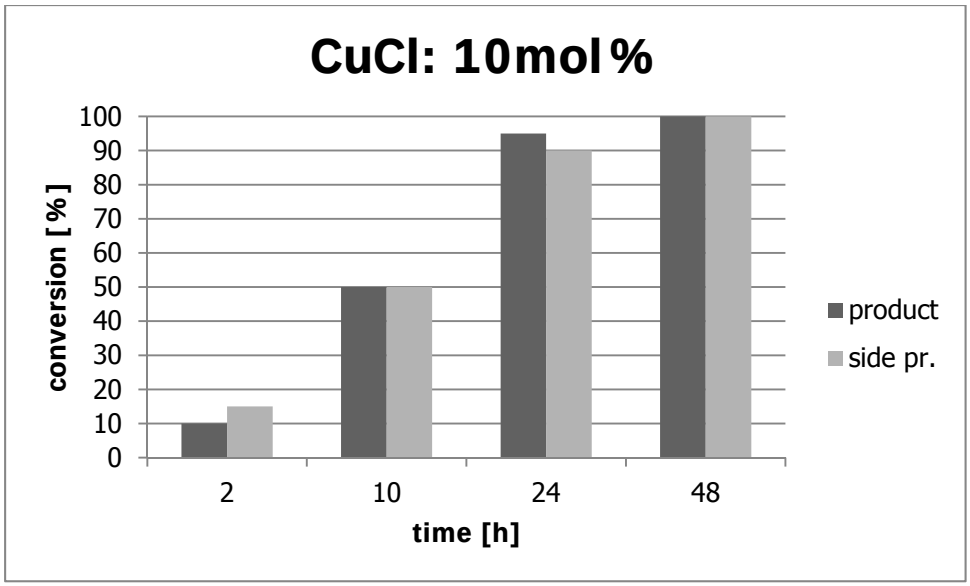
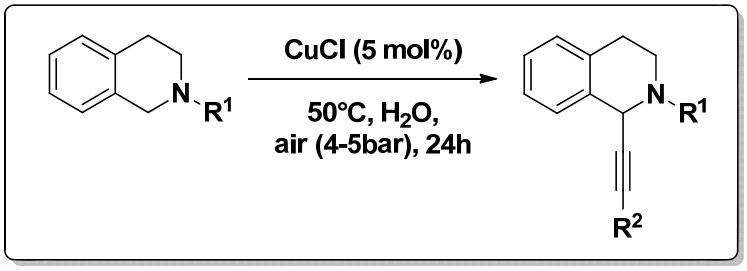


Figure 18. Time Screening for the alkynylation reaction in water with 10mol% of CuCl.

Using 10 mol% of CuCl led to high formation of oxidized side product **X** (Figure 18). After 48h, quantitative conversion to 1 equiv. of **3a** and 1 equiv. of **X** was observed (100%). When using 5 mol% of CuCl (Figure 17), the reaction time could be shortened to 24h, leading to 0.97 equiv. of **3a** and 0.1 equiv. of **X**. After 24h, conversion to **3a** only increased in 1%, but conversion to **X** increased in 15%. After 10h only 50% of product **3a** was formed.

1.8.5 Variation of THIQ's and alkynes

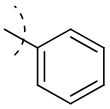
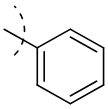
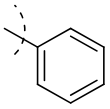
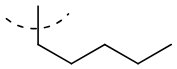
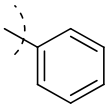
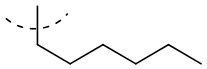
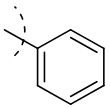
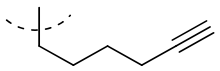
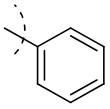
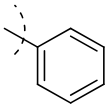
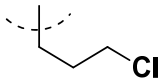
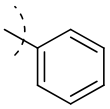
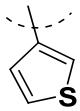
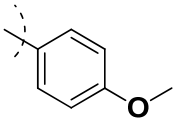
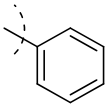
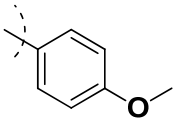
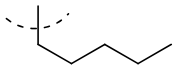
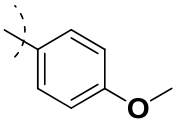
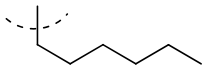
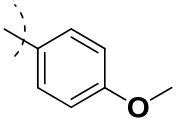
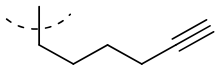
Applying the findings from above, alkynylation reactions were carried out with various alkynes and on N-phenyl-, N-pmp- and N-benzyl-THIQ under the following conditions (Scheme 21):

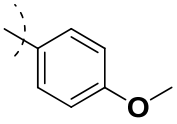
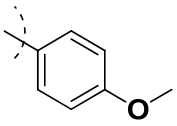
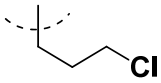
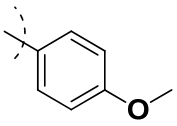
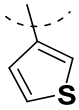
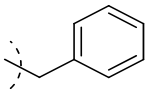
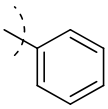
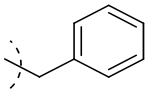
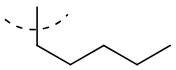
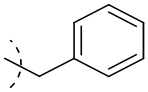
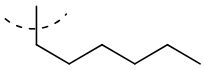
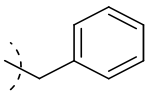
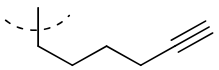
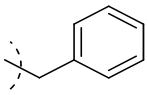
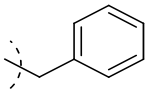
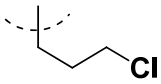
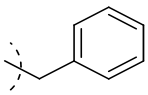
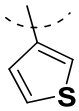


Scheme 21. Conditions for alkynylation reactions in water.

Results are shown in Table 15.

Table 15. Alkynylation reactions in water under air atmosphere.

Entry	Substance	R^1	R^2	Yield [%]
1	3a			97
2	3b			93
3	3c			91
4	3d			88
5	3e			78
6	3f			95
7	3g			71
8	4a			traces
9	4b			n.c.
10	4c			n.c.
11	4d			n.c.

12	4e			n.c.
13	4f			n.c.
14				n.c.
15				n.c.
16	5a			n.c.
17	5b			n.c.
18				n.c.
19	5c			n.c.
20	5d			n.c.
21				n.c.

Unfortunately, this protocol only worked on N-phenyl-THIQ, but with high yields from 71 to 97% (Table 15, entries 1-7). Except for product **3d**, where a yield of 93% could be obtained with the MeCN/Ar protocol, all other yields were significantly higher under water/air conditions. Since product 4a could be detected in traces via GC-MS (Table 15, entry 8), the reaction was repeated several times, but with no further success. For the phenyl-THIQ's, the water/air protocol is much more favorable due to the greener conditions.

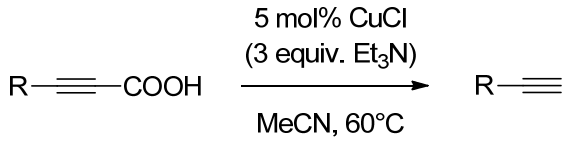
Summarizing, alkynylation reactions could be successfully carried out on phenyl-, pmp- and benzyl-THIQ's with various alkynes. Compared to literature, with an optimized protocol (CuCl, MeCN, t-BuOOH, 50 °C, 2d), alkynes with long aliphatic chains, or with functional groups such as Cl, thiophene and cyclopropane could be introduced to the C1 position. Furthermore, alkynylation on benzyl-THIQ's via Cu-catalyzed CH-activation has not been reported so far. Additionally, phenyl-THIQ's could be alkynylated under water/air conditions in high yields.
Yet, the alkyne scope is limited to non-volatile liquid or solid alkyne sources with these protocols.

1.9 Decarboxylation-Alkynylation reactions on 1,2,3,4-Tetrahydroisoquinolines

1.9.1 Literature Background - State of the Art

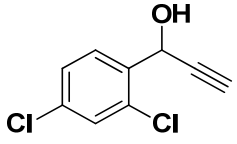
In 2009, Kolarovic and colleagues published a protocol for copper-catalyzed decarboxylation of 2-alkynoic acids.[133] They performed decarboxylation reactions with various copper catalysts, such as $CuCl_2$, CuCl, Cu bronze, $CuSO_4$, CuO and Cu_2O. Their experiments showed that Cu(II) catalysts have almost no activity concerning the decarboxylation of alkynoic acids. With Cu(I) salts they obtained 100% conversion in almost all cases, $CuCl_2$ was the only Cu(II) source where they observed decarboxylation.

Using CuCl as catalyst, decarboxylation of various 2-alkynoic acids was performed (Scheme 22, Table 16), with high yields from 63 to 95%, and reaction times from 1 to 15h.

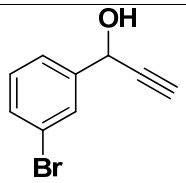
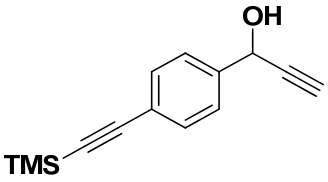
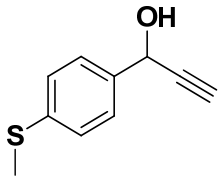
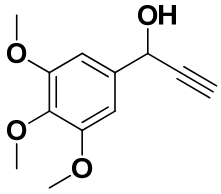
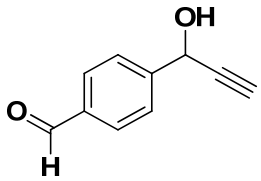
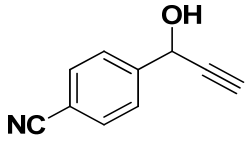
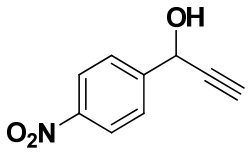


Scheme 22. Decarboxylation of 2-Alkynoic Acids.

Table 16. Examples for Decarboxylation of 2-Alkynoic Acids.

Entry	Product	Time [h]	Yield [%]
1		2	94

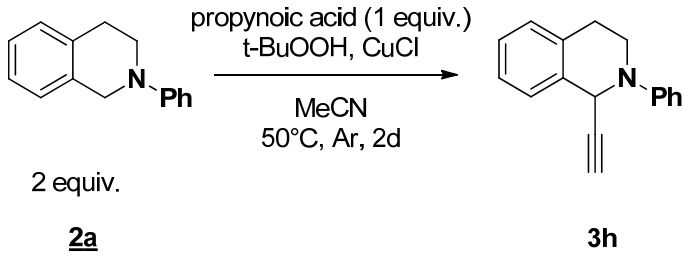
[133] Kolarovic, A.; Fáberová, Z.; *J. Org. Chem.*, **2009**, 74, 7199

2		1	95
3		2	94
4		15	83
5		2	64
6		15	88
7		15	88
8		15	63

Acid-protected alkynes are easier to handle than their unprotected analogues, since they are liquids or solids already in the case of short chain alkynes such as ethyne. As a terminal alkyne functionality at the C1-position of tetrahydroisoquinolines is also interesting for further reactions, it was tried to investigate a copper catalyzed one-pot protocol, where the alkyne source first undergoes decarboxylation and then couples with the 1,2,3,4-tetrahydroisoquinoline substrate (X).

1.9.2 Decarboxylation-Alkynylation Experiment

First decarboxylation-alkynylation experiments were carried out with propynoic acid as alkyne source, under previously used conditions (Ar, *t*-BuOOH, CuCl, see Scheme 23).



2 equiv.

2a **3h**

Scheme 23. Decarboxylation-Alkynylation reaction.

Further investigations showed that the ratio of THIQ:alkyne could be reduced to 1:1, leading to 90% of product. Excess of N-phenyl-THIQ of 4 equivalents did not lead to any product formation. Use of THF as a solvent reduced the conversion to only 21%.

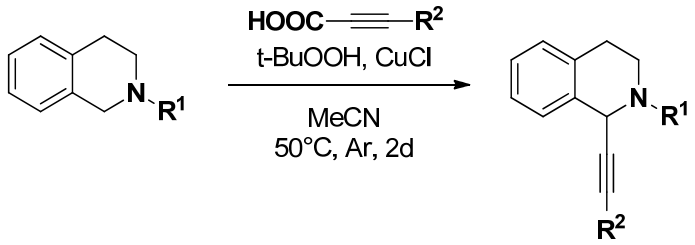
Variation of catalysts showed best overall activity for CuCN and CuCl (see Table 17). $(CuOTf)_2$ toluene complex instead led to a low conversion of 33%. With $Fe(NO_3)_2.9H_2O$ as catalyst no product was detected via GC-MS.

Table 17. Catalyst screening for decarboxylation-alkynylation reactions.

Catalyst	Yield [%]
$Cu(NO_3)_2.3H_2O$	68
CuCN	75
$(CuOTf)_2$ toluene complex	33
CuBr	traces
CuCl	90
$Fe(NO_3)_2.9H_2O$	n.p.
CuÖÖ1	28

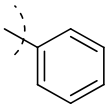
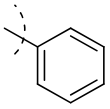
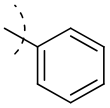
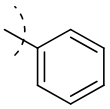
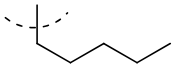
1.9.3 Variation of alkynoic acids

With proynoic acid as alkyne source, the question arose whether alkynylation preceeds decarboxylation or whether the opposite order of events occurs. To test whether the decarboxylation step occurs first, experiments were carried out with 2-alkynoic acids with alkyl substituents at the 3-position (see Scheme 24) since in these cases alkynylation can only occur if decarboxylation preceeds alkynylation. Good to excellent yields of the alkynylated products were achieved (see Table 18).



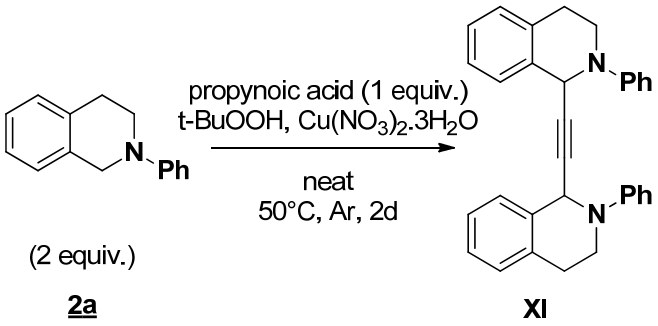
Scheme 24. Decarboxylation-alkynylation with various alkynoic acids.

Table 18. Decarboxylation-alkynylation with various alkynoic acids.

Entry	Substance	R^1	R^2	Yield [%]
1	3i		CH_3	80
2	3j		C_2H_5	90
3	3k		C_3H_7	85
4	3b			75

1.9.4 Bis-alkynylation

One screening experiment, with $Cu(NO_3)_2.3H_2O$ and without solvent, lead to the following bis-alkynylated product **XI** in 20% conversion:



Scheme 25. Bis-alkynylation on N-phenyl-THIQ.

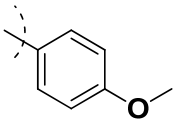
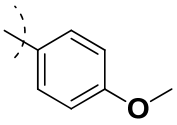
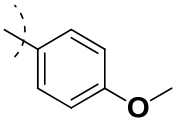
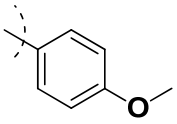
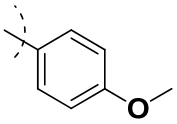
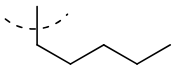
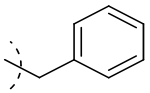
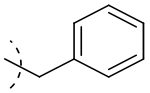
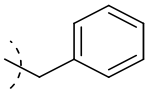
Unfortunately, the reaction could not be reproduced in further experiments.

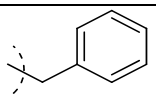
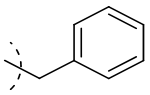
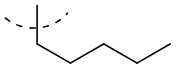
1.9.5 Variation of THIQ's

Since the conversion of the alkynylation-decarboxylation was high on phenyl-THIQ, experiments were carried out with pmp-, benzyl-, BOC-, methyl- and benzyl-protecting groups.

Product formation was only observed in the case of pmp- and benzyl-substituted substrate, but therefore moderate to high yields could be achieved (see Table 19).

Table 19. Decarboxylation-alkynylation on various THIQ's.

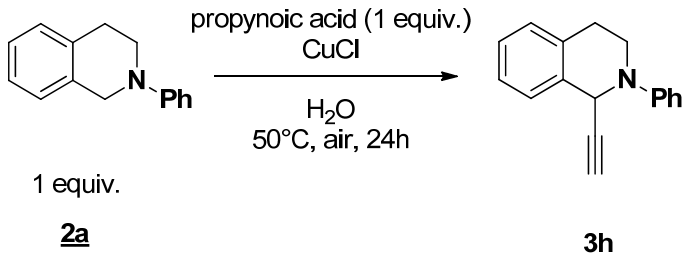
Entry	Substance	R^1	R^2	Yield [%]
1	4g		H	32
2	4h		CH_3	47
3	4i		C_2H_5	67
4	4j		C_3H_7	57
5	4b			71
6	5e		H	81
7	5f		CH_3	70
8	5g		C_2H_5	90

9	5h		C_3H_7	66
10	5a			80

Compared to the alkynylation protocol in chapter 1.8.5, short chain alkynes can be additionally introduced to the C1-position of phenyl-, pmp- and benzyl-THIQ's. Compounds **3b**, **4b** and **5a** can be synthesized via both ways and allow comparison of the yields. In the case of **4b** there is no difference (both protocols yielded in 71%), for **3b** the yield with the decarboxylative protocol is slightly higher (75% instead of 67%) and for **5a** there is significant difference (80% instead of 30%).

1.9.6 Decarboxylation-Alkynylation reactions in water under air atmosphere

Since the decarboxylative reaction worked well with the *t*-BuOOH/Ar/MeCN protocol, further experiments were carried out with the water/air protocol (see Scheme 26).



Scheme 26. Decarboxylation-Alkynylation in water under air.

Yet, only traces of product **3h** could be detected via GC-MS. Assuming that the decarboxylation process does not tolerate water as a solvent, reactions were carried out in MeCN, leading to higher conversion, but with no reproducible yields due to the instability of the pressure vial sealing in presence of MeCN and high pressure. Further reactions were carried out in different water/MeCN mixtures, as listed below in Table 20.

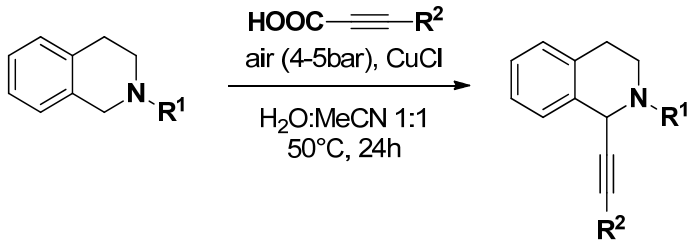
Table 20.

Entry	Ratio H_2O/MeCN	Ratio THIQ/alkyne	Yield [%]

1	100:0	2:1	traces
2	99:1	2:1	traces
3	90:10	2:1	traces
4	50:50	2:1	traces
5	100:0	1:1	traces
6	99:1	1:1	5
7	90:10	1:1	50
8	50:50	1:1	80

When changing the water/MeCN ratio to 50:50, an isolated yield of 80% could be achieved. Ratios with higher MeCN content resulted in decomposition of the sealing.

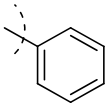
Further experiments with different alkynes and THIQ's were carried out, as seen in Scheme 27.

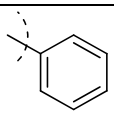
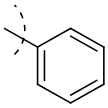
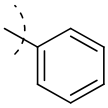
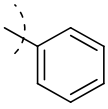
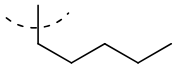
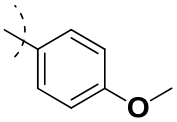
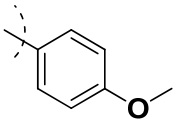
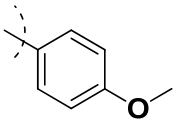
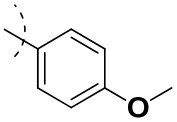
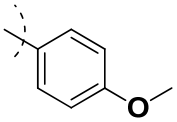
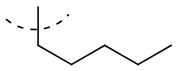
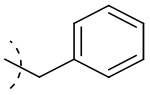
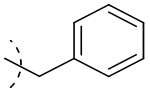
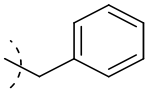
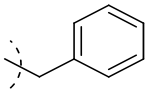


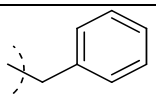
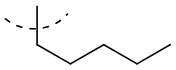
Scheme 27. Decarboxylation-Alkynylation reactions in water/MeCN.

Results are listed below in Table 21.

Table 21. Decarboxylation-Alkynylation reactions in water/MeCN under air.

Entry	Substance	R^1	R^2	Yield [%]
1	**3h**		H	80

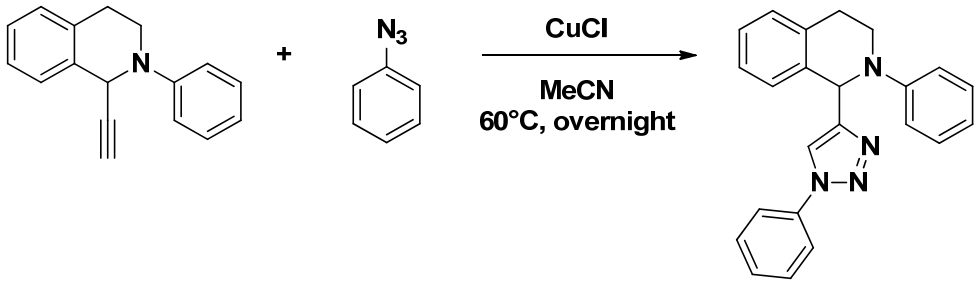
2	**3i**		CH_3	32
3	**3j**		C_2H_5	47
4	**3k**		C_3H_7	95
5	**3b**			98
6	4g		H	n.c.
7	4h		CH_3	n.c.
8	4i		C_2H_5	n.c.
9	4j		C_3H_7	n.c.
10	4b			n.c.
11	5e		H	n.c.
12	5f		CH_3	n.c.
13	5g		C_2H_5	n.c.
14	5h		C_3H_7	n.c.

15	5a			n.c.

Unfortunately, the water/air protocol again seemed only to work with phenyl-THIQ. Further unsuccessful experiments were carried out with octynoic acid and Boc-, Piv-, benzyl- and benzoyl-THIQ, at 75 °C and 100°C, in different water/MeCN ratios. In the cases of Boc-THIQ traces of the desired product could be detected via GC-MS at 75 °C and 100 °C, with Benzyl-, Piv- and Benzoyl-THIQ no conversion was observed at all.

1.10 Click Reactions

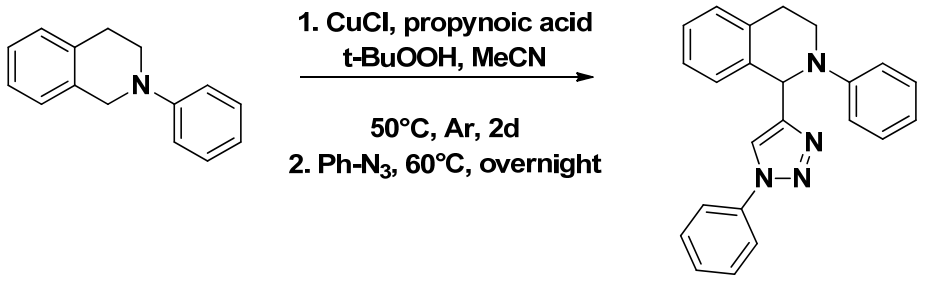
The first click-experiment was carried out with the alkynylated 2-phenyl-1,2,3,4-tetrahydroisoquinoline (**3h**) with CuCl and azidobenzene to find out, if the reaction works under conditions of the *t*-BuOOH/Ar/MeCN alkynylation protocol. A further intention was to perform the Click-reaction without peroxide first, due to safety issues. After stirring overnight at 60°C overnight the desired click-product **6a** was obtained in 100% yield by precipitation in an EtOAc/EtOH mixture.



3h **6a**

1.10.1 One-pot Decarboxylation-Alkynylation-Click reactions

After successful preparation of click-product **6a** it was tried to synthesize it via a three-step one-pot reaction starting from 2-phenyl-1,2,3,4-tetrahydroisoquinoline (**2a**).

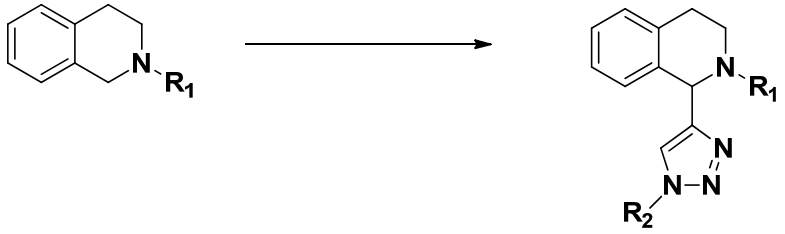


2a **6a**

After step 1 was completed (determined via GC-MS), the azide was added and the reaction mixture was stirred overnight at 60 °C. The reaction was not further optimized.

When full conversion of the first step was determined via GC-MS, after the second step via ^{1}H-NMR of the crude reaction mixture. The overall isolated yield was 90%.

Since the one-pot protocol was working, other azides were tried as well as the alkynylated benzyl and pmp-products (see Scheme 28).

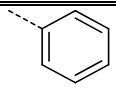
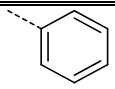
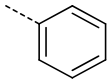
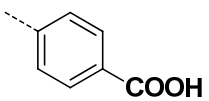
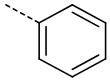
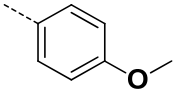
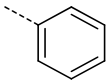


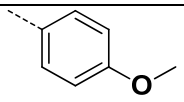
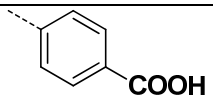
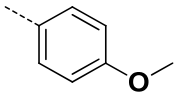
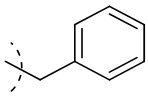
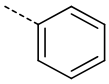
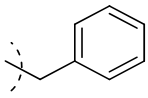
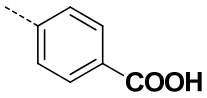
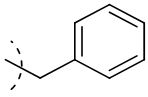
2a, b, c **6a,b**

Scheme 28. One-Pot Experiments.

Results are listed below in Table 22.

Table 22. One-Pot Decarboxylation-Alkynylation-Click experiments.

Entry	Compound	R_1	R_2	Yield
1	6a			90%
2				80%* of 6a
3			-H[a]	n.c.
4	6b			50%

5			43%* of 6b
6		-H[a]	n.c.
7			n.c.
8			n.c.
9		-H[a]	n.c.

*Conversion of starting material. Cleavage of aromatic carboxy group observed.
[a]Use of NaN_3 as substrate.

Products were purified via precipitation in EtOAc/EtOH. In the case of Phenyl-THIQ a high yield of 90% for **6a** could be achieved. With pmp-THIQ only a moderate yield of 50% for **6b** was obtained, experiments with Benzyl-THIQ showed no conversion to the click-product at all. Even starting from the alkynylated Benzyl-THIQ **5e** did not lead to any product formation.

When using p-azidobenzoic acid as azide source (Table 22, entries 2 and 5), formation of compounds **6a** and **6b** was observed, showing cleavage of the aromatic carboxy group.

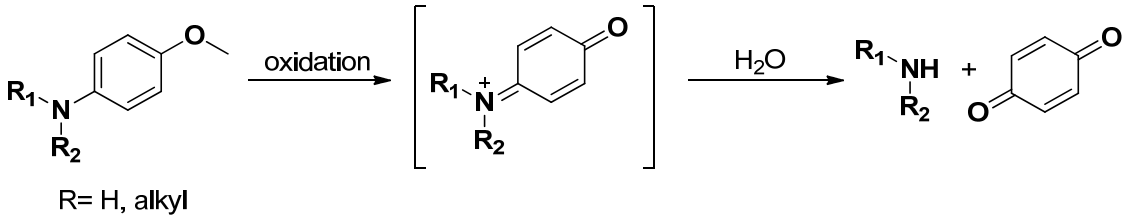
When using sodium azide as reagent (Table 22, entries 3, 6 and 9), no conversion to the click-product was observed, indicating that the reaction only works with bulkier organic azides.

1.11 Deprotection Experiments

1.11.1 Cleavage of the pmp-group

1.11.1.1 Oxidative Protocols

In general, N-pmp-groups can be cleaved via oxidation to the benzoquinone species (Scheme 29).

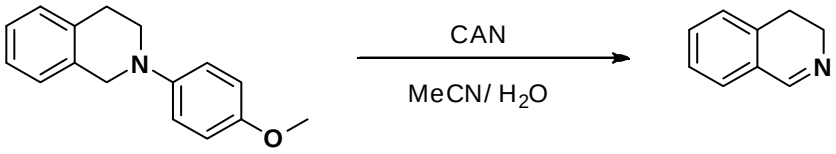


Scheme 29. Oxidative cleavage of a pmp-group.

The most common method to remove N-pmp-groups is via ceric ammonium nitrate (CAN) at low temperatures around 0°C.

1.11.1.1.1 Ceric Ammonium nitrate (CAN)

Ghobrial[134] reported a method in MeCN/H_2O at -20°C for cleavage of the pmp-group starting from N-pmp-1,2,3,4-Tetrahydroisoquinoline (**2b**), resulting in 66% of 3,4-Dihydroisoquinoline (see Scheme 30).



Scheme 30. Cleavage of the pmp-group via CAN.

Yet, when applying this protocol to the alkynylated substrate **4g**, complete decomposition to unknown products was observed via TLC and crude NMR.

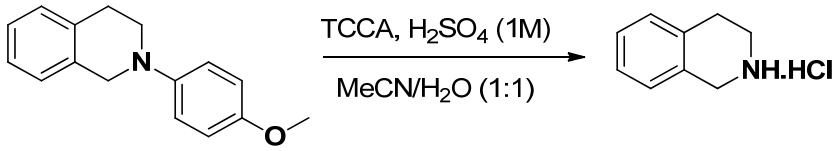
1.11.1.1.2 Trichloroisocyanuric acid (TCCA)

In 2006, Verkade et. al.[135] reported a mild and efficient protocol for deprotection of the N-pmp-group via various electrophilic halide reagents, including periodic acid and trichloroisocyanuric acid (TCCA). In the case of TCCA, desired primary and secondary amines were obtained in yields up to 99% after stirring at room temperature for 16h with addition of 0.1M sulfuric acid.

A first experiment was carried out using N-pmp-1,2,3,4-tetrahydroisoquinoline (**2b**) as substrate and TCCA as oxidant (Scheme 31).

[134] Ghobrial, M.; Vienna UT, PhD Thesis, *2013*

[135] Verkade, J.M.M.; van Hemert, L.J.C.; Quaedflieg, P.J.L.M.; Alsters, P.L.; van Delft, F.L.; Rutjes, F.P.J.T.; *Tetr. Lett.*, **2006**, 47 (46), 8109



Scheme 31. Attempt to remove the pmp-group via TCCA.

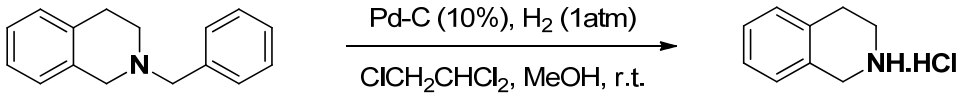
After stirring the reaction mixture overnight at room temperature, TLC showed 7 different spots, indicating decomposition, which was also confirmed via crude NMR.

1.11.2 Cleavage of the benzyl-group

1.11.2.1 Reductive Protocols

Various Methods using Pd-catalysts and H_2 have been reported,[136] obtaining the cleaved species in good to excellent yields.

A first experiment, starting from N-Bn-THIQ **2c** led to complete conversion after 6h, according to GC-MS and TLC (see Scheme 32). After workup, THIQ.HCl could be obtained in 87% yield.

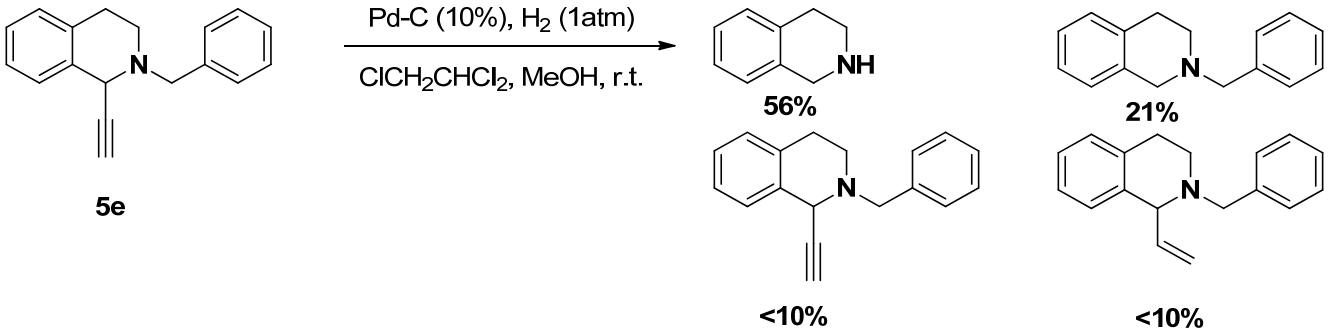


2c

Scheme 32. Pd-catalyzed cleavage of the benzyl-group.

When performing the reaction with N-Bn-alkynylated product **5e**, cleavage of the alkyne group was observed as a parallel reaction. According to GC-MS a mixture of N-Bn-THIQ, THIQ, alkynylated N-Bn-THIQ (<10%) and alkenylated N-Bn-THIQ (<10%) was obtained (see Scheme 33).

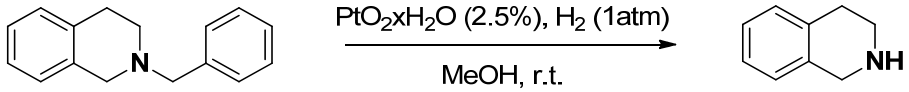
[136]Cheng, C.; Sun, J.; Xing, L.; Xu, J.; Wang, X.; Hu, Y. ; *J.Org.Chem.*, **2009**, 74, 5671



Scheme 33. Products and byproducts of the cleavage attempt of the Bn group.

The main product of the reaction that could be isolated in 56% yield was N-Bn-THIQ **2c**, followed by 21% of THIQ.
To avoid the cleavage of the alkyne group the amount of catalyst was reduced to 5%, 2% and 1%, but with no success in reducing the amount of by-products.

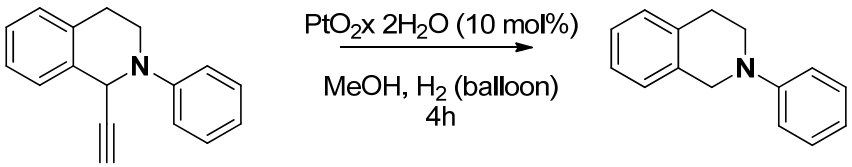
Since reductive cleavage of the Bn-group with Pd-catalysts was not very promising due to low selectivity and cleavage of the alkyne group, a further experiment was carried out with PtO_2xH_2O (see Scheme 34).



Scheme 34. Pt-catalyzed cleavage of the benzyl-group.

Since the benzyl-group was not removed under these conditions, an experiment with the alkynylated product (**5e**) was carried out, to see if the alkyne group can be reduced to the corresponding alkene or alkane.

Unfortunately, the main reaction turned out to be the cleavage of the alkyne (see Scheme 35).

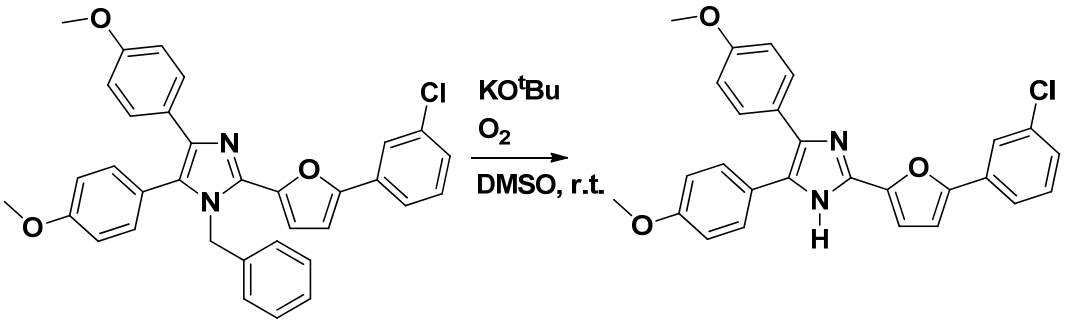


Scheme 35. Pt-catalyzed reduction experiment.

Only traces of the alkene and alkane could be detected via GC-MS, when using 5 mol% of catalyst.

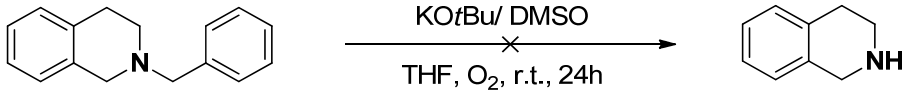
1.11.2.2 Oxidative Protocols

Haddach[137] reported a method, where a benzyl-group is cleaved via KOtBu/ DMSO under oxygen atmosphere at room temperature.



Scheme 36. Oxidative method for cleavage of the N-benzyl group.

A first experiment, stirring the reaction mixture at r.t. for 24h did not result in any conversion of the starting material, according to GC-MS and TLC (Scheme 37).



Scheme 37. Attempt to remove the benzyl-group via KOtBu/DMSO.

Performing the reaction under harsher conditions of 5bar of oxygen atmosphere and at higher temperatures did not lead to any improvements. TLCs and GC-MS samples were taken after 4h, 8h, and 24h, showing no conversion of the starting material. The reaction parameters are listed below in Table 23.

Table 23. Reaction parameters for Oxidative Cleavage Protocol of Bn-Group.

Temperature [°C]	Pressure [bar]
22	1
22	5
50	1
50	5
80	1
80	5

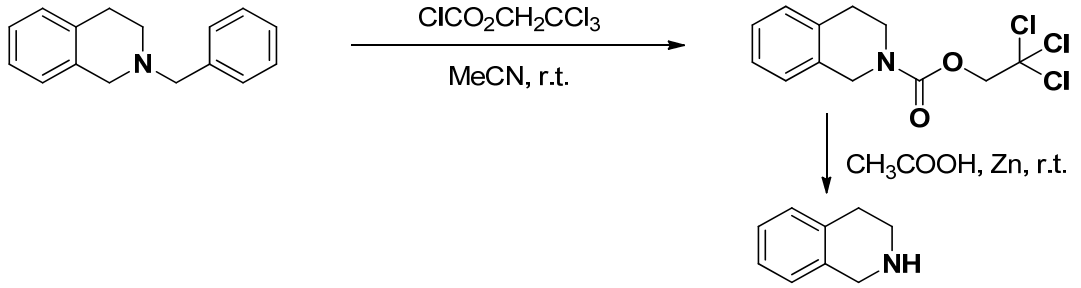
[137] Haddach, A. A.; Kelleman, A.; Deaton-Rewolinski, M. V.; *Tetrahedron Lett.* **2002**, 43, 399

1.11.2.3 Acylative Protocols

Since reductive and oxidative methods did not lead to direct cleavage of the benzyl group and to the desired products, conversion of the benzyl group was taken into consideration.

Via variation of the von Braun reaction, Benzyl groups can be converted to various carbamates. Using trichloroethyl chloroformate, Rawal et. a.l [138] reported a debenzylation protocol via transformation to the carbamate, followed by cleavage with Zn in acetic acid and workup with sodium bicarbonate solution.

A first experiment was carried out in small scale with substrate **2c**, showing 75% conversion to the carbamate and overall conversion to the THIQ of 60% (Scheme 38), determined via crude ^{1}H-NMR.



Scheme 38. Cleavage of the benzyl group via transformation to the carbamate.

Since the reaction on substrate **2c** was successful, an experiment was carried out with alkynylated product **5e**. Unfortunately, no conversion to the carbamate was observed in the first step.

Summarizing, all deprotection experiments carried out, such as oxidative methods for the removal of pmp-groups (CAN, TCCA), or reductive, oxidative and acylative methods to remove the benzyl group, did not lead to the desired products. So far, it was not possible to remove the protecting groups without cleaving the alkyne or decomposition of the product. No further investigations were made towards cleaving the pmp- and the benzyl-group.

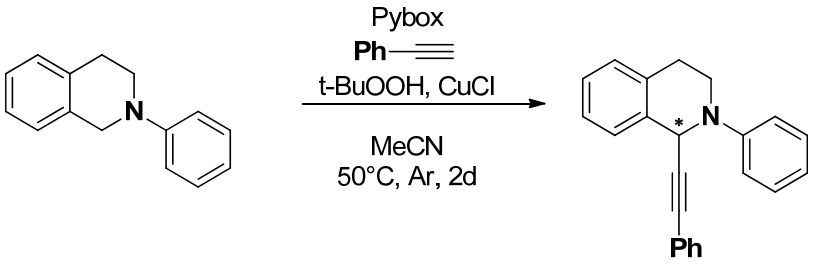
1.12 Asymmetric C-H activation reactions

Since enantioselective alkynylation could be achieved using Li's protocol (Scheme 14), experiments were carried out with various catalysts and ligands to see if similar

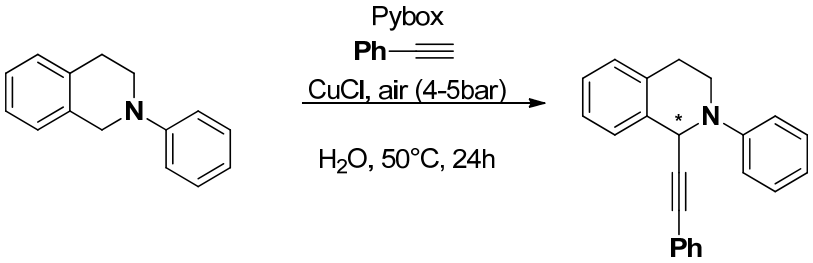
[138] Rawal, V. H.; Jones, R. J.; Cava, M. P.; *J. Org. Chem.*, **1987**, 52, 19

ee's could be obtained with the modified protocols, as well as with the decarboxylation-alkynylation reaction.

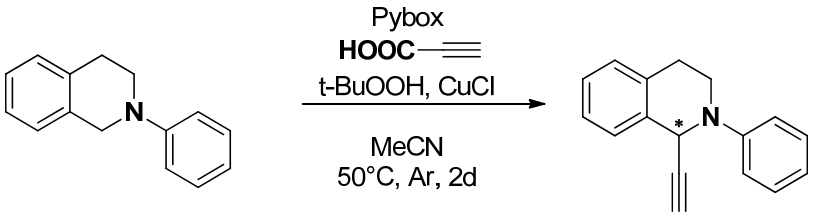
The following experiments were carried out with slightly different parameters than in Li's protocol:



Scheme 39. Alkynylation of THIQ with Pybox ligand, using *t*-BuOOH/Ar/MeCN protocol.



Scheme 40. Alkynylation of THIQ with Pybox ligand, using water/air protocol.

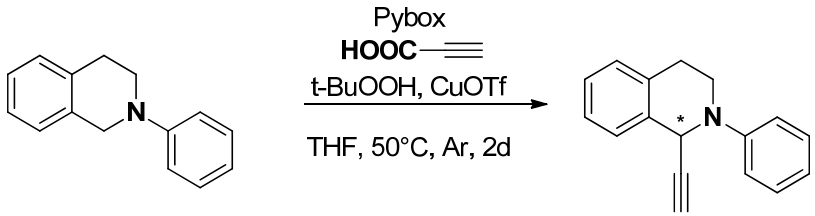


Scheme 41. Decarboxylation-alkynylation of THIQ with Pybox ligand, using *t*-BuOOH/Ar/MeCN protocol.

Unfortunately, with the protocols used above, no ee was obtained, showing that the conditions used by Li et al. already provide best results for enantioselective

alkynylation. The difference to Li's conditions are in all cases the solvent (MeCN or water instead of THF) and the catalyst (CuCl instead of CuOTf).

Therefore, the decarboxylation-alkynylation reaction was performed under Li's original conditions (Scheme 42), but only 30% of racemic product was obtained, showing that copper triflate is not a good catalyst for the decarboxylative protocol in terms of the yield and indicating that the processes during the decarboxylative step might influence the activity of the chiral ligand or that the size of the alkyne might play a significant role.



Scheme 42. Decarboxylation-alkynylation of THIQ with Pybox ligand, using the protocol of Li et al.

At last, a screening was done for the decarboxylative reaction, using Li's conditions and various chiral ligands (Figure 19), but all cases were unsuccessful.

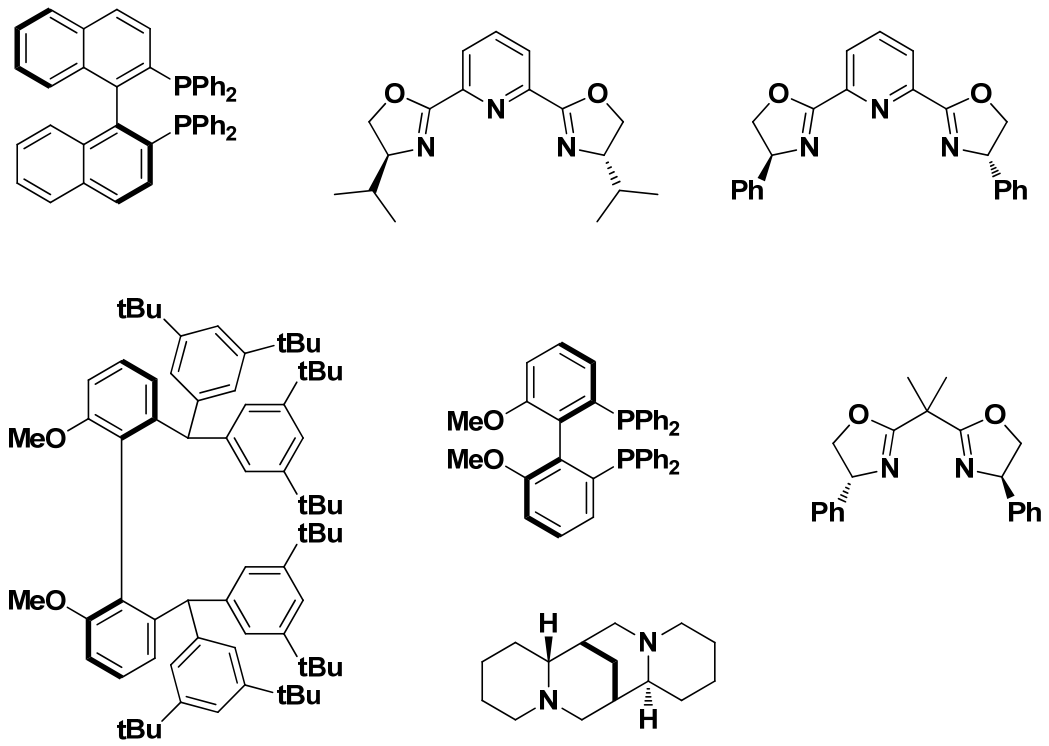


Figure 19. Chiral ligands used for the decarboxylation-alkynylation reaction.

Since the experiments were not successful, no further investigations towards enantioselective reactions were made.

1.13 Conclusion

Summarizing, four different alkynylation methods were established on N-phenyl, N-pmp and N-benzyl-1,2,3,4-tetrahydroisoquinoline.

First, parameters of Li's protocol[81] were changed to a different solvent (MeCN) and catalyst (CuCl). Under these conditions, it was possible to introduce different alkynes to N-phenyl-, N-pmp- and also N-benzyl-THIQ's in moderate to high yields.

After mechanistic considerations, it was possible to change the reaction conditions to water as solvent and air as oxidant (instead of MeCN and *t*-BuOOH). The water protocol showed to be only applicable to N-phenyl-THIQ's, leading to higher yields under greener conditions than with the original procedure in MeCN.

To introduce also shorter alkynes and terminal alkynes to the C1-position, a decarboxylative protocol was developed, using alkynoic acids as alkyne sources. N-Phenyl-, N-pmp- and N-benzyl-THIQ's with a terminal alkyne functionality or short aliphatic substituents were obtained in high yields. When applying the water conditions to the decarboxylative protocol, product formation was only observed with N-phenyl-THIQ's, but in lower yields.

Additionally, investigations were made towards further reactions of the terminal alkyne functionality, resulting in a one-pot decarboxylation/alkynylation/Click reaction, leading to triazole products.

Deprotection experiments were carried out both on N-pmp- and N-benzyl-products. Several conditions, such as oxidative ones for removal of the pmp-group, reductive, oxidative and acylative ones for removal of the benzyl-group did either lead to cleavage of the alkyne group or to decomposition.

After the literature experiment could be reproduced with similar ee, enantioselective experiments were carried out for both the alkynylation and the decarboxylative-alkynylation protocols. Variation of parameters, such as solvent or catalyst did only result in racemic mixtures, as well as applying the original conditions to the decarboxylative protocol.

2. H-D exchange reactions on Heterocycles

Deuterium labeled compounds can be used in a wide range of applications such as studying biologically active systems or reaction mechanisms, or as solvents for NMR-spectroscopy.[139, 140, 141, 142]

H-D exchange in nitrogen-containing heterocycles has been achieved by using acid or base catalysts in liquid D_2O,[143] by heating in neutral D_2O at elevated temperatures and by using a solid metal catalyst with gaseous D_2[144] or D_2O.[145, 146] Over the past decade, reports have appeared describing the use of iridium complexes to promote the incorporation of tritium and deuterium into arenes at positions ortho- to a directing group such as carbonyl.[147, 148]

Bergman and co-workers have shown excellent results in activating a wide range of organic molecules using a variety of deuterium sources, such as D_2, CD_3OD, $(CD_3)_2CO$ and D_2O with a $Cp^*Ir^{III}(PMe_3)$ catalyst.[149, 150, 151]

There have also been published a few examples using Crabtree's catalyst [(cyclooctadiene)(pyridine)(tricyclohexylphosphine)iridium(I)hexafluorophosphate],[156] Raney nickel,[154] Pd/PVP (poly-N-vinylpyrolidone) colloid catalyst systems,[155] $NaBD_4$-activated Rh, Pt or Pd catalysts,[158] Pd or Pt metal surfaces,[152] or CuI.[153]

In 2009, Guy and Shapley published an H-D exchange protocol for several N-containing heterocycles, such as pyridines, nicotinic acid, N-methylimidazole and quinoline based on a Pd/PVP catalyst system with an excess of D_2O at room temperature.[155]

Since the published catalyst/solvent systems often suffer from certain limitations, such as requiring a large excess of deuteration reagent,[154, 155, 156] basic or acidic

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[139] Potavathri, S.; Pereira K. C.; Gorelsky, S. I., Pike, A.; LeBris, A. P.; DeBoef, B.; *J. Am. Chem. Soc.,* **2010**, 132, 14676
[140] Perrin, C. L.; Karri, P.; *J. Am. Chem. Soc.,* **2010**, *132*, 12145
[141] Bakac, A. in: *Physical Inorganic Chemistry John Wiley & Sons, Inc.*, **2010**, 367
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[143] Biddiscombe, D. P.; Herington, E. F. G.; Lawrenson, I. J.; Martin, J. F. *J. Chem. Soc.* **1963**, 444
[144] Moyes, R. B.; Wells, P. B. *J. Catal.* **1971**, 21, 86
[145] Calf, G. E.; Garnett, J. L. *Aust. J. Chem.* **1968**, 21, 1221
[146] Calf, G. E.; Garnett, J. L.; Pickles, V. A. *Aust. J. Chem.* **1968**, 21, 961
[147] Herbert, J.M.; *J. Labelled Cpd. Radiopharm.,* **2010**, 53 (11-12), 658
[148] Nilsson, G.M.; Kerr, W.J.; *J. Labelled Cpd. Radiopharm.,* **2010**, 53 (11-12), 662
[149] Yung, C. M.; Skaddan, M. B.; Bergman, R. G.; *J. Am. Chem. Soc.* **2004**, 126, 13033
[150] Golden, J. T.; Andersen, R. A.; Bergman, R. G.; *J. Am. Chem. Soc.* **2001**, 123, 5837
[151] Klei, S. R.;Golden J. T.; Tilley, T. D.; Bergman, R. G. *J. Am. Chem. Soc.* **2002**, 124, 2092
[152] Alexakis, E.; Jones, J. R.; Lockley, W. J. S. *Tetrahedron Lett.* **2006**, 47, 5025
[153] Gonda, Z.; Lörincz, K.; Novak, Z. *Tetrahedron Lett.* **2010**, 51, 6275
[154] Yau, W.-M.; Gawrisch, K. *J. Labelled Cpd. Radiopharm.* **1999**, 42, 709
[155] Guy, K. A.; Shapley, J. R. *Organometallics* **2009**, 28, 4020

additives,[157] long reaction times,[154, 158, 159] high catalyst loadings and/or expensive or difficult to access catalysts,[155] or such as unselective deuteration leading to different deuteration degrees (DDs) in the different positions,[154, 156] an approach towards a cheaper method of H-D exchange was made.

2.1 Calculation of the theoretically possible deuteration degree

One step protocol:

If 1 equivalent of deuteration agent is used per exchangeable position a maximum of 50% deuteration degree (dd) can be obtained since 1 equiv of D and 1 equiv of H are available. The equivalent of H remains always at one and only the amount of added deuteration reagent can be varied. Hence the theoretical values for various equivalents of deuteration reagents calculate as follows:

$$\%\,dd = \frac{x}{\underbrace{x + 1}_{y}} * 100$$

With x = (equiv. of D source)/(deut. Pos.)

Theoretical deuteration grades are listed below in Table 24.

Table 24. Theoretically possible deuteration degrees for one-step deuteration.

D source [equiv./deut. pos.]	Calculation	%D
0.5	0.5/1.5	33.33
1.0	1/2	50
1.25	1.25/2.25	55.55
2.5	2.5/3.5	71.40
3.75	3.75/4.75	78.90
5	5/6	83.33
10	10/11	90.90

[156] Ellames, G. J.; Gibson, J. S., Herbert, J. M., McNeill, A. H. *Tetrahedron* **2001**, 9487
[157] Gonda, Z.; Lörincz, K.; Novak, Z. *Tetrahedron Lett.* **2010**, 51, 6275
[158] Derdau, V.; Atzrodt, J. *Synlett* **2006**, 12, 1918
[159] Derdau, V.; Atzrodt, J.; Zimmermann, J.; Kroll, C.; Brückner, F. *Chem. Eur. J.* **2009**, 15, 10397

Two step protocol:

$$\%\ \text{dd step two} = \frac{x}{\underbrace{x + (1 / y)}_{z}} * 100$$

Calculating the theoretically possible dd of a two step protocol is based on the calculations for the one step protocol. For example, using 1 equivalent deuteration agent in the first step leads to a maximum dd of 50% with 50% H remaining. If in a second cycle another equivalent of deuterating agent is added, 1:1.5 = 0.667 * 100 = 66.7% of deuterium incorporation can be obtained at maximum.

Theoretical deuteration grades are listed below in Table 25.

Table 25. Theoretically possible deuteration degrees for two-step deuteration.

D source [equiv./deut. pos.]	Calculation step 1	%D after the first step	Calculation step 2	%D after the second step
0.5	0.5/1.5	33.33	0.5/1.167	42.86
1.0	1/2	50	1/1.5	66.67
1.25	1.25/2.25	55.55	1.25/1.695	73.76
2.5	2.5/3.5	71.40	2.5/2.786	89.73
3.75	3.75/4.75	78.90	3.75/3.961	94.67
5	5/6	83.33	5/5.166	96.77
10	10/11	90.90	10/10.091	99.10

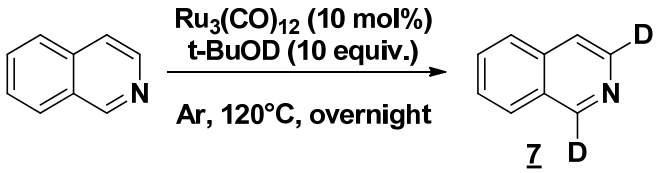
A third step would be calculated according to:

$$\%\ \text{dd step three} = \frac{x}{x + (1 / z)} * 100$$

2.2 Ru-mediated deuteration experiments

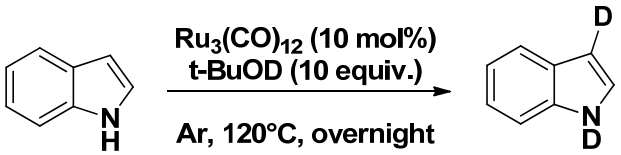
Based on a report indicating the capability of $Ru_3(CO)_{12}$ to insert into pyridine C-H bonds even though in an unselective manner,[160] it was hypothesized that successful H-D exchange could be implemented with this catalyst by concomitantly employing a protic deuterated solvent.

First deuteration experiments were carried out with isoquinoline and indole with 10 equivalents of *t*-BuOD and 10mol% of $Ru_3(CO)_{12}$ as a catalyst at 120°C overnight (see Scheme 43 and Scheme 44). They resulted in moderate deuteration degrees of 80% in both 1- and 3-positions for isoquinoline and 77% for indole in the 3-position, which were determined via ^{1}H-NMR after evaporation of *t*-BuOD.



7

Scheme 43. Ru-mediated Deuteration of isoquinoline.



8

Scheme 44. Ru-mediated Deuteration of indole.

2.3 Determination of deuteration grades

Deuteration grades were determined via ^{1}H-NMR. The peak integrals of the deuterated positions were compared with the integrals of the other positions. The higher the deuteration degree, the more the integrals of deuterated positions were decreasing.

2.4 Reaction optimization

Reaction conditions, such as deuteration reagent loading, catalyst loading, time and temperature were screened (see Table 26, Table 27 and Lowering the catalyst

[160] Sames, D.; *J. Am. Chem. Soc.*, **2006**, 128, 3102, as a comment to the retraction of Godula, K.; Sezen, B.; Sames, D. *J. Am. Chem. Soc.,* **2005**, 127, 3648

loading to 1 mol% did not affect the deuteration degree on indole; with this substrate a DD of 37% was obtained even without catalyst. In the isoquinoline series, deuteration was significantly more susceptible to changes of catalyst loading: 2.5 mol% gave only 24% of deuterated isoquinoline. In general, the best results were obtained when 5 mol% of catalyst were applied.

Table 28).

Table 26. Deuteration degrees of indole and isoquinoline at various temperatures (t=3h, *t*-BuOD= 5equiv./deuteration position, $Ru_3(CO)_{12}$= 5mol%)

T [°C]	%D	
	Indole	Isoquinoline
25	8	0
50	11	0
75	44	0
100	75	39
115	77	80

In the case of indole, deuteration occurs even close to room temperature. Deuteration on isoquinoline is only possible at temperatures above 100 °C. Best results were obtained at 115 °C.

Table 27. Deuteration degrees of indole and isoquinoline with various catalyst loadings (t= 3h, T= 115°C, *t*-BuOD= 5equiv./deuteration position)

$Ru_3(CO)_{12}$ [mol%]	%D	
	Indole	Isoquinoline
0	37	0
1	78	0
2.5	76	24
5	77	80
10	67	49

Lowering the catalyst loading to 1 mol% did not affect the deuteration degree on indole; with this substrate a DD of 37% was obtained even without catalyst. In the isoquinoline series, deuteration was significantly more susceptible to changes of catalyst loading: 2.5 mol% gave only 24% of deuterated isoquinoline. In general, the best results were obtained when 5 mol% of catalyst were applied.

Table 28. Deuteration degrees of indole and isoquinoline with various amounts of *t*-BuOD (t= 3h, T= 115°C, $Ru_3(CO)_{12}$= 5mol%).

c [equiv./deut. pos.]	%D		
	theor.[a]	Indole	Isoquinoline
0.5	33.33	34[b]	10
1.25	55.55	52	30
2.5	71.40	63	60
3.75	78.90	71	73
5	83.33	77	80
10	90.90	83	85

[a]For calculation of theoretical deuteration degrees see chapter 2.1.
[b]Measurement error due to inaccuracies in integration of ^{1}H NMR peaks.

Increasing the amount to 10 equiv. of *t*-BuOD led to 85% deuteration on isoquinoline and 83% on indole. Further lowering the amount of the deuterium source expectedly led to lower DDs; however, in all cases, the observed deuterium incorporation was close to the theoretically possible values.
Reaction optimization led to a shorter reaction time of 30min for indole, a slight decrease in temperature to 100-115°C and deuteration reagent loading of 5 equivalents per deuteration position, but no great increase of the deuteration grade. A deuteration grade above 80% is not possible anyways within one H-D exchange cycle because of the equilibration of *t*-BuOH and *t*-BuOD, which lies at a 4:1 ratio.

Figure 20 and Figure 21 show the dependence of the deuteration grade of deuteration reagent loading and catalyst loading for both indole and isoquinoline:

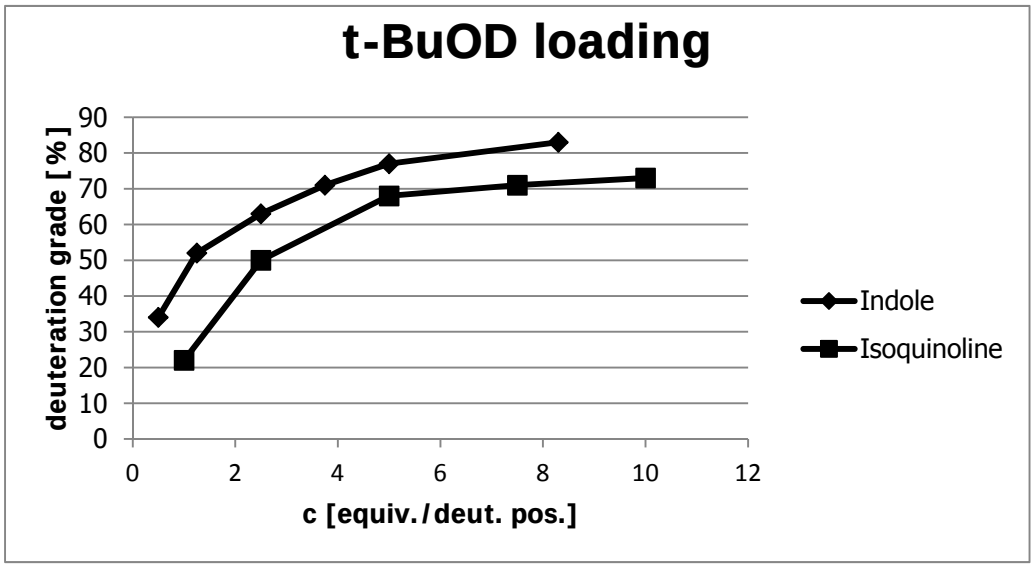


Figure 20. Dependence of the deuteration grade on the t-BuOD loading.

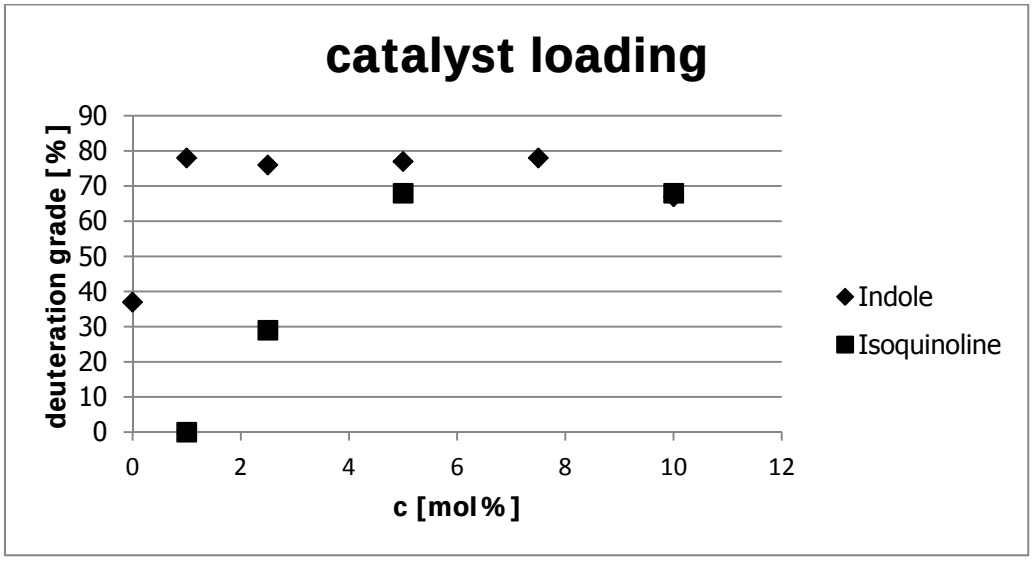
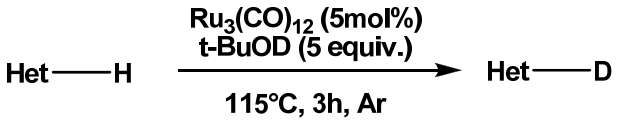


Figure 21. Dependence of the deuteration grade on the catalyst loading.

In the case of indole, only 1mol% of catalyst was sufficient to provide a deuteration grade of 77%. When no catalyst was added, a deuteration degree of 37% could be achieved. In the case of isoquinoline no H-D exchange was observed in the absence of a catalyst. Deuteration experiments were also carried out with CuCl and $Fe(NO_3)_2.3H_2O$ as catalysts, which led to deuteration degrees of 63% and 78% for indole, but no deuteration on isoquinoline.

The temperature profile showed that H-D exchange already takes place for indole at room temperature, but with only 8% deuteration degree after 3h. In the case of isoquinoline no remarkable H-D exchange was observed beyond 100°C.

Further deuteration experiments were then carried out with 5 mol% $Ru_3(CO)_{12}$ and 5 equivalents of *t*-BuOD at 115°C under argon atmosphere for 3h (see Scheme 45).



Scheme 45. Reaction conditions for Ru-mediated deuteration of heterocycles.

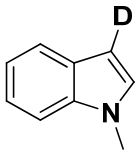
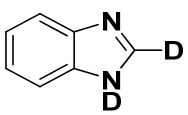
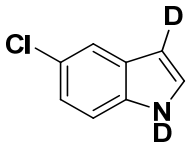
2.5 Deuteration of electron-rich and electron-poor heterocycles

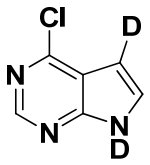
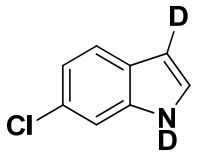
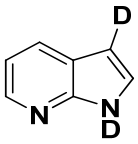
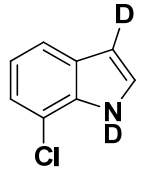
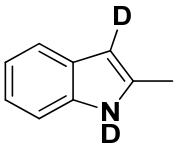
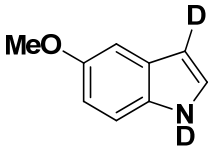
With this protocol (Scheme 45), several electron-rich and electron-poor N-containing heteroarenes could be deuterated selectively, as listed below in Table 29 and Table 30.

The solvent was then evaporated and the deuteration grade determined via ^{1}H-NMR spectroscopy and/ or GC-MS.

The outlined deuteration protocol can be carried out in repetitive cycles in order to reach higher deuteration degrees. After the first deuteration reaction, the deuteration reagent was removed and fresh *t*-BuOD and catalyst were added. Simple exchange of the deuterium source for fresh material did not improve deuteration grades, indicating catalyst inactivation after a reaction cycle.

Table 29. Deuteration of electron-rich N-heteroarenes.

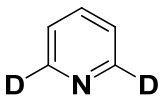
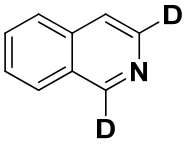
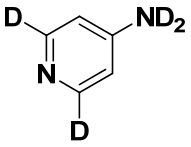
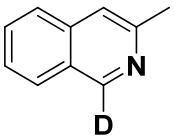
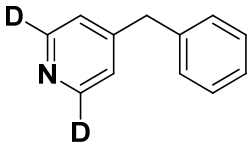
Entry	Substance	Structure	D° [%]	Entry	Substance	Structure	D° [%]
1	8		77 90*	6	13		66
2	9		71	7	14		69

3	10		78	8	15		77
4	11		70	9	16		77
5	12		50	10	17		50

*applying 2 deuteration cycles

Concerning π-electron-rich heterocycles the scope was rather limited to indoles, azaindoles, and benzimidazoles. For most indoles a deuteration grade of above 70% in the 3-position was achieved in the first step. Unfortunately, indoles turned out to decompose during a third deuteration step. For thiazoles and oxazoles no deuteration was observed.

Table 30. Deuteration of electron-poor N-heteroarenes.

Entry	Substance	Structure	D° [%]	Entry	Substance	Structure	D° [%]
1	18		80	4	7		80 93*
2	19		50	5	21		58
3	20		68				

*applying 2 deuteration cycles

The deuteration of electron poor compounds generally occurs in α-position to the nitrogen atom, again representing the most electron rich site. Best results were obtained on isoquinoline and pyridine. A high deuteration grade of 80% could be achieved after 1 cycle, 2 cycles yielded in 93% H-D exchange for both 1- and 3-position in isoquinoline. 4-Aminopyridine showed significantly lower D-incorporation,

possibly due to the free amino group competing with the ring nitrogen for complexation of the catalyst. Introducing a methyl group (3-methylisoquinoline) led again to a lower deuteration degree. In this case the steric bulk of the methyl group might disfavor Ru-N complexation.

There was also an attempt to deuterate acetophenone with the same reaction conditions, but no deuteration was observed. Substrates which did not show any H-D exchange with this reaction protocol are listed below in Figure 22.

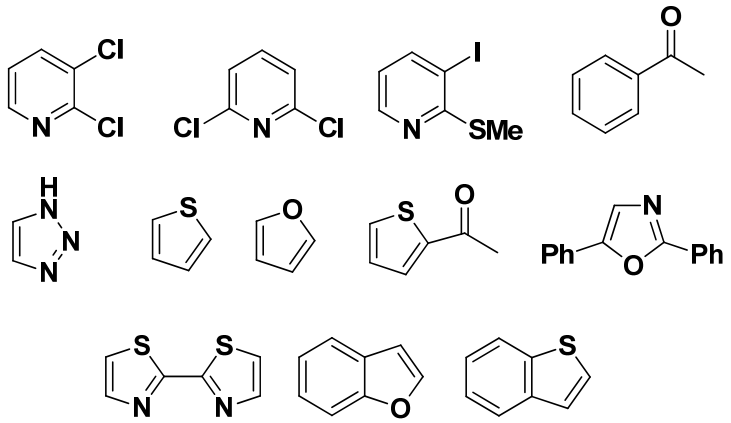
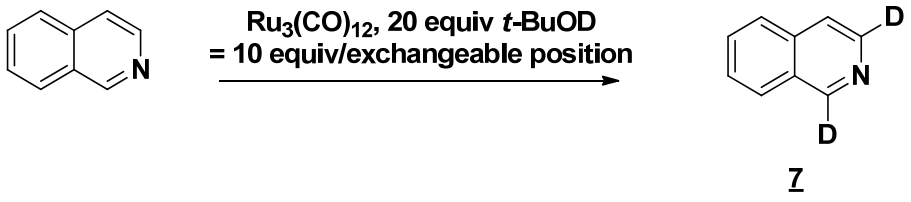


Figure 22. Substrates where deuteration was not successful.

2.6 Microwave reactions

Deuteration experiments were also carried out in the microwave, where it turned out that a shorter reaction time was sufficient to reach the same deuteration degrees as in batch.

The reaction conditions were optimized using indole as substrate (Scheme 46):



7

Scheme 46. Deuteration of Indole via microwave.

Optimization parameters and results are shown in Table 31 and Table 32.

Table 31. Deuteration degrees of indole at various reaction times (T= 115°C, *t*-BuOD= 10equiv./deuteration position, $Ru_3(CO)_{12}$= 5mol%)

t [min]	%D

	theor.	Indole
5	90.9	67
10	90.9	80
15	90.9	85
20	90.9	78
30	90.9	75
60	90.9	73

Table 32. Deuteration degrees of indole with various amounts of *t*-BuOD (t= 15min, T= 115°C, $Ru_3(CO)_{12}$= 5mol%).

c [equiv./deut. pos.]	%D	
	theor.[a]	Indole
2.5	71.4	60
5	83.33	72
7.5	88.24	77
10	90.9	85

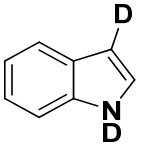
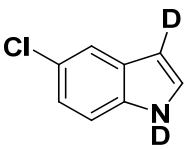
[a]For calculation of theoretical deuteration degrees see chapter 2.1.

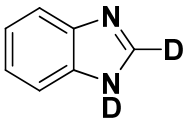
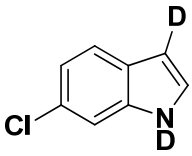
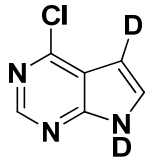
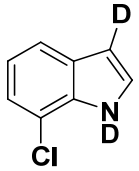
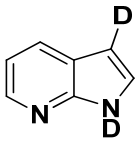
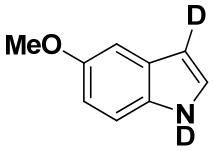
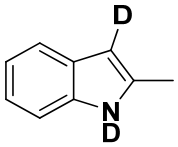
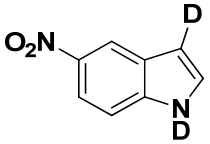
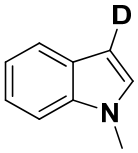
Experiments showed that the reaction is finished after 15 Minutes at 115°C. Lowering or increasing the temperature led both to a decrease in the deuteration degree, which is comparable to the reactions carried out in the heating block.

The theoretical deuteration degree using 10 equivalents of deuteration reagent is 90%. Since applying 2 cycles with 5 equivalents of *t*-BuOD only gave 90% in the case of indole and 93% in the case of isoquinoline, using a bigger excess of deuteration reagent and only applying one step turned out to be the more economical method.

Examples for the deuteration in the microwave are shown in Table 33.

Table 33. Deuteration of heterocycles using the microwave protocol.

Entry	Substance	Structure	D° [%]	Entry	Substance	Structure	D° [%]
1	8		88	7	14		85

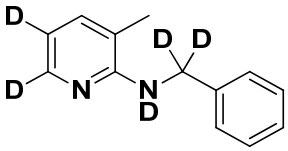
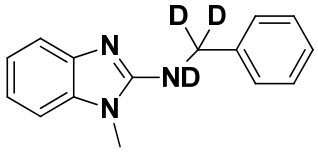
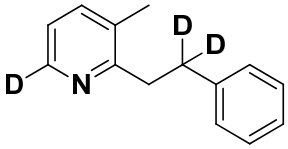
2	9		40	8	15		87
3	10		0	9	16		86
4	11		80	10	17		84
5	12		70	11	22		45
6	13		85				

Interestingly, electron deficient compounds could not be deuterated efficiently under these conditions even after extensive optimization efforts. The reason for the failure in these cases remains unclear. In contrast, deuteration of electron rich substrates proceeded very well. With the shorter microwave protocol 5-nitroindole could be deuterated with 45% deuteration degree, but only 25% of product was obtained due to decomposition which required purification of the crude material by column chromatography. Still, under conventional heating this product was not obtained at all. For benzimidazole a decreased deuteration degree of 40% was obtained and with 6-Cl-7-deazapurine no H-D exchange was observed at all, even after 1h in the microwave. These two substrates and the deuterated electron deficient compounds can be obtained using the protocol where conventional heating is applied.

2.7 Deuteration of benzylic positions

In an attempt to expand the methodology also to aliphatic carbon centers, benzylic positions attached to an N-heterocycle could be deuterated with high deuteration degrees under slightly altered reaction conditions (T= 140°C, t=24h, *t*-BuOD= 5equiv./deuteration position, $Ru_3(CO)_{12}$= 5mol%). Examples are shown in Table 34.

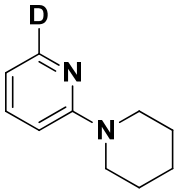
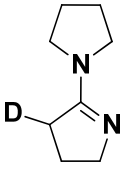
Table 34. Examples for deuteration of benzylic positions.

Entry	Compound	Product	D° [%]
1	24		51 (Pyr-5) 22 (Pyr-6) 89 (Bn)
2	25		88
3	26		42 (Pyr) 87 (Bn)

The capability of such systems to form a 5-membered metallacycle intermediate after C-H activation turned out as critical requirement. In compounds **24** and **26** also an exchangeable pyridine position is present which was also deuterated, but to a lesser extent compared to the benzylic positions. This shows that on the investigated substrates aliphatic C-H activation is preferred over aromatic (pyridine) C-H activation. Interestingly, the 5-position on the pyridine ring was also deuterated in compound **24**, even to a higher extent (51%) than the 6-position (22%), which was not observed with any other pyridine derivatives.

With the following substrates, deuteration was observed, but not in the desired sp^3 positions:

Table 35. Substrates where any deuteration was observed.

Entry	Product	D° [%]
1		<10%
2		70%

Desired deuteration positions would have been the 2-positions of the piperidine (Table 35, entry 1) or pyrrolidine (Table 35, entry 2) functionalities. In the case of entry 1 only deuteration below 10% was observed on the 2-position of the pyridine. Interestingly, in the case of entry 2, the 3-position of the pyrroline was deuterated in 70%. The reaction was repeated without catalyst, resulting in the same deuteration grade. This can be explained by the imine-enamine tautomerism, allowing the H-D exchange on the N-H position, and subsequent transfer to the 3 position by tautomerization.

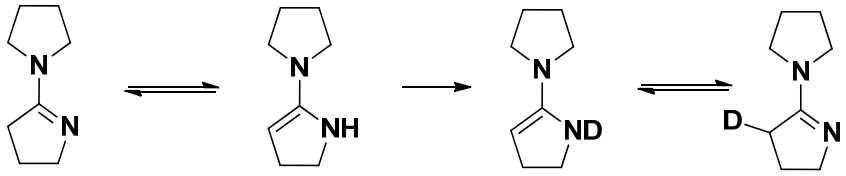


Figure 23. H-D exchange followed by imine-enamine tautomerism.

On the following substrates no deuteration was observed:

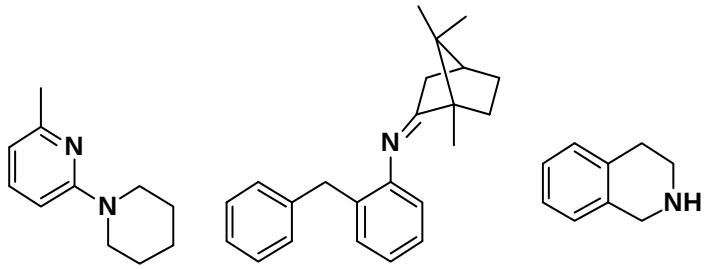


Figure 24. Substrates where deuteration was not successful.

2.8 Applicability to Tritiation

Finally, the possibility was investigated to use the presented methodology for tritiation reactions based on the high importance of radiolabelled compounds for medicinal applications.[161, 162, 163, 164, 165, 166, 167, 168] For that purpose it is necessary to enable access to *t*-BuOT. According to literature reports CF_3COOT was employed in

[161] Campos, J.; Esqueda, A. C.; Lopez-Serrano, J.; Sanchez, L.; Cossio, F. P.; de Cozar, A.; Alvarez, E.; Maya, C.; Carmona, E.; *J. Am. Chem. Soc.* **2010**, *132*, 16765
[162] Saljoughian, M.; *Synthesis* **2002**, 1781
[163] Dehnhardt, C.; McDonald, M.; Lee, S.; Floss, H. G.; Mulzer, J.; *J. Am. Chem. Soc.* **1999**, *121*, 10848
[164] Shu, A. Y. L.; Saunders, D.; Levinson, S. H.; Landvatter, S. W.; Mahoney, A.; Senderoff, S. G.; Mack, J. F.; Heys, J. R.; *J. Labelled Cpd. Radiopharm.* **1999**, *42*, 797
[165] Filer, C. N.; *J. Labelled Cpd Radiopharm.* **2010**, *53*, 739
[166] Johansen, S. K.; Sorensen, L.; Martiny, L.; *J. Labelled Cpd. Radiopharm.* **2005**, *48*, 569
[167] Nugent, R. P.; Pounds, S.; Filer, C. N.; *App. Radiat. Isot.* **2011**, *69*, 423
[168] Shevchenko, V. P.; Nagaev, I. Yu; Myasoedov, N. F.; *Russ. Chem. Rev*. **2003**, *72*, 423

the synthesis of chiral methyl groups.[169] It was hypothesized that CF_3COOT would react with *t*-BuONa to the more stable salt CF_3COONa and *t*-BuOT. As proof of principle the corresponding reaction using commercially available CF_3COOD instead of CF_3COOT was carried out and *t*-BuOD was formed successfully in a high deuteration degree. Since the corresponding reaction works analogously using tritium instead of deuterium this demonstrates the principal feasibility of tritiation reactions.

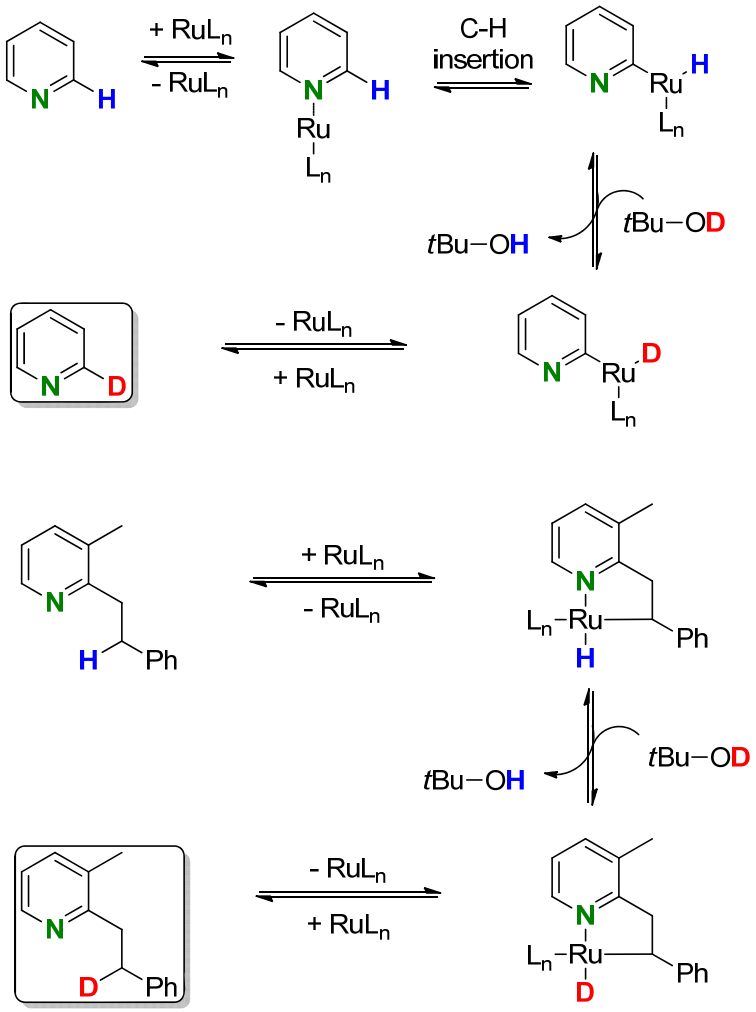
2.9 Mechanistic proposal

A mechanism for both the pyridine deuteration (see the upper part) and deuteration of the aliphatic position (see the lower part) is shown in Scheme 47. After coordination of the catalyst by the pyridine nitrogen, [170] the metal insertion takes place in the closest C-H bond, located in position 2. While there is no possibility in the case of the pyridine deuteration, in the case of the aliphatic substrate the usually favored 5-membered ruthenacycle can be formed when the insertion takes place in the benzylic position. The next step is hydrogen-deuterium exchange, followed by reductive elimination leading to the deuterated compound. The steps are reversible and an equilibrium of deuterated and non-deuterated compounds is established.

In the case of indole the insertion takes place in the electron-rich position 3, in analogy to the deuteration on pyridine.

[169] Dehnhardt, C.; McDonald, M.; Lee, S.; Floss, H. G.; Mulzer, J.; *J. Am. Chem. Soc.* **1999**, *121*, 10848

[170] Chatani, N.; Asaumi, T.; Yorimitsu, S.; Ikeda, T.; Kakiuchi, F.; Murai, S;. J*. Am. Chem. Soc.* **2001,** 123, 10935



Scheme 47. Proposed mechanism.

2.10 Conclusion

In conclusion, a protocol for selective Ru(0)-catalyzed deuteration of both electron rich and electron deficient N-heteroarenes as well as benzylic CH_2 groups under conventional heating was developed. Furthermore, for electron rich N-heterocycles a very effective microwave promoted protocol could be elaborated, where deuteration degrees of above 80% could be achieved within 15 minutes employing only 5 or 10 equivalents of *t*-BuOD as deuterium source.

Moreover, it was demonstrated that deuteration degrees above 90% can be achieved by repeating the deuteration step several times.

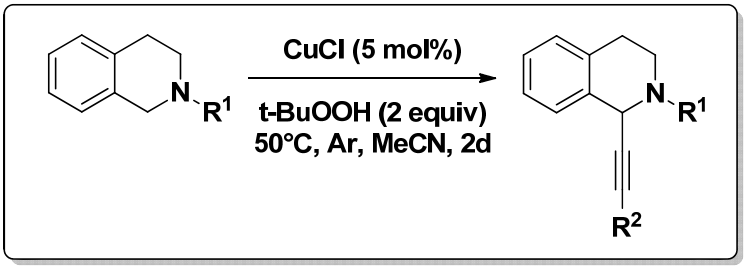
In principal, the presented methodology can also be extended to the corresponding tritiation reactions, which is of interest for the synthesis of radiolabeled compounds for medicinal applications.

Conclusion

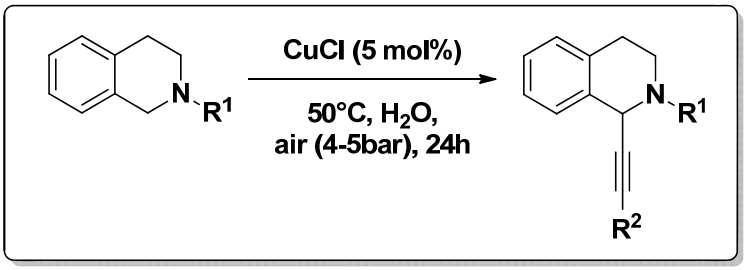
Within this thesis 4 different alkynylation methods were established on N-phenyl, N-pmp and N-benzyl-1,2,3,4-tetrahydroisoquinoline, as listed below:

Alkynylation with terminal alkynes

METHOD A:

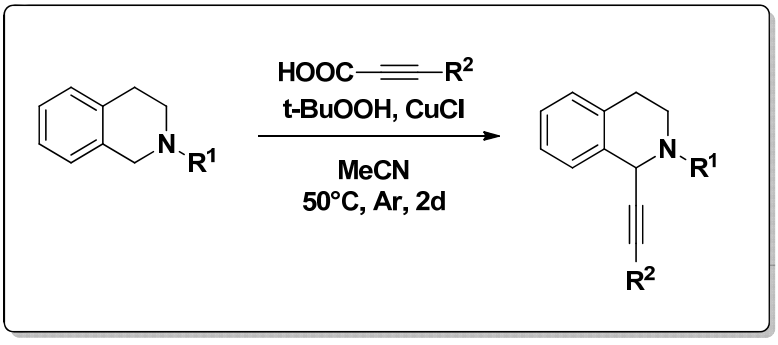


METHOD B:

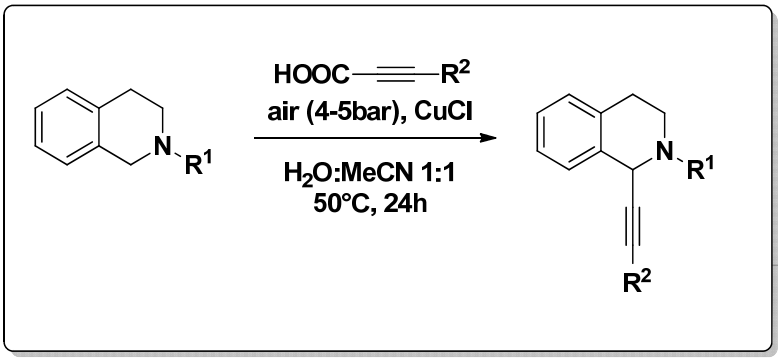


Decarboxylation / Alkynylation with alkynoic acids

METHOD C:

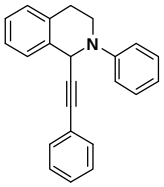
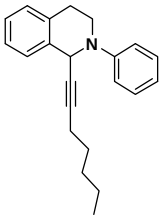
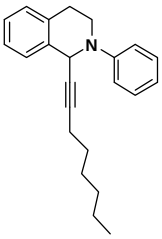
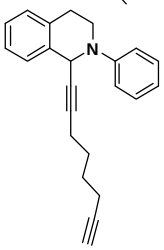
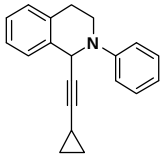


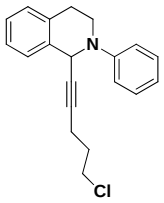
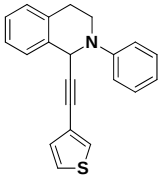
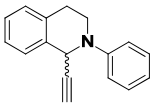
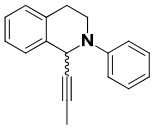
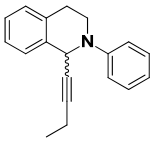
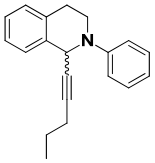
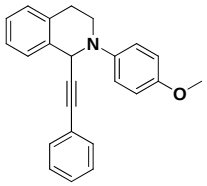
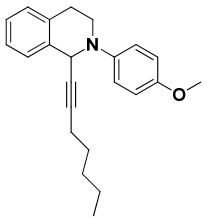
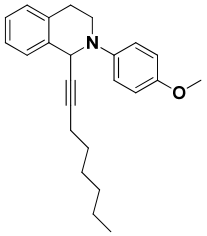
METHOD D:

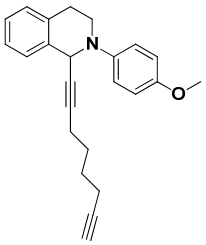
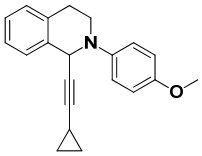
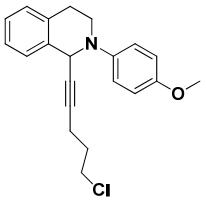
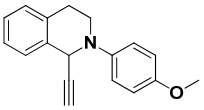
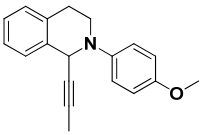
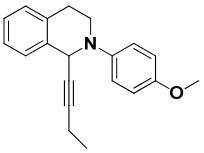
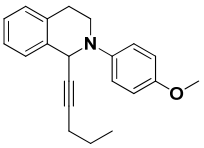
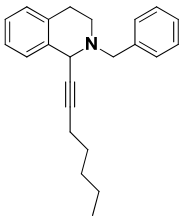
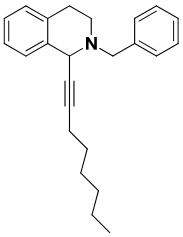
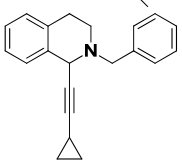


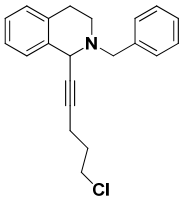
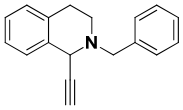
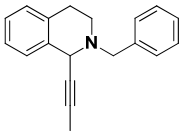
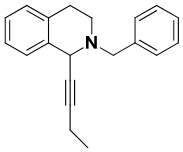
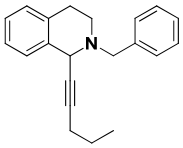
Various alkynylated products were obtained in moderate to high yields. Table 36 shows an overview of all alkynylated products synthesized via the 4 different protocols.

Table 36. Comparison of alkynylated substances by the 4 different methods.

Entry	Substance	Structure	Yield M1 [%]	Yield M2 [%]	Yield M3 [%]	Yield M4 [%]
1	3a		86	97	/	/
2	3b		67	93	75	98
3	3c		49	91	/	/
4	3d		93	88	/	/
5	3e		42	78	/	/

6	3f		77	95	/	/
7	3g		57	71	/	/
8	3h		/	/	90	80
9	3i		/	/	80	32
10	3j		/	/	90	47
11	3k		/	/	85	95
12	4a		42	traces	/	/
13	4b		75	/	71	/
14	4c		61	/	/	/

15	4d		25	/	/	/
16	4e		93	/	/	/
17	4f		52	/	/	/
18	4g		/	/	32	/
19	4h		/	/	47	/
20	4i		/	/	67	/
21	4j		/	/	57	/
22	5a		30	/	80	/
23	5b		40	/	/	/
24	5c		53	/	/	/

25	5d		48	/	/	/
26	5e		/	/	81	/
27	5f		/	/	70	/
28	5g		/	/	90	/
29	5h		/	/	66	/

With Method A, various alkynylated N-phenyl-, N-pmp- and N-benzyl-THIQ's were obtained using alkynes with long aliphatic chains (C7+) or other substituents (Entries 1-7, 12-17, 22-25).

Method B showed to be only applicable to N-phenyl-THIQ, leading to higher yields under greener conditions than with Method A (Entries 1-7).

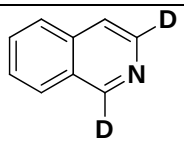
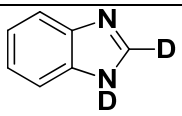
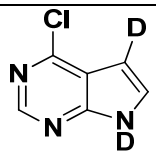
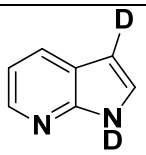
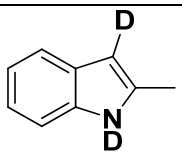
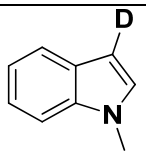
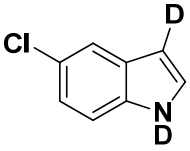
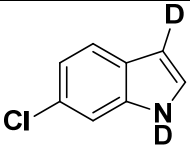
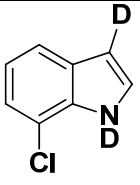
With method C, various alkynylated N-phenyl-, N-pmp- and N-benzyl-THIQ's with a terminal alkyne functionality or short aliphatic substituents were obtained (Entries 8-11, 13, 18-22, 26-29).

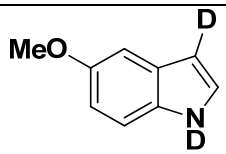
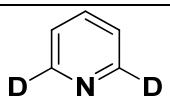
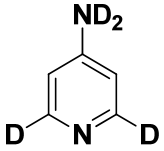
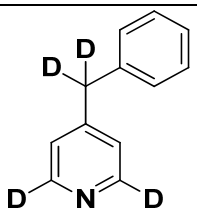
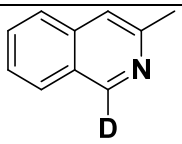
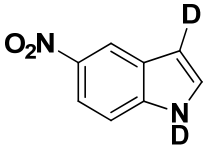
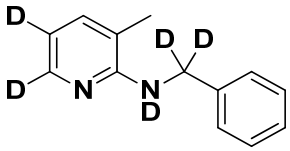
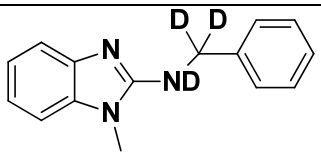
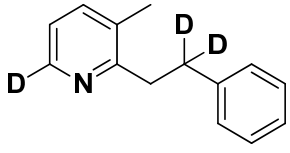
As Method B, Method D showed to be only applicable to N-phenyl-THIQ, but yields were lower as with Method C (Entries 8-11).

Moreover, a one-pot protocol for the decarboxylation/alkynylation reaction, followed by subsequent Click reaction on the terminal alkyne functionality, could be established.

Any attempts to remove the pmp- and benzyl groups of the alkynylated products, as well as to generate an ee by using chiral ligands for the alkynylation, were unsuccessful.

Furthermore, two ruthenium-mediated protocols in *t*-BuOD (batch / microwave) were investigated, where the following compounds could be successfully deuterated.

Entry	Compound	Product	%D Batch	%D Microw.
1	7		80/ 93*	/
2	8		77/90*	88
3	9		71	40
4	10		78	/
5	11		70	80
6	12		50	70
7	13		66	85
8	14		69	85
9	15		77	87
10	16		77	86

11	17		50	84
12	18		79	/
13	19		50	/
14	20		50(Pyr) 87(Bn)	/
15	21		58	/
16	22		/	45
17	23		51 (Pyr-5) 22 (Pyr-6) 89 (Bn)	/
18	24		88	/
19	25		42 (Pyr) 87 (Bn)	/

* applying 2 circles of batch protocol

Experimental Part

1. General Notes

Unless otherwise noted, chemicals were purchased from commercial suppliers and used without further purification.

Flash column chromatography

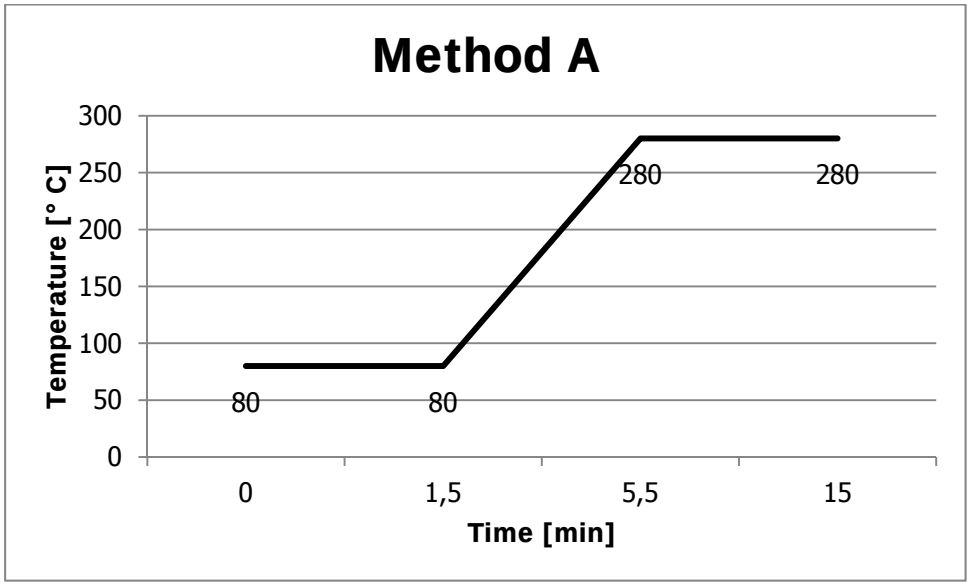
Flash column chromatography was performed on silica gel 60 from Merck (40-63µm) whereas separations were carried out using a Büchi SepacoreTM MPLC system. For TLC aluminum coated silica gel was used and signals were visualized with UV light (254nm).

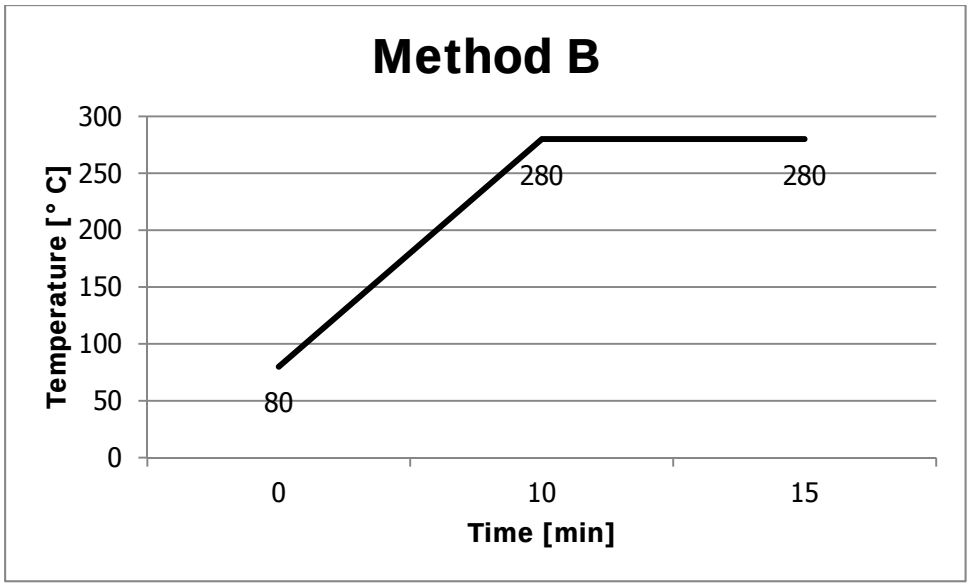
GC-MS

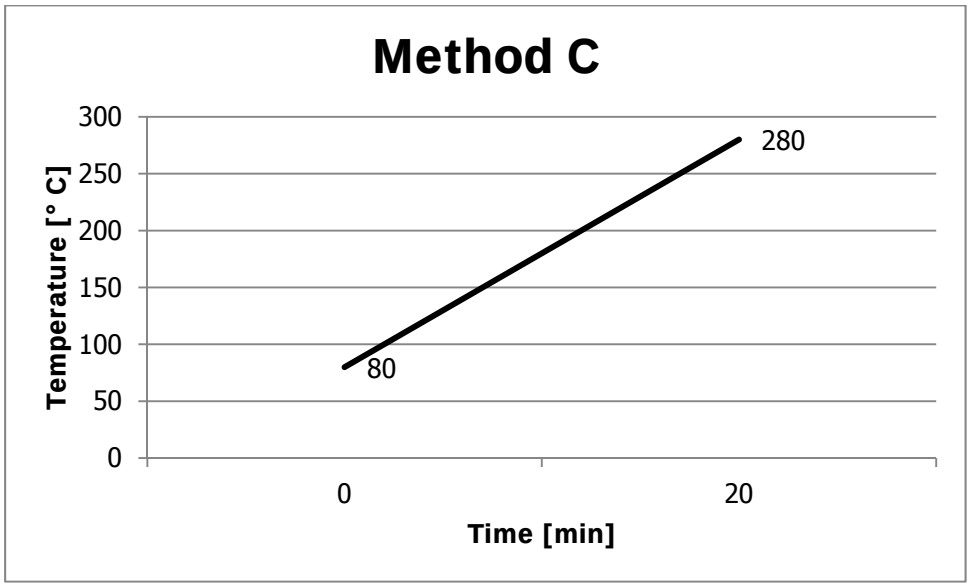
GC-MS runs were performed on a Thermo Finnigan Focus GC / DSQ II using a standard capillary column BGB 5 (30m x 0.32 mm ID) and the following settings were used as standard:

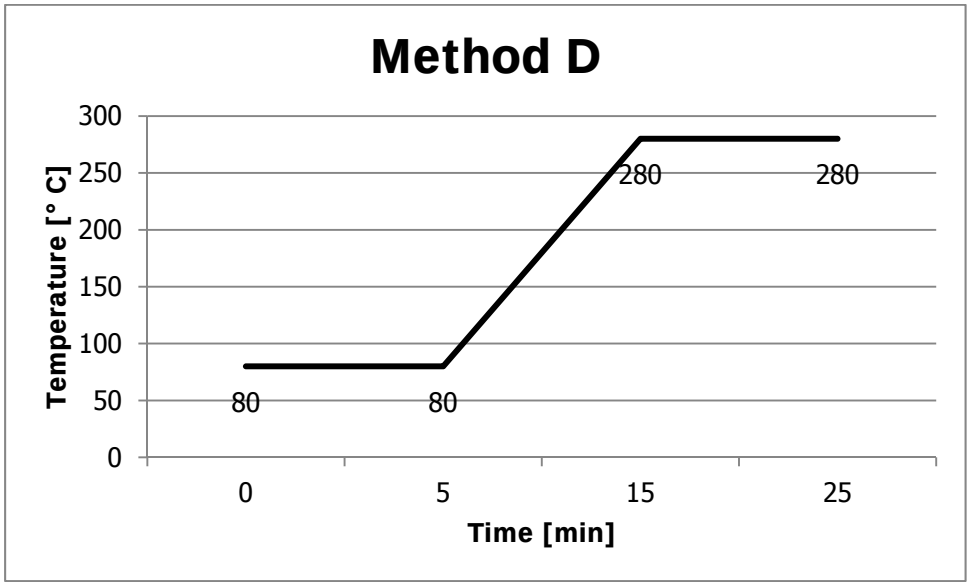
- Injection: 1 µL (hot needle-technique), split-injection (split-ratio:1:8)
- Flow: 2 ml/min Helium
- Injectorblock temperature: 250 °C
- MS-Transferline Temperature: 280 °C

Heating methods:




Method B
Temperature [° C]
300
250
200
150
100
50
0
280
280
80
0
10
15
Time [min]


Method C
Temperature [° C]
300
250
200
150
100
50
0
280
80
0
20
Time [min]


Method D
Temperature [° C]
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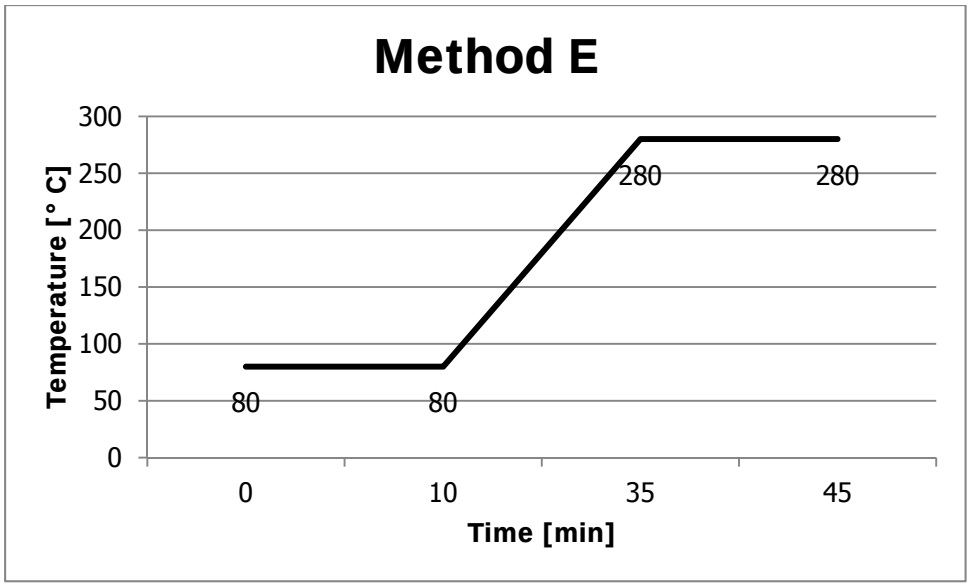
250
200
150
100
50
0
280
280
80
80
0
5
15
25
Time [min]



HR-MS

HR-MS was carried out by E. Rosenberg at the Vienna University of Technology, Institute for Chemical Technologies and Analytics.

Analytical method

All samples were analyzed by LC-IT-TOF-MS in only positive ion detection mode upon recording of MS and MS/MS spectra. For the evaluation in the following, only positive ionization spectra were used (where the quasi-molecular ion is the one of $[M+H]^+$), and further data or information were not taken into consideration.

Instrumental parameters
Shimadzu Prominence HPLC, consisting of: solvent degassing unit (DGU-20 A3), binary gradient Pump (2 x LC-20AD), auto-injector (SIL-20A), column oven (CTO-20AC), control module (CBM-20A), and diode array detector (SPD-M20A).
MS System: Shimadzu IT-TOF-MS with electrospray interface.

Chromatography (parameters: Short_Col_MS_PI_NI_12 min.lcm):

- Column: Phenomenex Kinetex ODS(3), 30 mm x 4.6 mm, 2.6 µm core-shell particles, operated at 40°C
- Gradient: 0 min: 70% A, 30% B (1 min); linear gradient to 6 min to 10% A, 90% B (hold until 10 min); at 10.01 min back to 70% A, 30% B, hold until 12.0 min); A: H_2O + 0.1% formic acid, B: MeOH + 0.1% formic acid.
- Injection volume: 0.2 µl
- Column flow: 0.5 mL/min

MS Parameters:

MS parameters as in autotune. Data recorded with detector voltage at autotune value.

- Scan range: 100-1000 amu for MS (PI and NI) detection
- ES ionization
- Cycle time < 0.6 s
- CDL-Temp.: 200 °C
- Heating block temp.: 200 °C

DAD Parameters:

- Scan range: 200-400 nm
- Data recording rate: 1.5 Hz

Microwave Reactions

Microwave reactions were performed on a BIOTAGE InitiatorTM sixty microwave unit.

Melting points

Melting points were determined using a Kofler-type Leica Galen III micro hot stage microscope and are uncorrected.

NMR-spectroscopy

^{1}H-NMR and ^{13}C-NMR spectra were recorded on a Bruker AC 200 (200 MHz) or on a Bruker Avance UltraShield 400 (400 MHz) spectrometer. Chemical shifts are reported as ppm downfield from TMS (tetramethylsilane) as internal standard with multiplicity, number of protons, allocation, and coupling constant(s) in Hertz.
For structural fragments, which were not allocated with certainty the following prediction program was used:

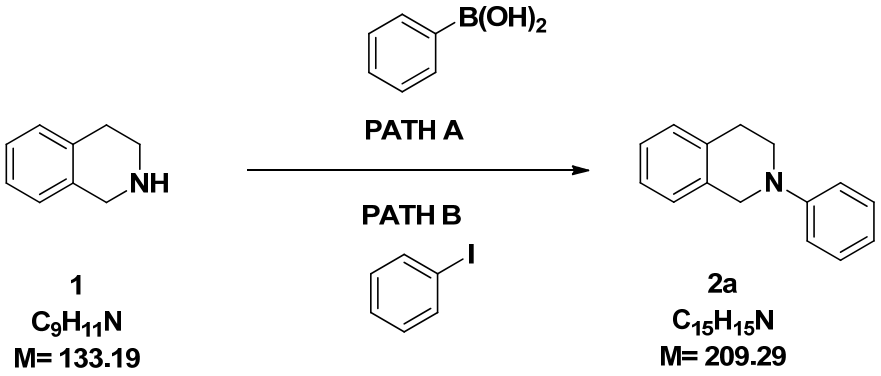
- ChemBioDraw Ultra, Version: 12.0

2. Abbreviations

aq.	aqueous
Bp.	boiling point
DCM	dichloromethane
Dp.	decomposition point
Et_2O	diethyl ether
EtOAc	ethyl acetate
Hz	Hertz
J	coupling constant
Bp.	boiling point
Mp.	melting point
MPLC	medium pressure liquid chromatography
PE	petroleum ether
r.t.	room temperature
TEA	triethylamine
THF	tetrahydrofurane
THIQ	1,2,3,4-tetrahydroisoquinoline
TLC	thin layer chromatography

3. Synthesis of 1,2,3,4-Tetrahydroisoquinolines

N-Phenyl-1,2,3,4-tetrahydroisoquinoline (2a)



PATH A:

Procedure:

A suspension of phenylboronic acid (2.51 g, 20.6 mmol, 2.06 equiv.), copper(II)acetate trihydrate (198 mg, 0.8 mmol, 0.08 equiv.) and powdered molecular sieves (4 Å, 7.62 g) in DCM (20 ml) was stirred for 10 minutes at room temperature. 1,2,3,4-Tetrahydroisoquinoline (1.33 g, 1.27 ml, 10 mmol, 1 equiv.) was added dropwise to the reaction mixture, which was then refluxed and stirred for 24 hours. The reaction mixture was then filtered through a plug of Celite to remove the molecular sieves and any insoluble by-products and concentrated in vacuo, and then separated via MPLC (PE:EtOAc = 20:1).

Yield: 26% (0.54 g, 2.6 mmol)

PATH B:

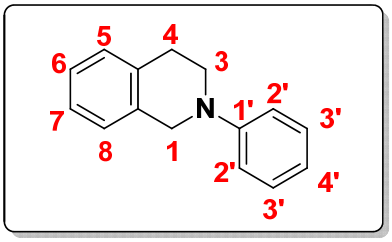
Procedure:

Copper(I)iodide (39.8 mg, 0.21 mmol, 0.1 equiv.) and potassium phosphate (887.3mg, 4.18 mmol, 2.09 equiv.) were weighed into a round flask which was evacuated and back filled with nitrogen for 3 times. 2-Propanol (2 ml), ethylene glycol (0.23 ml), iodobenzene (426.4 mg, 0.23 ml, 2.09 mmol, 1.05 equiv.) and 1,2,3,4-tetrahydroisoquinoline (0.27 g, 0.26 ml, 2.0 mmol, 1 equiv.) were added via micro syringe at room temperature. The reaction mixture was heated to 85-90°C, stirred for 24 h and then allowed to cool to room temperature. Diethyl ether (5 ml) and water (5 ml) were then added to the reaction mixture. The organic layer was extracted by diethyl ether (2 x 20 ml). The combined organic phases were washed

with brine and dried over magnesium sulfate. The solvent was removed under vacuo and the crude mixture purified by column chromatography on silica gel (PE:EtOAc =20:1).

Yield: 83% (0.347 g, 1.66 mmol)
Appearance: light brown solid
M.p.: 43-46 °C
TLC: R_f = 0.69 (PE:EtOAc = 10:1)

NMR:

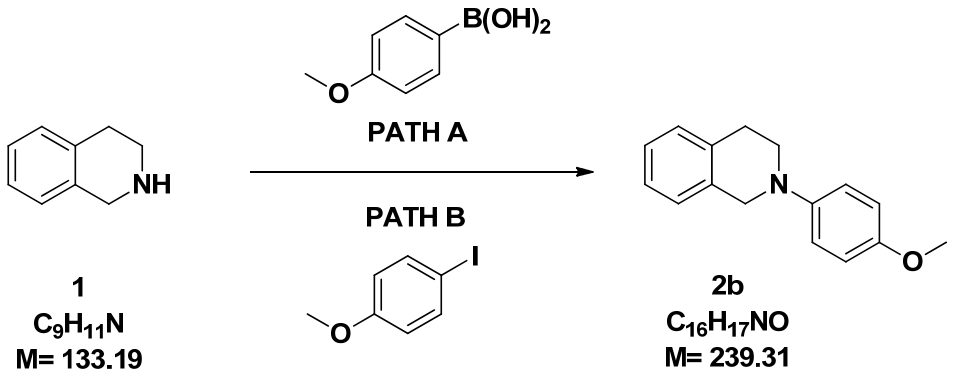


^{1}H-NMR (200 MHz, $CDCl_3$): δ = 3.01 (t, ^{3}J = 5.8 Hz, 2H, H4), 3.59 (t, ^{3}J = 5.9 Hz, 2H, H3), 4.44 (s, 2H, H1), 6.85 (t, ^{3}J = 7.2 Hz, 1H, H4'), 7.01 (d, ^{3}J = 7.9 Hz, 2H, H2'), 7.19-7.36 (m, 6H, H3', H5-H8)

^{13}C-NMR (200 MHz, $CDCl_3$): δ = 29.8 (t, C4), 47.2 (t, C3), 51.4 (t, C1), 115.8 (d, C2'), 119.3 (d, C3'), 126.7 (d, C7), 127.0 (d, C6), 126.5 (d, C5), 129.2 (d, C8), 129.8 (d, C4') 135.1 (s, C4a), 135.5 (s, C8a), 151.2 (s, C1´)

GC-MS:
Method: A
Retention time: 5.69 min
Main fragments: 209 (M^+, 18), 208 (100), 206 (33), 193 (7), 128 (7), 115 (13), 104 (9), 77 (8)

N-(4-Methoxyphenyl)-1,2,3,4-tetrahydroisoquinoline (2b)



1
$C_9H_{11}N$
M= 133.19

2b
$C_{16}H_{17}NO$
M= 239.31

Path A:

Procedure:

A suspension of 4-methoxyphenylboronic acid (1.52 g, 10.0 mmol, 2.0 equiv.), copper(II)acetate trihydrate (123 mg, 0.5 mmol, 0.1 equiv.) and powdered molecular sieves (4 Å, 3.30 g) in DCM (10 ml) was stirred for 10 minutes at r.t. To this stirred solution 1,2,3,4-tetrahydroisoquinoline (0.67 g, 0.64 ml, 5 mmol, 1.0 equiv.) was added dropwise. The reaction mixture was then flushed with oxygen, refluxed and stirred for 24 hours. The reaction mixture was then filtered through a plug of Celite to remove the molecular sieves and any insoluble by- products and concentrated in vacuo, and then separated via MPLC (PE:EtOAc = 20:1).

Yield: 36% (0.43 g, 1.8 mmol)

Path B:

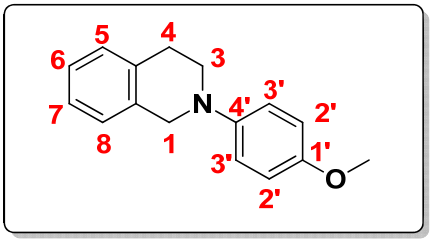
Procedure:

Copper(I)iodide (39.8 mg, 0.21 mmol, 0.1 equiv.), potassium phosphate (887.3mg, 4.18 mmol, 2.09 equiv.) and 4-iodoanisole (489.1 mg, 2.09 mmol, 1.05 equiv.) were put into a round flask which was evacuated and back filled with nitrogen for 3 times. 2-Propanol (2 ml), ethylene glycol (0.23 ml) and 1,2,3,4-tetrahydroisoquinoline (0.27 g, 0.26 ml, 2.0 mmol, 1.0 equiv.) were added via Hamilton syringe at room temperature. The reaction mixture was heated to 85-90°C, stirred for 24 h and then allowed to cool to room temperature. Diethyl ether (5 ml) and water (5 ml) were then added to the reaction mixture. The organic layer was extracted by diethyl ether (2 x 20 ml). The combined organic phases were washed with brine and dried over

magnesium sulfate. The solvent was removed under vacuo and the product purified by column chromatography on silica gel (PE: EtOAc = 20:1).

Yield: 79% (0.38 g, 1.58 mmol)
Appearance: white solid
M.p.: 89-91 °C
TLC: R_f = 0.56 (PE:EtOAc = 5:1)

NMR:

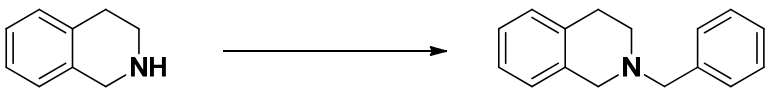


^{1}H-NMR (200 MHz, $CDCl_3$): δ = 3.01 (t, ^{3}J = 5.8 Hz, 2H, H4), 3.47 (t, ^{3}J = 5.9 Hz, 2H, H3), 3.80 (s, 3H, O-CH_3), 4.32 (s, 2H, H1), 6.90 (d, ^{3}J = 9.2 Hz, 2H, H2´), 7.01 (d, ^{3}J = 9.2 Hz, 2H, H3´), 7.11-7.24 (m, H5-H8)

^{13}C-NMR (50 MHz, $CDCl_3$): δ = 29.1 (t, C4), 48.4 (t, C3), 52.6 (t, C1), 55.6 (q, O-CH_3), 114.5 (d, C2'), 118.0 (d, C3'), 125.9 (d, C7), 126.2 (d, C6), 126.5 (d, C5), 128.6 (d, C8), 134.50 (s, C4a), 134.56 (s, C8a), 145.3 (s, C1´), 153.4 (s, C4´)

GC-MS:
Method: B
Retention time: 9.36 min
Main fragments: 239 (M^+, 97), 238 (100), 224 (22), 135 (26), 120 (27), 104 (25), 77 (10)

N-Benzyl-1,2,3,4-tetrahydroisoquinoline (2c)



1
$C_9H_{11}N$
M= 133.19

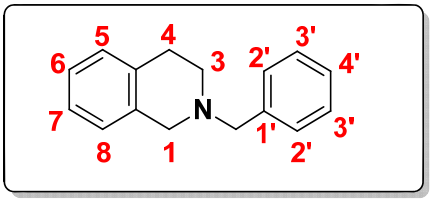
2c
$C_{16}H_{17}N$
M= 223.31

Procedure:

To an argon degassed solution of THIQ (2.66 g, 2.53ml, 20 mmol, 1.0 equiv.) and TEA (6.07 g, 8.4 ml, 60 mmol, 3.0 equiv.) in 50 ml dry DCM, benzylbromide (5.13 g, 3.4 ml, 30 mmol, 1.5 equiv.) was added at 0°C. After 10 minutes, the reaction mixture was warmed to r.t. and stirred under argon for 5 hours. The reaction mixture was quenched with aq. saturated sodium carbonate solution, and extracted three times with EtOAc. The collected organic layers were washed twice with brine, dried over sodium sulfate, filtered and evaporated. The crude product was purified via column chromatography (PE:$CHCl_3$ = 3:1).

Yield: 82 % (3.68 g, 16.5 mmol)
Appearance: pale yellow solid
M.p: 35-37 °C
TLC: R_f = 0.36 (PE:$CHCl_3$ = 3:1)

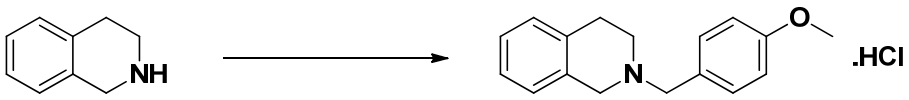
NMR:



^{1}H-NMR (200 MHz, $CDCl_3$): δ = 2.79 (t, ^{3}J = 5.8 Hz, 2H, H4), 2.95 (t, ^{3}J = 5.9 Hz, 2H, H3), 3.69 (s, 2H, H1), 3.74 (s, 2H, Ph-CH_2), 6.98-7.07 (m, 1H, H4'), 7.08-7.49 (m, 8H, H5-H8, H2', H3')
^{13}C-NMR (50 MHz, APT, $CDCl_3$): δ = 29.1 (t, C4), 50.6 (t, C3), 56.1 (t, C1), 62.8 (t, Ph-CH_2), 125.5 (d, C7), 126.0 (d, C6), 126.6 (d, C4'), 127.0 (d, C5), 128.2 (d, C3´), 128.6 (d, C8), 129.0 (d, C2´), 134.3 (s, C4a), 134.9 (s, C8a), 138.4 (s, C1´)

GC-MS:
Method: A
Retention time: 5.53 min
Main fragments: 223 (M^+, 48), 222 (96), 146 (16), 132 (53), 117 (10), 104 (42), 91 (100), 78 (14), 65 (15)

N-(4-Methoxybenzyl)-1,2,3,4-tetrahydroisoquinoline (2d)



1
$C_9H_{11}N$
M= 133.19

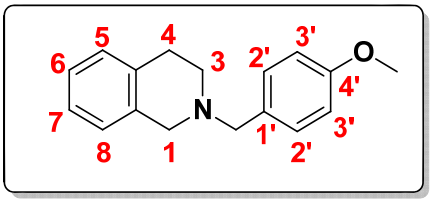
2d
$C_{17}H_{20}ClNO$
M= 289.80

Procedure:

To an argon degassed solution of 1,2,3,4-tetrahydroisoquinoline (1.33 g, 1.27 ml, 10 mmol, 1.0 equiv.) and TEA (3.04 g, 4.2ml, 30 mmol, 3.0 equiv.) in 15 ml dry DCM, 4-methoxybenzylchloride (2.35 g, 2.03 ml, 15 mmol, 1.5 equiv.) was added at 0°C. After 10 minutes, the reaction mixture was warmed to r.t. and stirred under argon for 12 hours. The reaction mixture was diluted with aqueous 2M HCl, and extracted three times with EtOAc. The collected organic layers were washed twice with brine, dried over sodium sulfate, filtered and evaporated. The crude product was triturated in hot EtOAc, cooled down to -20 °C, and the colorless precipitate filtered.

Yield: 86 % (2.50 g, 8.63 mmol)
Appearance: colorless solid
Mp.: 210-212 °C
TLC: R_f = 0.55 (PE:EtOAc = 3:1)

NMR:



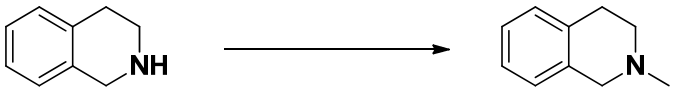
^{1}H-NMR (200 MHz, $CDCl_3$): δ = 2.86-3.29 (m, 2H, H4), 3.34-3.70 (m, 2H, H3), 3.79 (s, 3H, O-CH_3), 3.91-4.43 (m, 4H, H1 & Ph-CH_2), 6.91 (d, ^{3}J = 8.7 Hz, 2H, H3´), 6.94-7.05 (m, 1H), 7.10-7.30 (m, 3H), 7.60 (d, ^{3}J = 8.7 Hz, 2H, H2´), 12.76 (s, 1H, HCl)

^{13}C-NMR (50 MHz, $CDCl_3$): δ = 24.2 (t, C4), 47.9 (t, C3), 50.9 (t, C1), 55.3 (q, O-CH_3), 57.6 (t, Ph-CH_2), 114.5 (d, C3´), 120.2 (s, C1´), 126.6 (s, C8a), 126.8 (d, C6),

127.2 (d, C7), 128.3 (d, C8), 128.8 (d, C5), 130.5 (s, C4a), 132.7 (d, C2´), 160.7 (s, C4´)

GC-MS:
Method: E
Retention time: 18.93 min
Main fragments: 253 (M^+, 11), 252 (10), 132 (38), 121 (100), 105 (12), 91 (10), 77 (12)

N-Methyl-1,2,3,4-tetrahydroisoquinoline (2e)



1
$C_9H_{11}N$
M= 133.19

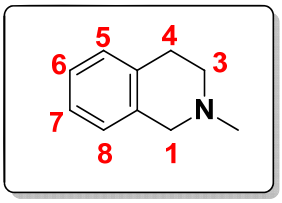
2e
$C_{10}H_{13}N$
M= 147.22

Procedure:

1,2,3,4-THIQ (1.332 g, 10 mmol) was added, under cooling, to formic acid (2.302 g, 50 mmol) and formaldehyde (0.751 g, 25 mmol). The reaction mixture was refluxed overnight, diluted with 2 M hydrochloric acid and then extracted with EtOAc. This solution was neutralized with brine and dried with sodium sulfate. The EtOAc was vaporized and the crude mixture separated via column chromatography (PE:EtOAc = 20:1).

Yield: 87.4 % (1.28 g, 8.7 mmol)
Appearance: yellow oil
TLC: R_f = 0.70 (PE: EtOAc = 10:1)

NMR:

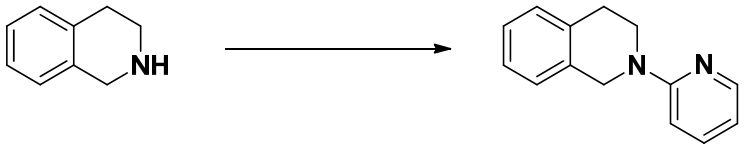


^{1}H-NMR (200 MHz, $CDCl_3$): δ = 2.46 (s, 3H, CH_3), 2.69 (t, ^{3}J = 5.9 Hz, 2H, H4), 2.93 (t, ^{3}J = 5.9 Hz, 2H, H3), 3.59 (s, 2H, H1), 6.97-7.18 (m, 4H, H5-H8)

^{13}C-NMR (50 MHz, $CDCl_3$): δ = 29.5 (t, C4), 46.4 (t, C3), 53.2 (q, CH_3), 58.3 (t, C1), 125.9 (d, C7), 126.4 (d, C6), 126.7 (d, C5), 128.9 (d, C8), 134.1 (s, C4a), 135.0 (s, C8a)

GC-MS:
Method: C
Retention time: 7.63 min
Main fragments: 147 (M^+, 39), 146 (100), 131 (8), 115 (6), 105 (7), 104 (49), 103 (17)

N-(Pyridin-2-yl)-1,2,3,4-tetrahydroisoquinoline (2f)



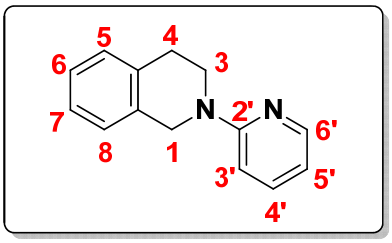
1
$C_9H_{11}N$
M= 133.19

2f
$C_{14}H_{14}N_2$
M= 210.27

1,2,3,4-Tetrahydroisoquinoline (666 mg, 0.63 ml, 5.00 mmol, 1.0 equiv.) and 2-fluoropyridine (510 mg, 0.45 ml, 5.05 mmol, 1.05 equiv.) were placed into a screw-capped glass vial at r.t., heated to 120°C and stirred for 15 hours. Completion of the reaction was monitored by TLC, the reaction mixture cooled to r.t. and directly subjected to flash column chromatography using gradient elution with PE:EtOAc (100:0 to 40:60) to afford the desired product.

Yield: 64 % (670 mg, 3.19 mmol)
Appearance: pale yellow solid
Mp.: 39-42 °C
TLC: R_f = 0.65 (PE:EtOAC = 10:1)

NMR:

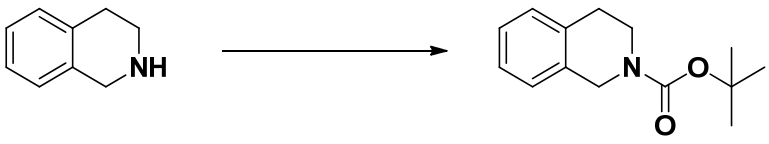


^{1}H-NMR (200 MHz, $CDCl_3$): δ = 2.98 (t, ^{3}J = 5.9 Hz, 2H, H4), 3.85 (t, ^{3}J = 5.9 Hz, 2H, H3), 4.71 (s, 2H, H1), 6.61 (dd, ^{3}J = 7.0 Hz, ^{3}J = 5.6 Hz, 1H, H5´), 6.68 (d, ^{3}J = 8.6 Hz, 1H, H3´), 7.16-7.24 (m, 4H, H5-H8), 7.50 (ddd, ^{3}J = 8.9 Hz, ^{3}J = 7.1, ^{4}J = 2.0 Hz, 1H, H4´), 8.23 (ddd, ^{3}J = 4.9 Hz, ^{4}J = 1.9 Hz, ^{5}J = 0.7 Hz, 1H, H6´)

^{13}C-NMR (50 MHz, $CDCl_3$): δ = 29.0 (t, C4), 42.5 (t, C3), 47.1 (t, C1), 106.6 (d, C3´), 112.4 (d, C5´), 126.1 (d, C6), 126.4 (d, C8), 126.5 (d, C7), 128.3 (d, C5), 134.3 (s, C8a), 135.3 (s, C4a), 137.5 (d, C4´), 147.7 (d, C6´), 158.5 (s, C2´)

GC-MS:
Method: B
Retention time: 10.43 min
Main fragments: 110 (M^+, 100), 109 (42), 195 (20), 193 (26), 132 (61), 130 (18), 117 (26), 115 (53), 104 (44), 94 (24), 79 (84), 78 (54)

N-Boc-1,2,3,4-tetrahydroisoquinoline (2g)



1
$C_9H_{11}N$
M= 133.19

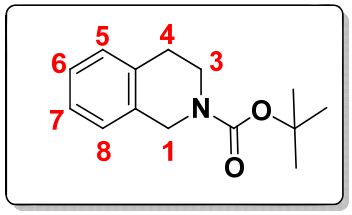
2g
$C_{14}H_{19}NO_2$
M= 233.31

Procedure:

To an argon degassed solution of 1,2,3,4-tetrahydroisoquinoline (2.66 g, 2.53 ml, 20.0 mmol, 1.0 equiv.) and TEA (6.07 g, 8.37 ml, 60.0 mmol, 3.0 equiv.) in 45 ml dry DCM, a solution of Boc_2O (4.80 g, 5.05ml, 22.0 mmol, 1.1 equiv.) in 5 ml DCM was added dropwise. The reaction was stirred under argon atmosphere at r.t. for 15 hours. Then, the solvent was evaporated under vacuo, and the residue directly subjected to flash column chromatography using gradient elution with PE:Et_2O (100:0 to 40:60) to afford the desired product.

Yield: 99 % (4.60 g, 19.7 mmol)
Appearance: colorless solid
Mp.: 27-35 °C
TLC: R_f = 0.79 (PE:Et_2O = 5:1)

NMR:

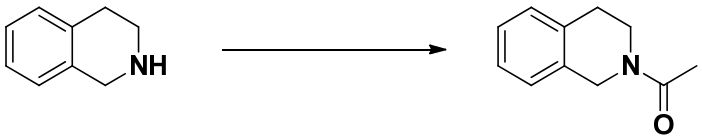


^{1}H-NMR (200 MHz, $CDCl_3$): δ = 1.49 (s, 9H, $(CH_3)_3$), 2.83 (t, ^{3}J = 5.9 Hz, 2H, H4), 3.64 (t, ^{3}J = 5.9 Hz, 2H, H3), 4.57 (s, 2H, H1), 7.03-7.24 (m, 4H, H5-H8)

^{13}C-NMR (50 MHz, $CDCl_3$): δ = 28.5 ($(CH_3)_3$), 29.0 (t, C4), 41.7 (t, C3), 45.6 (t, C1), 79.7 (s, $C(CH_3)_3$), 126.2 (d, C6), 126.3 (d, overlapping, C7 & C8), 128.7 (d, C5), 133.7 (s, C8a), 134.7 (s, C4a), 154.8 (s, C=O)

GC-MS:
Method: A
Retention time: 9.46 min
Main fragments: 177 (M^+, 32), 176 (100), 160 (18), 142 (10), 132 (60), 117 (10), 104 (39), 57 (69)

N-Acetyl-1,2,3,4-tetrahydroisoquinoline (2h)



1
$C_9H_{11}N$
M= 133.19

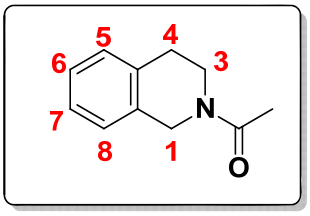
2h
$C_{11}H_{13}NO$
M= 175.23

Procedure:

A 50 ml flask was loaded with 1,2,3,4-tetrahydroisoquinoline (1.51 g, 1.44 ml, 11.3 mmol, 1.0 equiv.) and acetic acid anhydride (1.19 g, 1.10 ml, 11.3 mmol, 1.0 equiv.). The mixture was heated to 100°C for 3 hours. After one hour another equiv. of acetic acid anhydride was added to the reaction. The reaction mixture was cooled to rt and diluted with 200 ml DCM. The organic layer was washed twice with 2 M aqueous NaOH in order to get rid of excess acetic acid, washed twice with brine, dried over sodium sulfate, filtered and evaporated. The crude product was subjected to flash column chromatography using gradient elution with PE:EtOAc (100:0 to 50:50) to afford the desired product.

Yield: 75 % (1.49 g, 8.50 mmol)
Appearance: pale yellow crystals
Mp.: 44-46 °C
TLC: R_f = 0.29 (PE:EtOAc =10:1)

NMR:



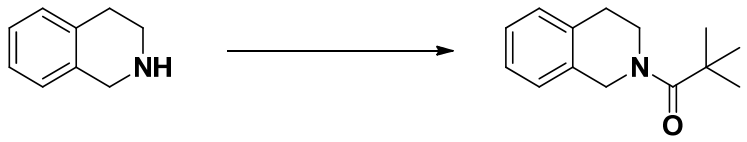
^{1}H-NMR (200 MHz, $CDCl_3$): δ = 2.17 (s, 5.15H, CH_3), 2.78-2.95 (m, 3.46H, H4), 3.67 (t, ^{3}J = 5.9 Hz, 2H, H3), 3.81 (t, ^{3}J = 6.0 Hz, 1.45H, H3), 4.61 (s, 1H, H1), 4.72 (s, 1.96H, H1), 7.04-7.24 (m, 6.78H, H5-H8)

^{13}C-NMR (50 MHz, $CDCl_3$): δ = 21.6 (q, CH_3), 21.9 (q, CH_3), 28.4 (t, C4), 29.4 (t, C4), 39.4 (t, C3), 43.9 (t, C3), 44.0 (d, C1), 48.0 (d, C1), 125.9 (d, C7), 126.3 (d,

C8), 126.4 (d, C7), 126.5 (d, C6), 126.6 (d, C8), 126.8 (d, C6), 128.2 (d, C5), 128.9 (d, C5), 132.5 (s, C8a), 133.4 (s, C8a), 134.0 (s, C4a), 135.0 (s, C4a), 169.3 (s, C=O), 169.4 (s, C=O)

GC-MS:
Method: E
Retention time: 12.72 min
Main fragments: 175 (M^+, 100), 160 (9), 132 (68), 117 (63), 104 (61), 78 (16), 77 (18)

N-Piv-1,2,3,4-tetrahydroisoquinoline (2i)



1
$C_9H_{11}N$
M= 133.19

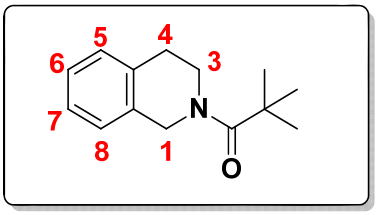
2i
$C_{14}H_{19}NO$
M= 217.31

Procedure:

To an argon degassed solution of 1,2,3,4-tetrahydroisoquinoline (2.66 g, 2.53 ml, 20.0 mmol, 1.0 equiv.) and TEA (6.07g, 8.37 ml, 60.0 mmol, 3.0 equiv.) in 50 ml dry DCM, pivaloylchloride (3.61 g, 3.68ml, 30.0 mmol, 1.5equiv.) was added slowly at 0°C. Then, the reaction mixture was warmed to r.t. and stirred at r.t. under argon for 2 hours. The reaction mixture was cooled to 0°C and diluted with aqueous 2N HCl, and extracted three times with Et_2O. The collected organic layers were washed twice with 2N NaOH, and once with brine, dried over sodium sulfate, filtered and evaporated. The crude product was subjected to flash column chromatography using gradient elution with PE:Et_2O (100:0 to 40:60) to afford the desired product.

Yield: 86 % (3.75 g, 17.3 mmol)
Appearance: pale yellow solid
Mp.: 63-65 °C
TLC: R_f = 0.47 (PE:EtOAc=5:1)

NMR:

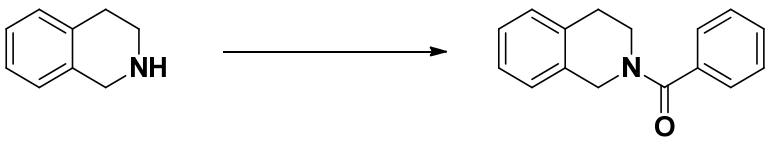


^{1}H-NMR (200 MHz, $CDCl_3$): δ = 1.32 (s, 9H, $(CH_3)_3$), 2.88 (t, ^{3}J = 5.9 Hz, 2H, H4), 3.85 (t, ^{3}J = 5.9 Hz, 2H, H3), 4.75 (s, 2H, H1), 7.06-7.22 (m, H5-H8)

^{13}C-NMR (50 MHz, APT, $CDCl_3$): δ = 28.2 ($(CH_3)_3$), 28.8 (t, C4), 38.7 (s, $C(CH_3)_3$), 43.2 (t, C3), 47.2 (t, C1), 126.2 (d, C7, C6), 126.4 (d, C5), 128.5 (d, C8), 133.4 (s, C4a), 134.2 (s, C8a), 176.5 (s, C=O)

GC-MS:
Method: E
Retention time: 14.19 min
Main fragments: 217 (M^+, 100), 202 (24), 175 (30), 174 (42), 160 (53), 142 (58), 132 (25), 117 (29), 115 (31)

N-Benzoyl-1,2,3,4-tetrahydroisoquinoline (2j)



1
$C_9H_{11}N$
M= 133.19

2j
$C_{16}H_{15}NO$
M= 237.30

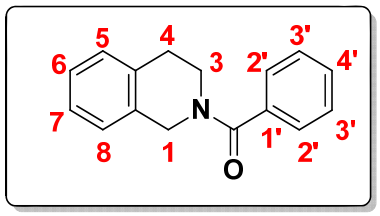
Procedure:

Benzoylchloride (4.22 g, 30.0 mmol, 1.5 equiv.), was added slowly to a solution of THIQ (2.66 g, 2.53 ml, 20.0 mmol, 1.0 equiv.) and TEA (6.07 g, 8.37 ml, 60.0 mmol, 3.0 equiv.) in 50 ml dry DCM at 0°C. The reaction mixture was warmed to r.t. after completion of the addition and stirred at r.t. under argon for 15 hours. Then, the reaction mixture was cooled to 0°C and diluted with aqueous 2N HCl, and extracted three times with Et_2O. The collected organic layers were washed twice with 2N

NaOH, and once with brine, dried over sodium sulfate, filtered and evaporated. The crude product was subjected to flash column chromatography using gradient elution with PE:Et_2O (100:0 to 40:60) to afford the desired product.

Yield: 98 % (4.67 g, 19.7 mmol)
Appearance: pale yellow solid
Mp.: 125-127 °C
TLC: R_f = 0.24 (PE:EtOAc = 5:1)

NMR:



^{1}H-NMR (200 MHz, $CDCl_3$): δ = 2.71-3.15 (m, 2H, H4), 3.45-4.21 (m, 2H, H3), 4.41-5.10 (m, 2H, H1), 7.00-7.31 (m, 4H), 7.37-7.51 (m, 5H)

^{13}C-NMR (50 MHz, APT, $CDCl_3$): δ = 28.0 (t, C4), 29.4 (t, C4), 40.4 (t, C3), 44.7 (t, C3), 45.1 (t, C1), 49.7 (t, C1), 125.7 (d), 126.4 (d), 126.5 (d), 126.6 (d), 126.7 (d), 128.0 (d), 128.4 (d), 128.6 (d), 129.7 (d), 132.6 (d), 132.7 (s, 2C overlap of C4a & C1´), 135.9 (s, C8a), 170.9 (s, C=O) (mixture of two rotamers)

GC-MS:
Method: E
Retention time: 19.40 min
Main fragments: 237 (M^+, 78), 236 (32), 132 (21), 117 (44), 105 (100), 77 (77)

4. C-H activation reactions

General Procedure A:

A mixture of copper(I)chloride (2mg, 0.02 mmol, 0.1 equiv.), the corresponding 1,2,3,4-tetrahydroisoquinoline (0.4 mmol, 2.0 equiv.) in 1ml MeCN was flushed with Ar for about 2 minutes and then *tert*-butyl hydroperoxide (0.04 ml, 5-6M in decane) was dropped into the mixture via syringe at room temperature, followed by the alkyne (0.2 mmol, 1.0 equiv.). The reaction temperature was raised to 50°C and the mixture was stirred at this temperature for 2 days and then cooled to room temperature. The resulting suspension was diluted with diethyl ether or dichloromethane and filtrated through a little amount of silica gel in a frit. The solvent was evaporated and the residue was purified by column chromatography or preparative TLC.

General Procedure B:

To a mixture of copper(I)chloride (4mg, 0.04 mmol, 0.1 equiv.) and the corresponding 1,2,3,4-tetrahydroisoquinoline (0.4 mmol, 1.0 equiv.) in water (1 ml) in a pressure vial, the alkyne (0.4 mmol, 1.0 equiv.) was added. The vial was quickly filled with air to a pressure of 4-5bar. The reaction mixture was then stirred at 50°C for 24h. After cooling down to room temperature, the reaction mixture was extracted 3x with 2ml EtOAc, organic phases were combined, the solvent was evaporated and the residue was purified by column chromatography or preparative TLC.

General Procedure C:

A mixture of copper catalyst (0.02 mmol, 0.1 equiv.) and the corresponding 1,2,3,4-tetrahydroisoquinoline (0.4 mmol, 2.0 equiv.) in 1ml MeCN was flushed with Ar for about 2 minutes. Then the alkynoic acid (0.2 mmol, 1.0 equiv.) and tert-butyl hydroperoxide (0.04 ml, 5-6M in decane) were added via syringe at room temperature. The temperature was then raised to 50°C over 10-15 minutes. The mixture was stirred at this temperature for 2 days and then cooled to room temperature. The resulting suspension was diluted with DCM and filtrated through a little amount of silica gel in a frit eluting with DCM. The solvent was evaporated ant the residue was purified by column chromatography or preparative TLC.

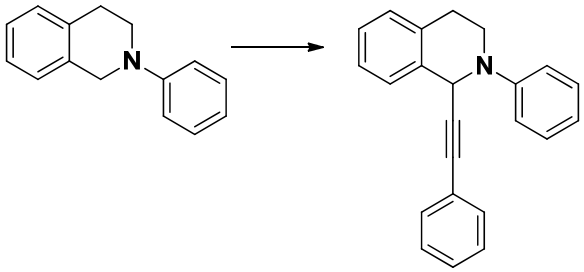
General Procedure D:

To a mixture of copper(I) chloride (4 mg, 0.04 mmol, 0.1 equiv.), 2-phenyl-1,2,3,4-tetrahydroisoquinoline (0.4 mmol, 83.7 mg, 1.0 equiv.) in water (1 ml) in a pressure vial, alkynoic acid (0.4 mmol, 1.0 equiv.) was added. The vial was quickly filled with air to a pressure of 4-5bar. The reaction mixture was then stirred at 50°C for 24h. After cooling down to room temperature, the solvent was evaporated and the residue was purified by column chromatography or preparative TLC.

4.1 Alkynylation of 1,2,3,4-Tetrahydroisoquinolines

4.1.1 Alkynylation of N-Phenyl-1,2,3,4-tetrahydroisoqinolines

Rac-2-Phenyl-1-phenylethynyl-1,2,3,4-tetrahydroisoquinoline (3a)



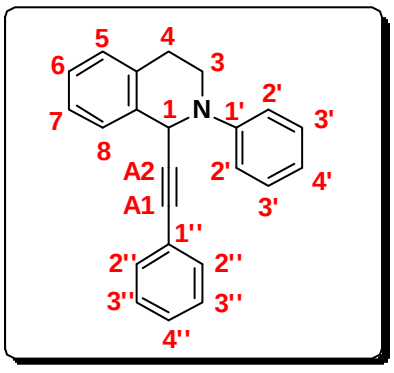
2a
$C_{15}H_{15}N$
M = 209.29

3a
$C_{23}H_{19}N$
M = 309.40

Prepared according to the General Procedure **A** (p. 118) and **B** (p. 118).
The product was isolated by column chromatography (PE:DCM = 10:3).

Yield:
General Procedure A: 86% (53 mg, 0.17 mmol)
General Procedure B: 97% (120 mg, 0.38 mmol)
Appearance: light yellow oil
TLC: R_f = 0.28 (PE:DCM = 10:3)

NMR:



^{1}H-NMR (200 MHz, $CDCl_3$): δ 2.95 (dt, ^3J = 16.0, ^3J = 4.0 Hz, 1H, H4), 3.09 (ddd, ^3J = 16.8, ^3J = 10.4, ^3J = 6.4 Hz, 1H, H4), 3.75-3.61 (m, 2H, H3), 5.62 (s, 1H, H1), 6.86 (dt, ^3J = 7.2, ^4J = 0.8 Hz, 1H, H4'), 7.09 (dd, ^3J = 8.4, ^4J = 0.8 Hz, 2H, H2'), 7.14-7.22 (m, 6H, H3', H5-H8), 7.25 – 7.35 (m, 5H, H2''-H4'');

^{13}C-NMR (50 MHz, $CDCl_3$): δ 29.1 (t, C4), 43.6 (t, C3), 52.5 (d, C1), 85.0 (s, CA1), 88.8 (s, CA2), 116.9 (d, C2'), 119.8 (d, C4'), 123.2 (s, C1''), 126.5 (d, C7), 127.4 (d, C6), 127.6 (d, C5), 128.2 (d, C8), 128.3 (d, C3''), 129.1 (d, C2''), 129.3 (d, C4''), 131.9 (d, C3'), 134.6 (s, C8a), 135.6 (s, C4a), 149.7 (s, C1')

GC-MS:
Method: E
Retention time: 24.62
Main fragments: 309 (M^+, 52), 308 (100), 293 (12), 232 (9), 204 (14), 202 (20)

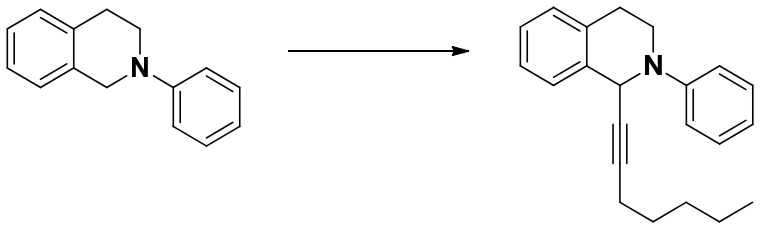
Chiral Experiment:

Prepared according to the General Procedure **A**, with THF instead of MeCN and 15 mol% Pybox (11 mg, 0.03 mmol). The product was isolated by column chromatography (PE:DCM = 10:3).

Yield: 56 % (87 mg, 0.11 mmol)

Chiral HPLC:
Sample ID: BMR236_004
Method: heptan_iproh_95_5_0.5ml_30min.met
Retention time: 9.6 (Peak 1), 10.1 (Peak 2)
Area: 6843909 (Peak 1), 22541004 (Peak 2)
Peak2/Peak1 = 3.3:1 =77:23
ee = 54 %

1-(hept-1-yn-1-yl)-2-phenyl-1,2,3,4-tetrahydroisoquinoline (3b)



$C_{15}H_{15}N$
M = 209.29

2a

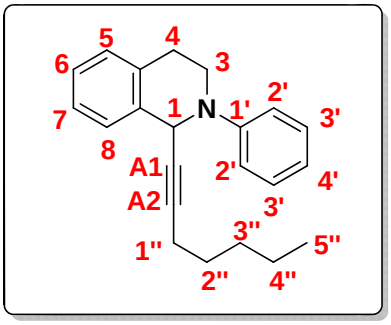
$C_{22}H_{25}N$
M = 303.44

3b

Prepared according to General Procedure **A** (p. 118), **B** (p. 118), **C** (p. 117) and **D** (p. 117).

The product was isolated by column chromatography (PE/DCM).

Yield:
General Procedure A: 67% (41 mg, 0.13 mmol)
General Procedure B: 93% (116 mg, 0.36 mmol)
General Procedure C: 75% (46 mg, 0.15 mmol)
General Procedure D: 98% (118 mg, 0.40 mmol)
Appearance: light yellow oil
TLC: R_f= 0.57 (PE:EtOAc = 20:1)



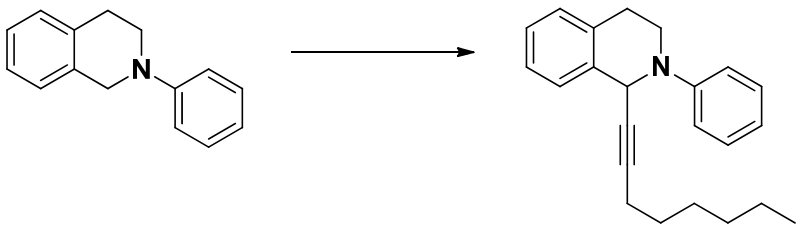
^{1}H-NMR (200 MHz, $CDCl_3$): δ = 0.78-1.02 (m, 3H, H5″), 1.22-1.56 (m, 6H, H2″-H4″), 1.99 (t, 2H, H1″), 2.86-3.27 (m, 2H, H4), 3.51-3.87 (m, 2H, H3), 5.45 (s, 1H, H1), 6.90 (m, 1H, H4′), 7.02-7.48 (m, 8H, H5-H8, H2′, H3′)
^{13}C-NMR (50 MHz, APT, $CDCl_3$): δ = 13.9 (q, C5″), 17.9 (t, C1″), 21.6 (t, C4″), 27.9 (t, C2″), 28.2 (t, C4), 30.2 (t, C3″), 42.0 (t, C3), 50.5 (d, C1), 79.9 (s, CA1), 84.5 (s, CA2), 116.1 (d, C2′), 118.9 (d, C4′), 125.9 (d, C7), 126.9 (d, C6), 127.4 (d, C5), 128.6 (d, C8), 128.9 (d, C3′), 133.8 (s, C8a), 135.9 (s, C4a), 149.2 (s, C1′)

GC-MS:
Method: B
Retention time: 10.50
Main fragments: 303 (M+, 52), 302 (100), 246 (20), 232 (57), 220 (28), 206 (19), 155 (68), 142 (55), 141 (62), 128 (42), 115 (71), 104 (26), 77 (64)

High-Res MS:

Calculated $[M+H]^+$: 304.2060
Found: 304.2064

1-(oct-1-yn-1-yl)-2-phenyl-1,2,3,4-tetrahydroisoquinoline (3c)



$C_{15}H_{15}N$
M = 209.29

2a

$C_{23}H_{27}N$
M = 317.47

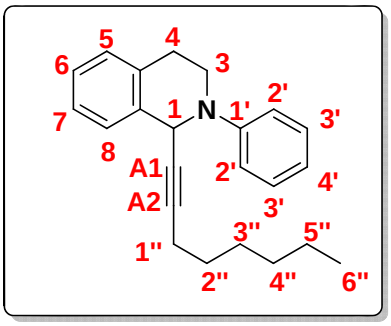
3c

Prepared according to General Procedure **A** (p. 117) and **B** (p. 117).

The product was isolated by column chromatography (PE/DCM).

Yield:
General Procedure A: 49% (31 mg, 0.1 mmol)
General Procedure B: 91% (116 mg, 0.36 mmol)
Appearance: light yellow oil
TLC: R_f = 0.62 (PE:EtOAc = 20:1)

NMR:



^{1}H-NMR (200 MHz, $CDCl_3$): δ = 0.61-0.93 (m, 3H, H6″), 0.97-1.48 (m, 8H, H2″-H5″), 1.99-2.12 (m, 2H, H1″), 2.81-3.17 (m, 2H, H4), 3.47-3.75 (m, 2H, H3), 5.39 (s, 1H, H1), 6.83 (t, ^{3}J=7.3Hz, 1H, H4′), 6.98-7.33 (m, 8H, H5-H8, H2′, H3′)

^{13}C-NMR (50 MHz, $CDCl_3$, APT): δ = 14.4 (q, C6″), 19.1 (t, C1″) 22.8 (t, C5″), 28.7 (t, C3″), 29.0 (t, C4), 30.0 (t, C2″), 31.6 (t, C4″), 43.5 (t, C3), 52.1 (d, C1), 79.4 (CA1), 85.6 (CA2), 116.9 (d, C2′), 119.6 (C4′), 126.4 (C7), 127.3 (C6), 127.6 (C5), 129.1 (C8), 129.3 (d, C3′), 134.4 (C8a), 136.5 (C4a), 149.9 (C1′)

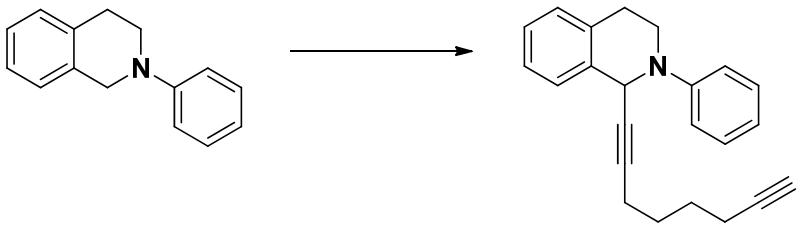
GC-MS:

Method: B
Retention time: 10.99
Main fragments: 317 (M^+, 50), 316 (100), 246 (25), 232 (63), 220 (28), 155 (48), 142 (47), 141 (46), 128 (29), 116 (35), 115 (47), 77 (36)

High-Res MS:

Calculated $[M+H]^+$: 318.2216
Found: 318.2206

1-(octa-1,7-diyn-1-yl)-2-phenyl-1,2,3,4-tetrahydroisoquinoline (3d)



$C_{15}H_{15}N$
M = 209.29

2a

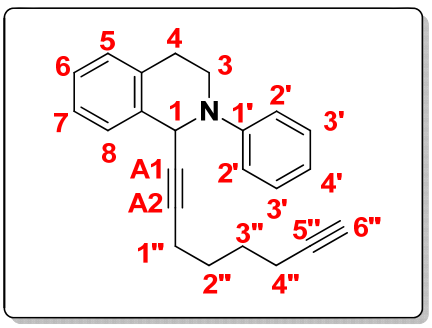
$C_{23}H_{23}N$
M = 313.44

3d

Prepared according to General Procedure **A** (p. 117) and **B** (p. 117).
The product was isolated by column chromatography (PE/DCM).

Yield:
General Procedure A: 93% (58 mg, 0.19 mmol)
General Procedure B: 88% (110 mg, 0.34 mmol)
Appearance: light yellow oil
TLC: R_f = 0.47 (PE:EtOAc = 20:1)

NMR:



^{1}H-NMR (200 MHz, $CDCl_3$): δ= 1.45-1.68 (m, 4H, H2″, H3″), 1.99 (s, 1H, H6″), 2.09-2.31 (m, 4H, H1″, H4″), 2.99-3.27 (m, 2H, H4), 3.55-3.83 (m, 2H, H3), 5.50 (s, 1H, H1), 6.88-7.46 (m, 9H, H5-H8, H2′, H3′)

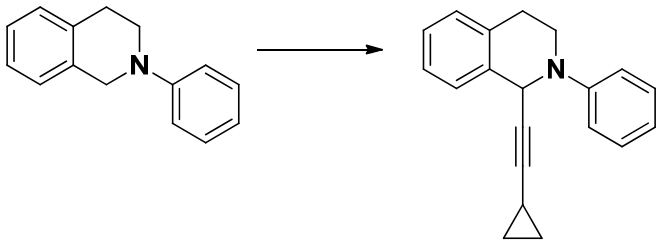
^{13}C-NMR (50 MHz, $CDCl_3$): δ= 18.2 (t, C4″), 18.6 (t, C1″), 27.6 (t, C3″), 27.8 (t, C2″), 29.1 (t, C4), 43.4 (t, C3), 52.2 (d, C1), 68.7 (d, C6″), 79.9 (s, CA1), 84.9 (s, CA2, C5″), 117.0 (d, C2′), 119.9 (d, C4′), 126.5 (d, C7), 127.3 (d, C6), 127.6 (d, C5), 129.2 (d, C8), 129.4 (d, C3′), 134.4 (s, C4a), 136.3 (s, C8a), 150.0 (s, C1′)

GC-MS:
Method: B
Retention time: 11.14
Main fragments: 313 (M^+, 48), 312 (100), 244 (33), 232 (30), 207 (80), 165 (22), 77 (19)

High-Res MS:

Calculated $[M+H]^+$: 314.1903
Found: 314.1900

Rac-1-(cyclopropylethynyl)-2-phenyl-1,2,3,4-tetrahydroisoquinoline (3e)



$C_{15}H_{15}N$
M= 209.29
2a

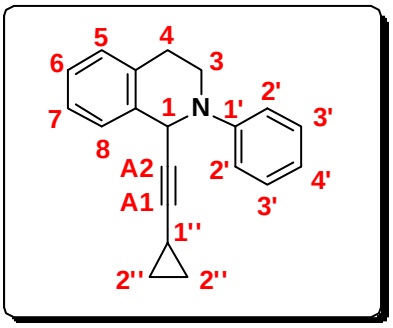
$C_{20}H_{19}N$
M= 273.37
3e

Prepared according to General Procedure **A** (p. 117) and **B** (p. 117).

The product was isolated by column chromatography (PE/DCM).

Yield:
General Procedure A: 42% (23 mg ,0.08 mmol)
General Procedure B: 78% (86 mg, 0.32 mmol)
Appearance: light yellow oil
TLC: R_f = 0.55 (PE:EtOAc = 20:1)

NMR:



^{1}H-NMR (200 MHz, $CDCl_3$): δ = 0.42-0.71 (m, 4H, H2″), 0.97-1.34 (m, 2H, H1″), 2.78-3.19 (m, 2H, H4), 3.43-3.76 (m, 2H, H3), 5.34 (s, 1H, H1), 6.83 (t, ^{3}J = 7.3Hz, 1H, H4′), 6.95-7.33 (m, 8H, H5-H8, H2′, H3′)

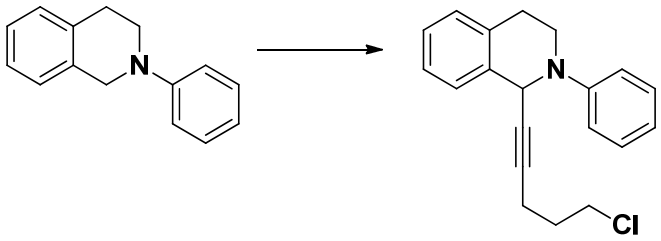
^{13}C-NMR (50 MHz, $CDCl_3$): δ = 0 (d, C1″), 8.6 (C2″), 29.1 (t, C4), 43.5 (t, C3), 52.0 (d, C1), 74.6 (s, CA1), 88.6 (s, CA2), 116.8 (d, C2′), 119.6 (d, C4′), 126.5 (d, C7), 127.3 (d, C6), 127.6 (d, C5), 129.1 (d, C8), 129.3 (d, C3′), 134.5 (s, C8a), 136.4 (s, C4a), 149.9 (s, C1′)

GC-MS:
Method: C
Retention time: 17.49
Main fragments: 273 (M^+, 48), 272 (100), 244 (76), 220 (36), 167 (45), 153 (35), 152 (41), 140 (72), 128 (38), 115 (67), 104 (32), 77 (99)

High-Res MS:

Calculated $[M+H]^+$: 274.1590
Found: 274.1574

1-(5-chloropent-1-yn-1-yl)-2-phenyl-1,2,3,4-tetrahydroisoquinoline (3f)



$C_{15}H_{15}N$
M= 209.29
2a

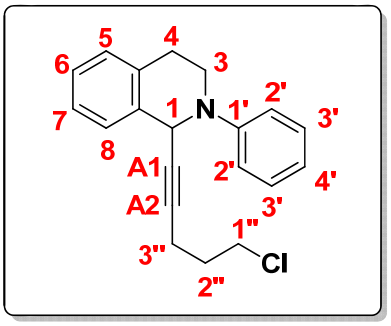
$C_{20}H_{20}ClN$
M= 309.83
3f

Prepared according to General Procedure **A** (p. 117) and **B** (p. 117).

The product was isolated by column chromatography (PE/DCM).

Yield:
General Procedure A: 77% (46 mg, 0.15 mmol)
General Procedure B: 95% (118 mg, 0.38 mmol)
Appearance: light yellow oil
TLC: R_f = 0.45 (PE:EtOAc = 20:1)

NMR:



^{1}H-NMR (200 MHz, $CDCl_3$): δ 1.83 (qui, ^3J = 6.5 Hz, 2H, H2″), 2.31 (dt, ^3J = 6.7 Hz, ^4J = 2.1 Hz, 2H, H3″), 2.87-3.23 (m, 2H, H4), 3.38-3.79 (m, 4H, H3, H2″) 5.46 (s, 1H, H1), 6.9 (dt, ^3J = 7.2 Hz, ^4J = 1.0 Hz, 1H, H4′), 7.08 (dd, ^3J = 8.7 Hz, ^4J = 1.0 Hz, 2H, H2′), 7.16-7.40 (m, 6H, H5-H8, H3′)

^{13}C-NMR (50 MHz, $CDCl_3$): δ 16.4 (t, C3″), 29.1 (t, C4) 31.5 (t, C2″), 43.2 (t, C1″), 43.7 (t, C3), 52.2 (d, C1), 80.5 (s, CA1), 83.2 (s, CA2), 116.9 (d, C2′), 119.8 (d, C4′), 126.4 (d, C7), 127.3 (d, C6), 127.5 (d, C5), 129.1 (d, C8), 129.3 (d, C3′), 134.3 (s, C8a), 135.9 (s, C4a), 149.9 (s, C1′)

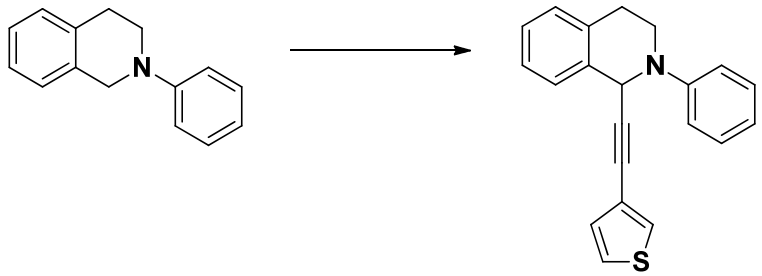
GC-MS:

Method: C
Retention time: 19.09
Main fragments: 311 (22), 310 (43), 309 (68), 308 (100), 232 (23), 176 (44), 141 (58), 128 (20), 115 (38), 77 (34)

High-Res MS:

Calculated $[M+H]^+$: 310.1357
Found: 310.1347

2-phenyl-1-(thiophen-3-ylethynyl)-1,2,3,4-tetrahydroisoquinoline (3g)



$C_{15}H_{15}N$
M = 209.29

2a

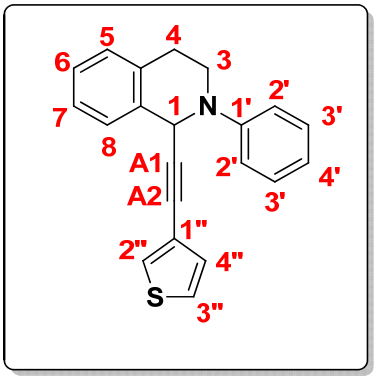
$C_{21}H_{17}NS$
M = 315.43

3g

Prepared according to General Procedure **A** (p. 117) and **B** (p. 117).
The product was isolated by column chromatography (PE/DCM).

Yield:
General Procedure A: 57% (36 mg, 0.11 mmol)
General Procedure B: 71% (90 mg, 0.28 mmol)
Appearance: light yellow oil
TLC: R_f = 0.49 (PE:EtOAc = 20:1)

NMR:



^{1}H-NMR (200 MHz, $CDCl_3$): δ=2.92-3.28 (m, 2H, H4), 3.55-3.87 (m, 2H, H3), 5.66 (s, 1H, H1), 6.84-7.48 (m, 12H, H5-H8, H2'-H4', H2", H3", H4")

^{13}C-NMR (50 MHz, $CDCl_3$): δ= 29.2 (t, C4), 43.7 (t, C3), 52.5 (d, C1), 80.11 (s, CA2), 88.42 (s, CA1), 116.9 (d, C2'), 119.9 (d, C4'), 122.3 (d, C2"), 125.3 (s, C1"), 126.6 (d, C7), 127.5 (d, C6), 127.7 (d, C5), 128.9 (d, C3"), 129.2 (d, C8), 129.4 (d, C3'), 130.3 (d, C4"), 134.7 (s, C4a), 135.6 (s, C8a), 149.8 (d, C4')

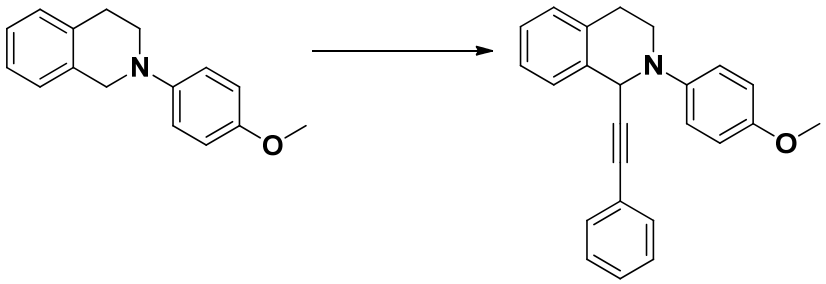
GC-MS:
Method: B
Retention time: 12.46
Main fragments: 315 (M+, 65), 314 (100), 210 (70), 209 (65), 208 (65), 165 (56), 104 (25), 77 (79)

High-Res MS:

Calculated $[M+H]^+$: 316.1154
Found: 316.1143

4.1.2 Alkynylation on 2-pmp-1,2,3,4-Tetrahydroisoquinolines

Rac-1-(2-phenylethynyl)-2-(4-methoxyphenyl)-1,2,3,4-tetrahydroisoquinoline (4a)



$C_{16}H_{17}NO$
M = 239.31

2b

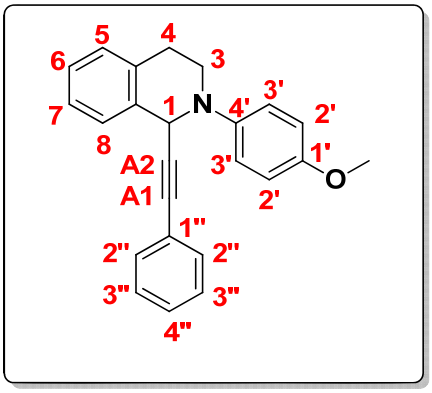
$C_{24}H_{21}NO$
M= 339.43

4a

Prepared according to General Procedure **A** (p. 117) and **B** (p. 117).
The product was isolated by column chromatography (PE/DCM).

Yield:
General Procedure A: 42% (29 mg, 0.08 mmol)
General Procedure B: traces
Appearance: light yellow oil
TLC: R_f = 0.30 (PE:EtOAc = 20:1)

NMR:



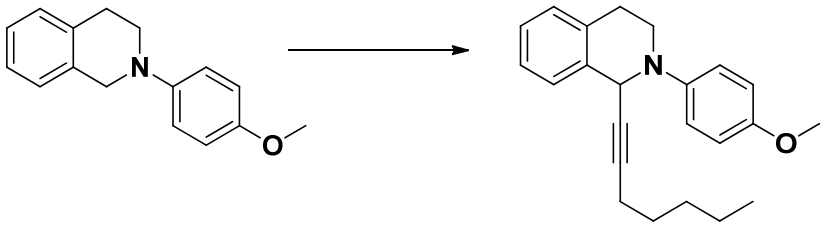
^{1}H-NMR (200 MHz, $CDCl_3$): δ= 2.86-3.26 (m, 2H, H4), 3.52-3.69 (m, 2H, H3), 3.80 (s, 3H, O-CH_3), 5.53 (s, 1H, H1), 6.91 (d, ^{3}J=9.1Hz, 2H, H3‘), 7.14 (d, ^{3}J=9.1Hz, 2H, H2‘), 7.17-7.40 (m, 9H, H5-H8, H2“-H4“)

^{13}C-NMR (50 MHz, $CDCl_3$): δ= 22.2 (t, C4), 44.4 (t, C3), 54.6 (q, O-CH_3), 55.8 (d, C1), 85.8 (s, CA1), 88.8 (s, CA2), 114.6 (d, C2′), 120.4 (d, C3′), 123.3 (s, C1″), 126.3 (d, C7), 127.3 (d, C6), 127.7 (d, C5), 128.1 (d, C8), 128.3 (d, C3″), 129.3 (d, C4″), 131.9 (d, C2″), 134.2 (s, C4a), 135.6 (s, C8a), 144.4 (s, C1′), 155.5 (s, C4′)

GC-MS:

Method: B
Retention time: 14.24
Main fragments: 340 (M^+, 20), 339 (72), 338 (61), 281 (17), 208 (23), 207 (100), 204 (59), 202 (50)

1-(hept-1-yn-1-yl)-2-(4-methoxyphenyl)-1,2,3,4-tetrahydroisoquinoline (4b)



$C_{16}H_{17}NO$
M = 239.31

2b

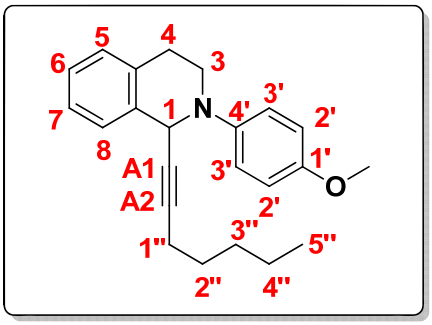
$C_{23}H_{27}NO$
M = 333.47

4b

Prepared according to General Procedure **A** (p. 117) and **C** (p. 117).
The product was isolated by preparative TLC ($CHCl_3$).

Yield:
General Procedure A: 75% (50 mg, 0.15 mmol)
General Procedure C: 71% (47 mg, 0.14 mmol)
Appearance: orange oil
TLC: R_f = 0.31 (PE:EtOAc = 20:1)

NMR:



^{1}H-NMR (200 MHz, $CDCl_3$): δ = 0.83 (t, ^{3}J=6.4Hz, ^{3}J=6.4Hz, 3H, H5''), 1.11-1.45 (m, CH_2, 6H, H2"-H4"), 2.07(dt, ^{3}J=6.8Hz, ^{3}J=6.9Hz, ^{4}J=1.9Hz, 2H, H1''), 2.87 (td, ^{3}J=16.3Hz, ^{4}J=3.5Hz, ^{4}J=3.5Hz, 1H, H4), 3.09 (ddd, ^{3}J=16.5Hz, ^{4}J=9.7Hz, ^{4}J=6.8Hz, 1H, H4), 3.45-3.58 (m, 2H, H3), 3.77 (s, 3H, O-CH_3), 5.28 (s, 1H, H1), 6.86 (d, ^{3}J=9.1Hz, 2H, H3'), 7.04 (d, ^{3}J=9.1Hz, 2H, H2'), 7.10-7.30 (m, 4H, H5-H8)

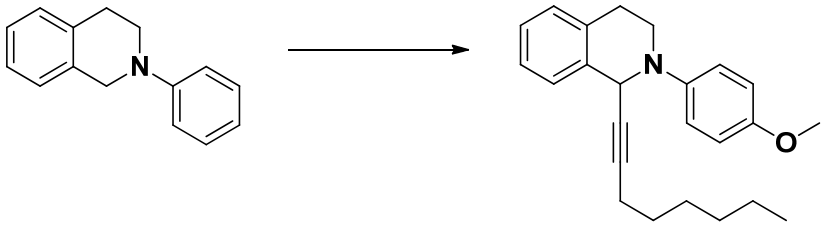
^{13}C-NMR (50 MHz, APT, $CDCl_3$): δ = 14.0 (q, C5''), 18.7 (t, C1''), 22.2 (t, C2''), 28.4 (t, C4''), 29.0 (t, C4), 30.9 (t, C3''), 44.0 (t, C3), 53.8 (q, O-CH_3), 55.5 (d, C1), 78.9 (s, CA1), 86.0 (s, CA2), 114.3 (d, C2'), 120.0 (d, C3'), 126.0 (d, C7), 126.9 (d, C6), 127.4 (d, C5), 129.0 (d, C8), 133.8 (s, C4a), 136.3 (s, C8a), 144.3 (s, C1'), 154.0 (s, C4')

GC-MS:
Method: D
Retention time: 11.71
Main fragments: 334 (M^+, 18), 333 (80), 332 (68), 262 (23), 262 (24), 155 (100), 142 (73), 141 (94), 129 (36), 128 (44), 120 (40), 116 (63), 115 (76), 92 (19), 77 (33)

High-Res MS:

Calculated $[M+H]^+$: 334.2165
Found: 334.2162

1-(oct-1-yn-1-yl)-2-(4-methoxyphenyl)-1,2,3,4-tetrahydroisoquinoline (4c)



$C_{15}H_{15}N$
M = 209.29

2b

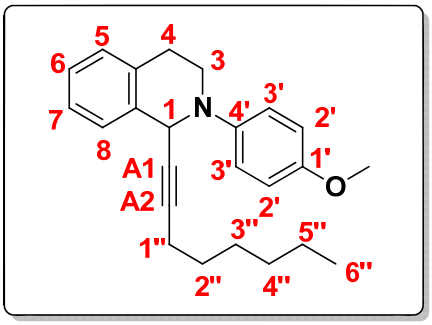
$C_{24}H_{29}NO$
M = 347.22

4c

Prepared according to General Procedure **A** (p. 117).
The product was isolated by preparative TLC ($CHCl_3$).

Yield: 61% (42 mg, 0.12 mmol)
Appearance: light yellow oil
TLC: R_f = 0.35 (PE:EtOAc = 20:1)

NMR:



^{1}H-NMR (200 MHz, $CDCl_3$): δ = 0.92 (t, ^{3}J=6.5Hz, 3H, H6‟), 1.18-1.54 (m, 8H, C2‟-C5‟), 2.07-2.23 (m, 2H, H1″), 2.88-3.27 (m, 2H, H4), 3.53-3.66 (m, 2H, H3), 3.86 (s, 3H, O-CH_3), 5.36 (s, 1H, H1), 6.89-7.01 (m, 2H, H3′), 7.07-7.18 (m, 2H, H2′), 7.20-7.41 (m, 4H, H5-H8)

^{13}C-NMR (50 MHz, $CDCl_3$): δ = 14.4 (q, C6″), 19.1 (t, C1″), 22.9 (t, C5″), 28.7 (t, C3″), 29.0 (t, C4″), 29.3 (t, C4), 31.6 (t, C2″), 44.4 (t, C3), 54.1 (q, O-CH_3), 55.9 (t, C1), 114.6 (d, C2′), 120.3 (d, C3′), 126.3 (d, C7), 127.2 (d, C6), 127.7 (d, C5), 129.3 (d, C8), 134.1 (s, C4a)

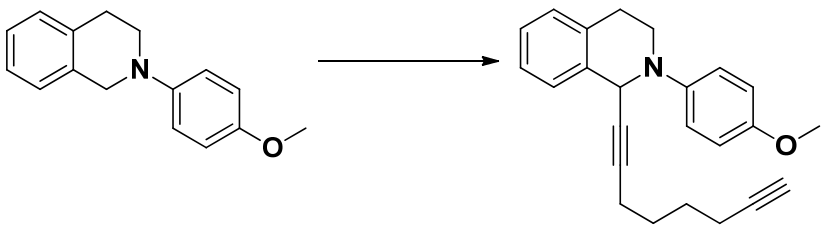
GC-MS:

Method: D
Retention time: 12.41
Main fragments: 348 (M^+, 22), 347 (100), 346 (84), 262 (18), 155 (41), 142 (30), 141 (135), 115 (28)

High-Res MS:

Calculated $[M+H]^+$: 348.2322
Found: 348.2325

1-(octa-1,7-diyn-1-yl)-2-(4-methoxyphenyl)-1,2,3,4-tetrahydroisoquinoline (4d)



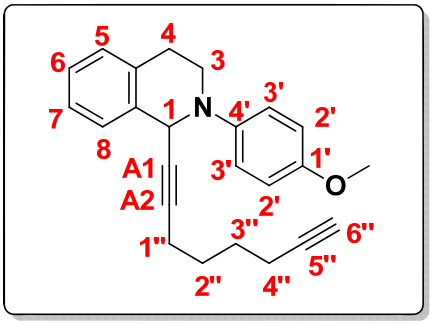
$C_{16}H_{17}NO$
M= 239.31
2b

$C_{24}H_{25}NO$
M=343.46
4d

Prepared according to General Procedure **A** (p. 117).
The product was isolated by preparative TLC ($CHCl_3$).

Yield: 25% (17 mg, 0.05 mmol)
Appearance: light yellow oil
TLC: R_f = 0.30 (PE:EtOAc = 20:1)

NMR:



^{1}H-NMR (200 MHz, $CDCl_3$): δ = 1.48-1.57 (m, 4H, Alkyl-CH_2), 1.99-2.02 (m, 1H, alkyne-CH), 2.13-2.29 (m, 4H, alkyl-CH_2), 2.88-3.30 (m, 2H, THIQ-CH2), 3.52-3.65 (m, 2H, THIQ-CH_2), 3.88 (s, 3H, O-CH_3), 5.38 (s, 1H, THIQ-CH), 6.91-7.40 (m, 8H, Ar-CH)

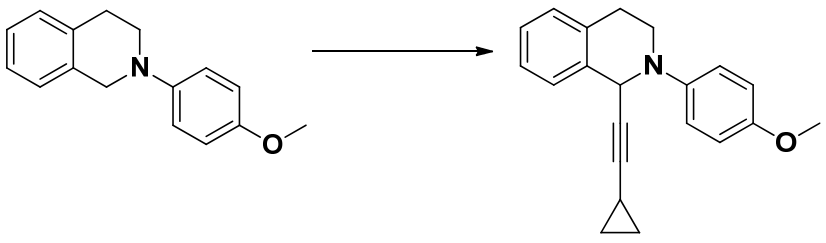
^{13}C-NMR (50 MHz, $CDCl_3$): δ = 18.2 (t, C4″), 18.6 (t, C1″), 27.6 (t, C3″), 27.9 (t, C2″), 29.3 (t, C4), 44.3 (t, C3), 54.1 (q, O-CH_3), 55.9 (d, C1), 56.3 (O-CH_3), 68.7 (C1), 79.7 (s, CA1), 84.6 (d, C6″), 85.5 (s, CA2), 94.8 (s, C5″), 114.6 (d, C2′), 118.4, 120.3 (d, C3′), 126.3 (d, C7), 127.2 (d, C6), 127.7 (d, C5), 129.3 (d, C8), 132.6, 134.1 (s, C4a), 136.4 (s, C8a), 144.6 (s, C1′), 154.3 (s, C4′)

GC-MS:
Method: D
Retention time: 12.63
Main fragments: 344 (M^+, 22), 343 (100), 342 (74), 262 (18), 207 (59), 179 (35), 178 (22), 165 (46), 153 (22), 141 (29), 128 (23), 115 (43), 77 (15)

High-Res MS:

Calculated $[M+H]^+$: 344.2009
Found: 344.2006

Rac-1-(cyclopropylethynyl)-2-(4-methoxyphenyl)-1,2,3,4-tetrahydroisoquinoline (4e)



$C_{16}H_{17}NO$
M = 239.31

2b

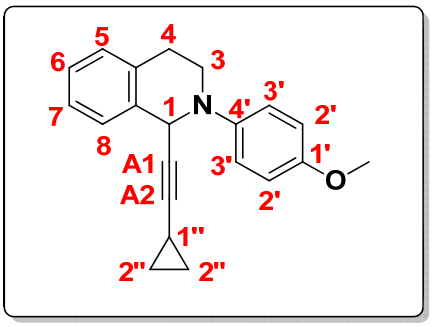
$C_{21}H_{21}NO$
M = 303.40

4e

Prepared according to General Procedure **A** (p. 117).
The product was isolated by preparative TLC ($CHCl_3$).

Yield: 93% (56 mg, 0.19 mmol)
Appearance: yellow oil
TLC: R_f = 0.31 (PE:EtOAc = 20:1)

NMR:



^{1}H-NMR (200 MHz, $CDCl_3$): δ= 0.49-0.76 (m, 4H, H2‟), 1.09-1.26 (m, 1H, C1‟), 2.84-3.23 (m, 2H, H4), 3.45-3.68 (m, 2H, H3), 3.83 (s, 3H, O-CH_3), 5.33 (s, 1H, H1), 6.91 (d, ^{3}J=9.1Hz, 2H, H3‘), 7.08 (d, ^{3}J=9.1Hz, 2H, H2‘), 7.14-7.35 (m, 4H, H5-H8)

^{13}C-NMR (50 MHz, $CDCl_3$): δ= 0 (d, C1‟), 8.6 (t, C2‟), 29.2 (t, C4), 44.3 (t, C3), 54.0 (q, O-CH_3), 55.9 (d, C1), 74.3 (s, CA1), 89.3 (s, CA2), 114.5 (d, C2’), 120.3 (d, C3’), 126.3 (d, C7), 127.2 (d, C6), 127.7 (d, C5), 129.3 (d, C8), 134.1 (s, C4a), 136.4 (s, C8a), 144.5 (s, C1’), 154.3 (s, C4’)

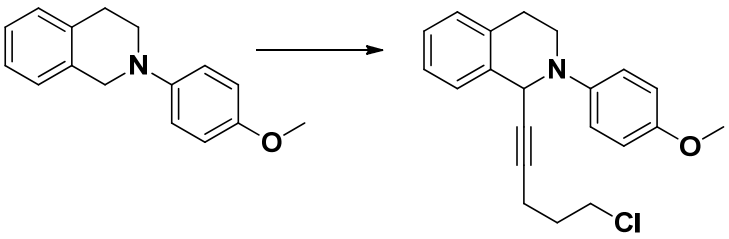
GC-MS:

Method: D
Retention time: 11.13
Main fragments: 303 (69), 302 (51), 288 (20), 274 (27), 260 (20), 250 (23), 207 (22), 167 (72), 165 (40), 153 (55), 152 (50), 140 (100), 139 (74), 120 (42), 115 (58), 77 (38)

High-Res MS:

Calculated $[M+H]^+$: 304.1696
Found: 304.1694

1-(5-chloropent-1-yn-1-yl)-2-(4-methoxyphenyl)-1,2,3,4-tetrahydroisoquinoline (4f)



$C_{16}H_{17}NO$
M= 239.31

2b

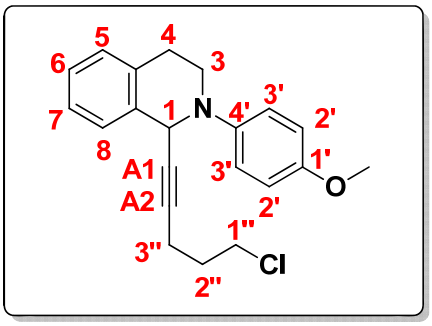
$C_{20}H_{20}ClN$
M= 309.83

4f

Prepared according to General Procedure **A** (p. 117).
The product was isolated by preparative TLC ($CHCl_3$).

Yield: 52% (32 mg, 0.10 mmol)
Appearance: light yellow oil
TLC: R_f = 0.28 (PE:EtOAc = 20:1)

NMR:



^{1}H-NMR (200 MHz, $CDCl_3$): δ= 1.72-1.88 (m, 2H, H2‟‟), 2.21-2.35 (m, 2H, H3‟‟), 2.81-3.23 (m, 2H, H4), 3.34-3.59 (m, 4H, H3, H1‟‟), 3.80 (s, 3H, O-CH_3), 5.32 (s, 1H, H1), 6.89 (d, ^{3}J=9.1 Hz, 2H, H3‟), 7.05 (d, ^{3}J=9.1 Hz, 2H, H2‟), 7.12-7.34 (m, 4H, H5-H8)

^{13}C-NMR (50 MHz, $CDCl_3$): δ= 16.5 (t, C3‟‟), 29.3 (t, C4), 31.7 (t, C2‟‟), 43.8 (t, C1‟‟), 44.3 (t, C3), 54.3 (q, O-CH_3), 55.9 (d, C1), 77.8 (s, CA1), 80.4 (s, CA2), 114.7 (d, C2‟), 120.4 (d, C3‟), 126.4 (d, C7), 127.3 (d, C6), 127.7 (d, C5), 129.3 (d, C8), 134.1 (s, C4a), 136.0 (s, C8a), 154.6 (s, C4‟)

GC-MS:
Method: D

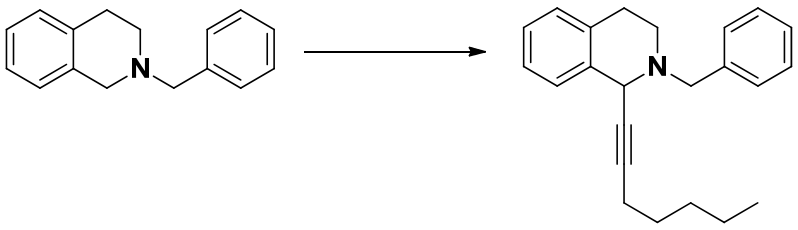
Retention time: 12.41
Main fragments: 341 (34), 340 (46), 339 (100), 338 (83), 178 (18), 176 (50), 155 (19), 141 (67), 120 (22), 115 (31)

High-Res MS:

Calculated $[M+H]^+$: 340.1463
Found: 340.1456

4.1.3 Alkynylation on 2-Benzyl-1,2,3,4-Tetrahydroisoquinolines

1-(hept-1-yn-1-yl)-2-benzyl-1,2,3,4-tetrahydroisoquinoline (5a)



$C_{16}H_{17}N$
M = 223.31

2c

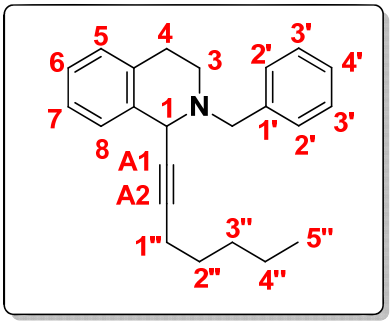
$C_{23}H_{27}N$
M = 317.47

5a

Prepared according to General Procedure **A** (p. 117) and **C** (p. 117).
The product was isolated by preparative TLC ($CHCl_3$).

Yield:
General Procedure A: 30% (19 mg, 0.06 mmol)
General Procedure C: 80% (51 mg, 0.16 mmol)
Appearance: light yellow oil
TLC: R_f = 0.65 (PE:$CHCl_3$ = 3:2)

NMR:



^{1}H-NMR (200 MHz, $CDCl_3$): 0.92 (t, 3H, H5″), 1.29-1.62 (m, 6H, H2″-H4″), 2.17-2.30 (m, 2H, H1″), 2.70-3.08 (m, 4H, H4, H3), 3.86 (dt, ^{3}J=17Hz, ^{4}J=7.8Hz, 2H, Ph-CH_2), 4.56 (s, 1H, H1), 7.05-7.50 (m, 9H, H5-H8, H2′-H4′)

^{13}C-NMR (50 MHz, $CDCl_3$): δ = 14.2 (q, C5″), 18.9 (t, C1″), 22.3 (t, C4″), 28.8 (t, C2″), 29.1 (t, C4), 31.2 (t, C3″), 45.7 (t, C3), 54.2 (t, Ph-CH_2), 59.6 (d, C1), 78.0 (s, CA1), 87.3 (s, CA2), 125.8 (d, C7), 126.8 (d, C4′), 127.2 (d, C6), 127.8 (d, C5),

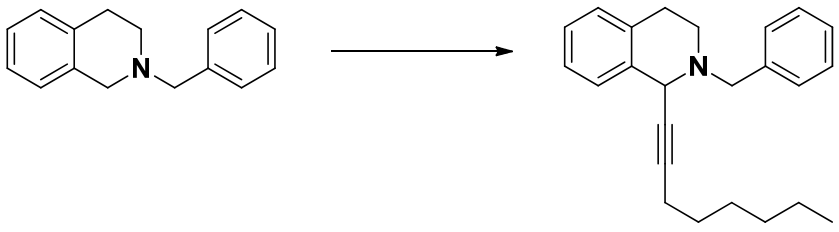
128.4 (d, C3'), 129.0 (d, C8), 129.4 (d, C2'), 133.9 (s, C4a), 136.4 (s, C8a), 138.6 (s, C1')

GC-MS:
Method: B
Retention time: 10.50
Main fragments: 317 (M+, 34), 316 (81), 290 (26), 246 (48), 226 (31), 155 (42), 142 (27), 141 (31), 116 (25), 115 (28), 105 (38), 91 (100)

HR MS:

Calculated $[M+H]^+$: 318.2216
Found: 318.2206

1-(oct-1-yn-1-yl)-2-benzyl-1,2,3,4-tetrahydroisoquinoline (5b)



$C_{16}H_{17}N$
M = 223.31

2c

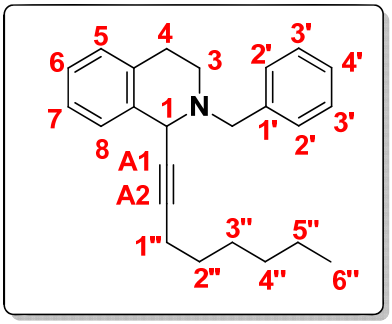
$C_{24}H_{29}N$
M = 331.49

5b

Prepared according to General Procedure **A** (p. 117).
The product was isolated by preparative TLC ($CHCl_3$).

Yield: 40% (27 mg, 0.08 mmol)
Appearance: yellow oil
TLC: R_f = 0.62 (PE:$CHCl_3$ = 3:2)

NMR:



^{1}H-NMR (200 MHz, $CDCl_3$): 0.77-1.04 (m, 3H, H6″), 1.21-1.68 (m, 8H, H2″-H5″), 2.20-2.32 (m, 2H, H1″), 2.65-3.10 (m, 4H, H4, H3), 3.78-3.97 (m, 2H, Ph-CH_2), 4.57 (s, 1H, H1), 7.05-7.51 (m, 9H, H5-H8, H2′-H4′)

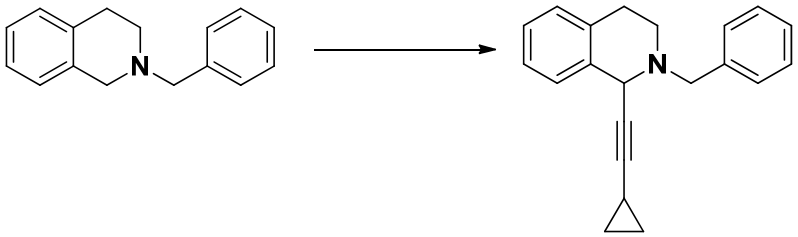
^{13}C-NMR (200 MHz, $CDCl_3$): 14.4 (q, C6″), 19.2 (t, C1″), 22.9 (t, C5″), 28.9 (t, C2″), 29.3 (t, C4″), 29.3 (t, C4), 31.7 (t, C3″), 45.9 (t, C3), 54.4 (t, Ph-CH_2), 59.8 (d, C1), 78.1 (s, CA1), 87.6 (s, CA2), 126.0 (d, C7), 127.0 (d, C4′), 127.4 (d, C6), 128.0 (d, C5), 128.6 (d, C3′), 129.2 (d, C8), 129.6 (d, C2′), 134.1 (s, C4a), 136.6 (s, C8a), 138.8 (s, C1′)

GC-MS:
Method: B
Retention time: 11.01
Main fragments: 330 (14), 246 (15), 155 (20), 142 (17), 141 (18), 116 (15), 115 (19), 105 (32), 91 (100)

HR MS:

Calculated $[M+H]^+$: 332.2373
Found: 332.2355

Rac-1-(cyclopropylethynyl)-2-benzyl-1,2,3,4-tetrahydroisoquinoline (5c)



$C_{16}H_{17}N$
M = 223.31

2c

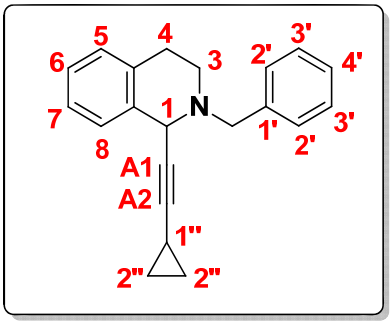
$C_{21}H_{21}N$
M = 287.40

5c

Prepared according to General Procedure **A** (p. 117).
The product was isolated by preparative TLC ($CHCl_3$).

Yield: 53% (30 mg, 0.11 mmol)
Appearance: light orange oil
TLC: R_f = 0.45 (PE:EtOAc = 20:1)

NMR:



^{1}H-NMR (200 MHz, $CDCl_3$): δ = 0.60-0.88 (m, 4H, H2″), 1.19-1.31 (m, 1H, H1″), 2.62-3.09 (m, 4H, H4, H3), 3.68-3.96 (m, 2H, Ph-CH_2), 4.54 (s, 1H, H1), 7.01-7.56 (m, 9H, H5-H8, H2′-H4′)

^{13}C-NMR (50 MHz, $CDCl_3$): δ = 0.0 (d, C1″), 8.8 (t, C2″), 29.3 (t, C4), 45.9 (t, C3), 54.4 (t, Ph-CH_2), 59.7 (d, C1), 73.4 (s, CA1), 90.6 (s, CA2), 126.0 (d, C7), 127.0 (d, C4′), 127.40 (d, C6), 128.0 (d, C5), 128.6 (d, C3′), 129.2 (d, C8), 129.6 (d, C2′), 134.2 (s, C4a), 136.4 (s, C8a), 138.8 (s, C1′)

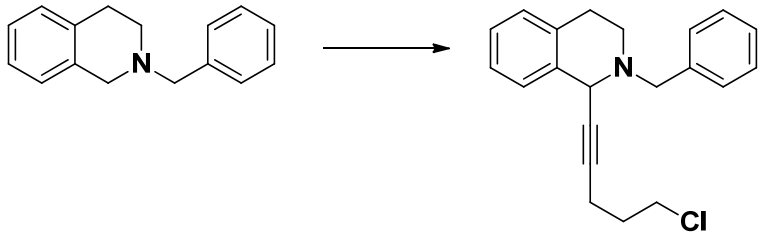
GC-MS:
Method: B

Retention time: 10.04
Main fragments: 287 (21), 286 (59), 281 (19), 208 (25), 207 (100), 129 (30), 96 (25), 91 (61), 73 (31), 70 (63), 61 (56)

HR MS:

Calculated $[M+H]^+$: 288.1747
Found: 288.1738

1-(5-chloropent-1-yn-1-yl)-2-benzyl-1,2,3,4-tetrahydroisoquinoline (5d)



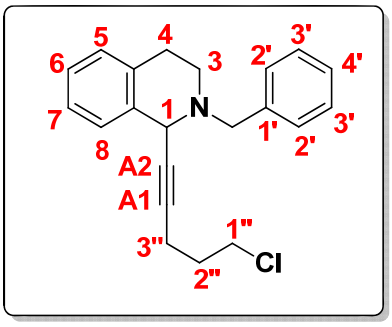
$C_{16}H_{17}N$
M= 223.31
2c

$C_{21}H_{22}ClN$
M=323.86
5d

Prepared according to General Procedure **A** (p. 117).
The product was isolated by preparative TLC ($CHCl_3$).

Yield: 48% (31mg, 0.10mmol)
Appearance: light yellow oil
TLC: R_f = 0.4 (PE:EtOAc = 20:1)

NMR:



^{1}H-NMR (200 MHz, $CDCl_3$): δ = 1.98 (qui, ^{3}J=6.6 Hz, 2H, H2″), 2.46 (dt, ^{3}J=6.8 Hz, ^{4}J=2.0 Hz, 2H, H3″), 2.68-2.86 (m, 2H, H4), 2.88-3.01 (m, 2H, H3), 3.67 (t, ^{3}J=6.4 Hz, 2H, H1″), 3.80 (d, ^{3}J=13.2 Hz, 1H, Ph-CH_2), 3.90 (d, ^{3}J=13.2 Hz, 1H, Ph-CH_2), 4.57 (s, 1H, H1), 7.05-7.49 (m, 9H, H5-H8, H2′-H4′)

^{13}C-NMR (50 MHz, $CDCl_3$): δ = 16.5 (t, C3″), 31.8 (t, C2″), 43.9 (t, C1″), 45.8 (t, C3), 54.2 (t, Ph-CH_2), 59.7 (d, C1), 79.3 (s, CA2), 85.2 (s, CA1), 125.9 (d, C7), 127.0 (d, C4′), 127.3 (d, C6), 127.8 (d, C5), 128.5 (d, C3′), 129.2 (d, C8), 129.4 (d, C2′), 134.1 (s, C4a), 136.2 (s, C8a), 138.5 (s, C1′)

GC-MS:
Method: B
Retention time: 10.99
Main fragments: 322 (24), 296 (13), 246 (24), 232 (13), 176 (21), 141 (36), 128 (15), 115 (22), 105 (29), 91 (100), 65 (15)

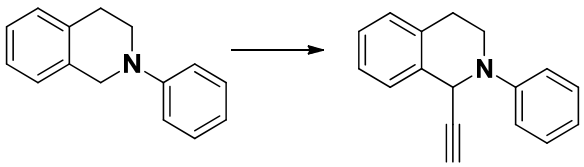
HR MS:

Calculated $[M+H]^+$: 324.1514
Found: 324.1504

4.2 One-pot Decarboxylation-Alkynylation reactions

4.2.1 Phenyl-Tetrahydroisoquinolines

Rac-1-ethynyl-2-phenyl-1,2,3,4-tetrahydroisoquinoline (X)



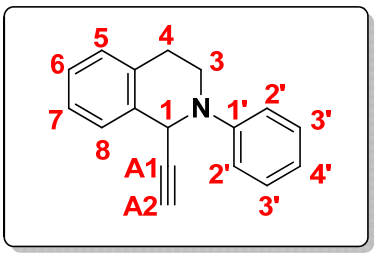
$C_{15}H_{15}N$
M = 209.29
2a

$C_{17}H_{15}N$
M = 233.31
3h

Prepared according to General Procedure **C** (p. 117) and **D** (p. 117).
The product was purified via preparative TLC (PE:$CHCl_3$ = 3:1).

Yield:
General Procedure C: 90% (42 mg, 0.18 mmol)
General Procedure D: 80% (75 mg, 0.32 mmol)
Appearance: colorless oil
TLC: R_f= 0.70 ($CHCl_3$)

NMR:



^{1}H-NMR ($CDCl_3$, 200MHz): δ = 2.33 (d, 1H, HA2), 3.00 (m, 2H, H4), 3.59 (m, 2H, H3), 5.48 (s, 1H, H1), 6.91 (t, ^{3}J=7.2 Hz, 1H, H4'), 7.03-7.42 (m, 8H, H5-H8, H2', H3')

^{13}C-NMR ($CDCl_3$, 50MHz): δ = 29.13 (t, C4), 43.42 (t, C3), 51.85 (d, C1), 73.07 (d, CA2), 83.18 (s, CA1), 116.87 (d, C2'), 120.13 (d, C4'), 126.66 (d, C7), 127.56 (d,

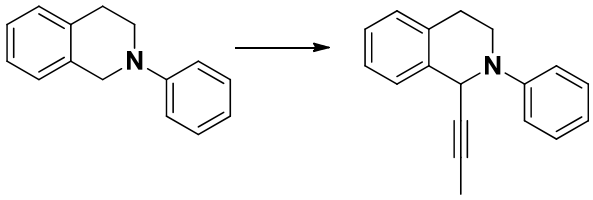
C6), 127.73 (d, C5), 129.31 (d, C8), 129.51 (d, C3'), 134.59 (s, C4a), 135.16 (s, C8a), 149.61 (s, C1')

GC-MS:
Method: A
Retention time: 5.87 min
Main fragments: 233 (M^+, 79), 232 (100), 208 (22), 128 (86), 104 (22), 77 (21)

HR MS:

Calculated $[M+H]^+$: 234.1277
Found: 234.1271

Rac-1-(propyn-1-yl)-2-phenyl-1,2,3,4-tetrahydroisoquinoline (3i)



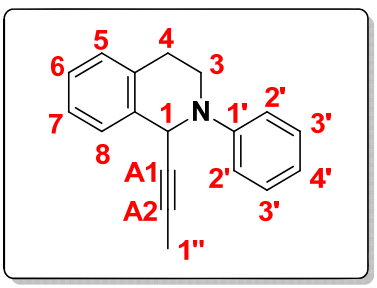
$C_{15}H_{15}N$
M = 209.29
2a

$C_{18}H_{17}N$
M = 247.33
3i

Prepared according to General Procedure **C** (p. 117) and **D** (p. 117).
The product was purified via preparative TLC (PE:$CHCl_3$ = 3:1).

Yield:
General Procedure C: 80% (40 mg, 0.16 mmol)
General Procedure D: 32% (32 mg, 0.13 mmol)
Appearance: light yellow oil
TLC: R_f= 0.18 (PE:$CHCl_3$ = 4:1)

NMR:



^{1}H-NMR (DMSO, 200MHz): δ = 1.77 (s, 3H, H1″), 2.90-3.22 (m, 2H, H4), 3.52-3.75 (m, 2H, H3), 5.42 (s, 1H, H1), 6.79-7.50 (m, 9H, H5-H8, H2′-H4′)

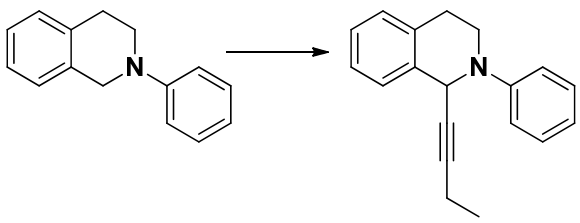
^{13}C-NMR (DMSO, 50MHz): 2.8 (q, C1″), 27.6 (t, C4), 41.6 (t, C3), 49.7 (d, C1), 78.4 (s, CA2), 79.7 (s, CA1), 115.3 (d, C2′), 118.2 (d, C4′), 125.5 (d, C7), 126.5 (d, C6), 126.9 (d, C5), 128.2 (d, C8), 128.5 (d, C3′), 133.4 (s, C4a), 135.4 (s, C8a), 148.5 (s, C1′)

GC-MS:
Method: A
Retention time: 6.22
Main fragments: 247 (M^+, 62), 246 (100), 142 (23), 141 (51), 114 (15)

HR MS:

Calculated $[M+H]^+$: 248.1434
Found: 248.1422

Rac-1-(butyn-1-yl)-2-phenyl-1,2,3,4-tetrahydroisoquinoline (3j)



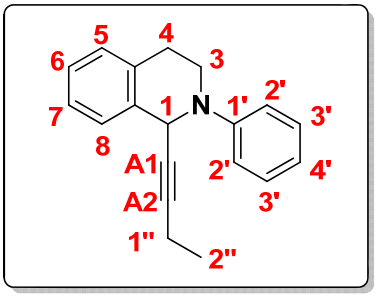
$C_{15}H_{15}N$
M = 209.29
2a

$C_{19}H_{19}N$
M = 261.36
3j

Prepared according to General Procedure **C** (p. 117) and **D** (p. 117).
The product was purified via preparative TLC (PE:$CHCl_3$ = 3:1).

Yield:
General Procedure C: 90% (47 mg, 0.18 mmol)
General Procedure A: 47% (49 mg, 0.19 mmol)
Appearance: orange oil
TLC: R_f= 0.22 (PE:$CHCl_3$ = 4:1)

NMR:



^{1}H-NMR ($CDCl_3$, 200MHz): δ = 1.10 (t, ^{3}J=7.5Hz, 3H, H2″), 2.91 (dq, ^{3}J=7.4Hz, ^{4}J=1.8Hz, 2H, H1″), 2.92-3.28 (m, 2H, H4), 3.60-3.86 (m, 2H, H3), 5.48 (s, 1H, H1), 6.94 (t, ^{3}J=7.2Hz, 1H, H4′), 7.09-7.44 (m, 8H)

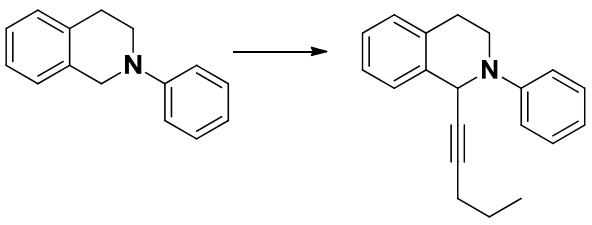
^{13}C-NMR ($CDCl_3$, 50MHz): δ = 12.81 (q, C2″), 14.29 (t, C1″), 29.13 (t, C4), 43.52 (t, C3), 51.94 (d, C1), 78.71 (s, CA2), 86.86 (s, CA1), 116.76 (d, C2′), 119.57 (d, C4′), 126.46 (d, C7), 127.29 (d, C6), 127.60 (d, C5), 129.15 (d, C8), 129.36 (d, C3′), 134.52 (s, C4a), 136.54 (s, C8a), 149.88 (s, C1′)

GC-MS:
Method: A
Retention time: 6.33
Main fragments: 261 (M^+, 69), 260 (100), 155 (19), 141 (65), 128 (23), 114 (40), 77 (25)

HR MS:

Calculated $[M+H]^+$: 262.1590
Found: 262.1584

Rac-1-(pentyn-1-yl)-2-phenyl-1,2,3,4-tetrahydroisoquinoline (3k)



$C_{15}H_{15}N$
M = 209.29

2a

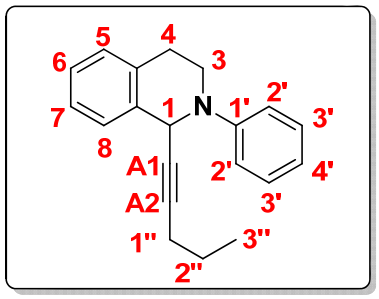
$C_{20}H_{21}N$
M = 275.39

3k

Prepared according to General Procedure **C** (p. 117) and **D** (p. 117).
The product was purified via preparative TLC (PE:$CHCl_3$ = 3:1).

Yield:
General Procedure C: 85% (47 mg, 0.17 mmol)
General Procedure D: 95% (105 mg, 0.38 mmol)
Appearance: orange oil
TLC: R_f= 0.25 (PE:$CHCl_3$ = 4:1)

NMR:



^{1}H-NMR (200 MHz, DMSO): δ = 0.87 (t, ^{3}J=7.3Hz, 3H, H3″), 1.44 (sext, ^{3}J=7.2Hz, 2H, H2″), 2.10 (dt, ^{3}J=6.8Hz, J=2Hz, 2H, H1″), 2.88-3.21 (m, 2H, H4), 3.32-3.84 (m, 2H, H3), 5.44 (s, 1H, H1), 6.88 (t, ^{3}J=7.1Hz, 1H, H4′), 7.03-7.41 (m, 8H, H5-H8, H2′, H3′)

^{13}C-NMR (50 MHz, APT, DMSO): δ = 12.8 (q, C3″), 19.6 (t, C1″), 21.4 (t, C2″), 27.8 (t, C4), 41.7 (t, C3), 50.2 (d, C1), 79.8 (s, CA2), 84.1 (s, CA1), 115.9 (d, C2′), 118.7 (d, C4′), 125.8 (d, C7), 126.8 (d, C6), 127.2 (d, C5), 128.5 (d, C8), 128.8 (d, C3′), 133.7 (s, C4a), 135.8 (s, C8a), 149.0 (s, C1′)

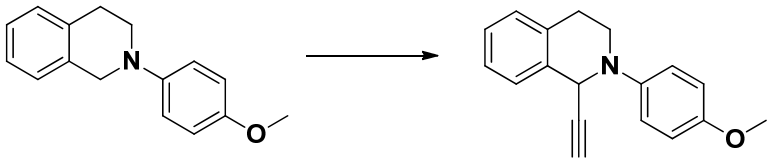
GC-MS:
Method: A
Retention time: 6.57
Main fragments: 275 (M^+, 65), 274 (100), 155 (30), 141 (23), 128 (16), 114 (25)

HR MS:

Calculated $[M+H]^+$: 276.1747
Found: 276.1744

4.2.2 Pmp-Tetrahydroisoquinolines

Rac-1-ethynyl-2-(4-methoxyphenyl)-1,2,3,4-tetrahydroisoquinoline (4g)



$C_{16}H_{17}NO$
M = 239.31

2b

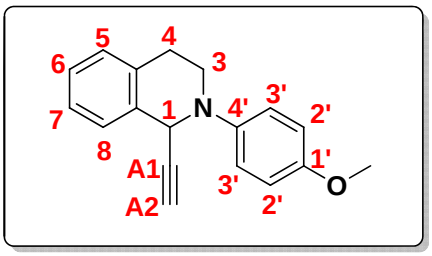
$C_{18}H_{17}NO$
M = 263.33

4g

Prepared according to General Procedure **C** (p. 117).
The product was purified via preparative TLC ($CHCl_3$).

Yield: 32% (25mg, 0.09mmol)
Appearance: light brown oil
TLC: R_f = 0.62 ($CHCl_3$)

NMR:



^{1}H-NMR (200 MHz, $CDCl_3$): δ = 2.30 (d, ^{3}J=2,1Hz, 1H, HA2), 2.89 (td, ^{3}J=3.5Hz, ^{3}J=3.5Hz, ^{3}J=16.3Hz, 2H, H4), 3.12 (td, ^{3}J=8.3Hz, ^{3}J=8.3Hz, ^{3}J=16.6Hz, 2H, H3), 3.53 (dd, ^{3}J=3.6Hz, ^{3}J=8,4Hz, 3H, O-CH_3), 5.32 (d, ^{3}J=1,9Hz, 1H, H1), 6.84-6.93 (m, 2H, H3'), 7.12-7.33 (m, 6H, H5-H8, H2')

^{13}C-NMR (50 MHz, APT, $CDCl_3$): δ = 28.9 (t, C4), 43.6 (t, C3), 53.5 (q, O-CH_3), 55.5 (d, C1), 73.4 (s, CA2), 82.6 (s, CA1), 114.4 (d, C2'), 119.9 (d, C3'), 126.2 (d, C7), 127.1 (d, C6), 127.3 (d, C5), 129.1 (d, C8), 134.0 (s, C4a), 134.9 (s, C8a), 143.8 (s, C1'), 154.2 (s, C4')

GC-MS:
Method: A
Retention time: 10.24

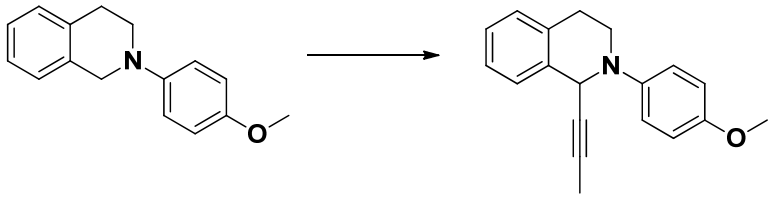
Main fragments: 263 (M^+, 100), 262 (74), 240 (10), 239 (52), 238 (56), 236 (12),

224 (10), 207 (21), 135 (36), 134 (12), 129 (18), 128 (73), 127 (12), 120 (27), 115 (10), 104 (15), 103 (14), 77 (12)

HR MS:

Calculated $[M+H]^+$: 264.1383
Found: 264.1375

Rac-2-(4-methoxyphenyl)-1-propynyl-1,2,3,4-tetrahydroisoquinoline (4h)



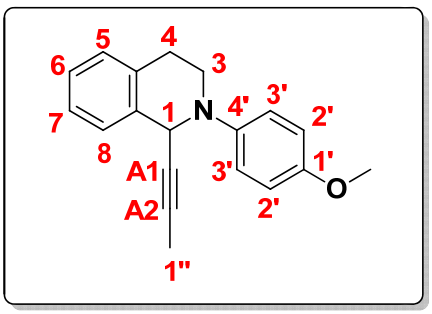
$C_{16}H_{17}NO$
M = 239.31
2b

$C_{19}H_{19}NO$
M = 277.36
4h

Prepared according to General Procedure **C** (p. 117).
The product was purified via preparative TLC ($CHCl_3$).

Yield: 47% (39mg, 0.14mmol)
Appearance: redbrown oil
TLC: R_f = 0.55 ($CHCl_3$)

NMR:



^{1}H-NMR (200 MHz, $CDCl_3$): δ = 1.73 (d, ^{3}J=2.2Hz, 3H, H1"), 2,87 (td, ^{3}J=16.2Hz, ^{4}J=3.6Hz, ^{4}J=3.6Hz, 1H, H4), 3.10 (ddd, ^{3}J=16.5Hz, ^{4}J=9.7Hz, ^{4}J=6.8Hz, 1H, H4),

3.50-3.61 (m, 2H, H3), 3.78 (s, 3H, O-CH_3), 5.26 (d, ^{4}J=1.9Hz, 1H, H1), 6,81-6,92 (m, 2H, H3'), 7.11-7.31 (m, 4H, H5-H8, H2')

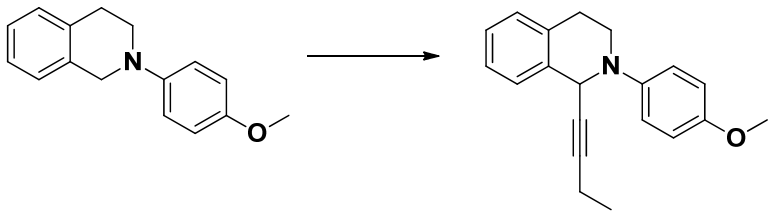
^{13}C-NMR (50 MHz, APT, $CDCl_3$): δ = 3.7 (q, C1''), 28.8 (t, C4), 44.0 (t, C3), 53.4 (q, O-CH_3), 55.5 (d, C1), 78.1 (s, CA1), 81.3 (s, CA2), 114.4 (d, C2'), 119.6 (d, C3'), 126.0 (d, C7), 127.0 (d, C6), 127.3 (d, C5), 129.0 (d, C8), 133.9 (s, C4a), 136.2 (s, C8a), 144.1 (s, C1'), 153.9 (s, C4')

GC-MS:
Method: D
Retention time: 10.13
Main fragments: 277 (M^+, 100), 276 (77), 208 (15), 207 (52), 191 (10), 142 (28), 141 (71), 118 (17), 117 (23), 116 (13), 115 (20), 91 (17), 70 (10), 61 (14)

HR MS:

Calculated $[M+H]^+$: 278.1539
Found: 278.1535

Rac-1-butynyl-2-(4-methoxyphenyl)-1,2,3,4-tetrahydroisoquinoline (4i)



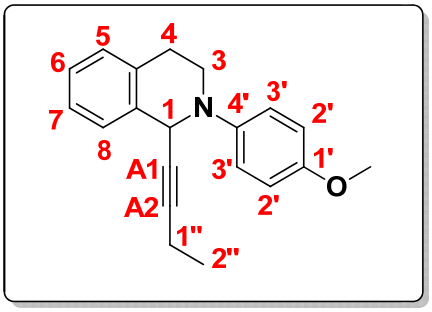
$C_{16}H_{17}NO$
M = 239.31
2b

$C_{20}H_{21}NO$
M = 291.39
4i

Prepared according to General Procedure **C** (p. 117).
The product was purified via preparative TLC ($CHCl_3$).

Yield: 67% (39 mg, 0.13 mmol)
Appearance: light orange oil
TLC: R_f = 0.62 ($CHCl_3$)

NMR:



^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.05 (t, ^{3}J=7.4 Hz, 3H, H2″), 2.14 (dq, ^{3}J=7.5 Hz, ^{4}J=2 Hz, 2H, H1″), 2.82-3.29 (m, 2H, H4), 3.40-3.71 (m, 2H, H3), 3.82 (s, 3H, O-CH_3), 5.31 (s, 1H, H1), 6.91 (d, ^{3}J=9 Hz, 2H, H3′), 7.09 (d, ^{3}J=9 Hz, 2H, H2′), 7.15-7.37 (m, 4H, H5-H8)

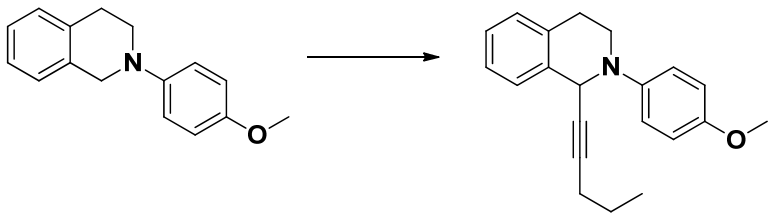
^{13}C NMR (50 MHz, APT, $CDCl_3$): δ = 12.7 (q, C2″), 14.3 (t, C1″), 29.2 (t, C4), 44.3 (t, C3), 53.9 (q, O-CH_3), 55.8 (d, C1), 78.4 (s, CA2), 87.5 (s, CA1), 114.5 (d, C3′), 120.2 (d, C3′), 126.2 (d, C7), 127.1 (d, C6), 127.6 (d, C5), 129.2 (d, C8), 134.1 (s, C4a), 136.5 (s, C8a), 144.5 (s, C1′), 154.2 (s, C4′)

GC-MS:
Method: D
Retention time: 10.30
Main fragments: 291 (60), 290 (43), 155 (32), 141 (100), 128 (36), 115 (57), 77 (18)

HR MS:

Calculated $[M+H]^+$: 292.1696
Found: 292.1698

Rac-2-(4-methoxyphenyl)-1-pentynyl-1,2,3,4-tetrahydroisoquinoline (4j)



$C_{16}H_{17}NO$
M = 239.31

2b

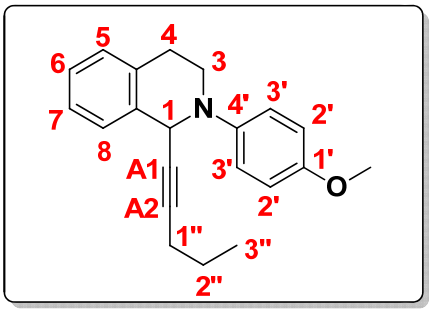
$C_{21}H_{23}NO$
M = 305.41

4j

Prepared according to General Procedure **C** (p. 117).
The product was purified via preparative TLC ($CHCl_3$).

Yield: 57% (52mg, 0.17mmol)
Appearance: orange oil
TLC: R_f = 0.65 ($CHCl_3$)

NMR:



^{1}H-NMR (200 MHz, $CDCl_3$): δ = 0.83 (t,^{3}J=7.3Hz, 3H, H3''), 1.24-1.49 (m, 2H, H1''), 2.05 (dt, ^{3}J=6.7Hz, ^{4}J=2.1Hz, 2H, H2''), 2.87 (td, ^{3}J=16.3Hz, ^{4}J=2.1Hz, 1H, H4), 3.09 (ddd, ^{3}J=16.5Hz, ^{4}J=9.9Hz, ^{4}J=6.7Hz, 1H, H4), 3.41-3.58 (m, 2H, H3), 3.77 (s, 3H, O-CH_3), 5.28 (s, 1H, H1), 6.82-6.91 (m, 2H, H3'), 6.99-7.09 (m, 2H, H2'), 7.11-7.31 (m, 4H, H5-H8)

^{13}C-NMR (50 MHz, APT, $CDCl_3$): δ = 13.4 (q, C3''), 20.8 (t, C1''), 22.2 (t, C2''), 29.0 (t, C4), 44.0 (t, C3), 53.8 (q, O-CH_3), 55.6 (d, C1), 79.1 (s, CA2), 85.8 (s, CA1), 114.3 (d, C3'), 119.9 (d, C2'), 126.0 (d, C7), 126.9 (d, C6), 127.4 (d, C5), 129.0 (d, C8), 133.8 (s, C4a), 136.3 (s, C8a), 144.3 (s, C1'), 154.0 (s, C4')

GC-MS:
Method: B

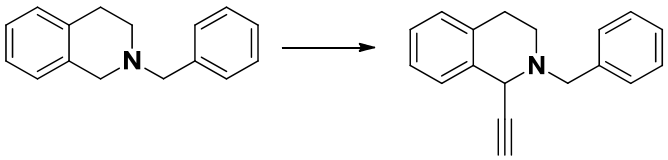
Retention time: 10.66 min
Main fragments: 305 (M^+, 43), 304 (33), 282 (10), 281 (33), 209 (15), 208 (23), 207 (100), 190 (12), 155 (13), 141 (11), 133 (8), 128 (6), 115 (8), 96 (12), 88 (7), 73 (15), 70 (27)

HR MS:

Calculated $[M+H]^+$: 306.1852
Found: 306.1840

4.2.3 Benzyl-Tetrahydroisoquinolines

Rac-1-Ethynyl-2-benzyl-1,2,3,4-tetrahydroisoquinoline (5e)



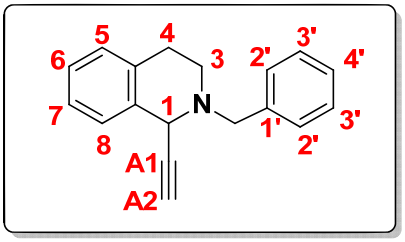
$C_{16}H_{17}N$
M = 223.31
2c

$C_{18}H_{17}N$
M = 247.33
5e

Prepared according to General Procedure **C** (p. 117).
The product was purified via preparative TLC (PE:$CHCl_3$ = 3:2).

Yield: 81% (40 mg, 0.16 mmol)
Appearance: light brown oil
TLC: R_f= 0.54 (PE:$CHCl_3$ = 3:2)

NMR:



^{1}H-NMR (200 MHz, $CDCl_3$): δ = 2.47 (m, 1H, HA2), 2.70-3.12 (m, 4H, H4, H3), 3.87 (m, 2H, Ph-CH_2), 4.60 (s, 1H, H1), 7.08-7.50 (m, 9H, H5-H8, H2'-H4')

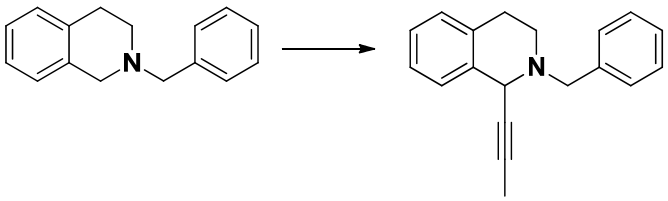
^{13}C-NMR (50 MHz, $CDCl_3$): δ = 29.2 (t, C4), 45.7 (t, C3), 53.9 (t, Ph-CH_2), 59.6 (d, C1), 74.9 (d, CA2), 81.9 (s, CA1), 126.1 (d, C7), 127.4 (d, C4'), 127.5 (d, C6), 127.8 (d, C5), 128.6 (d, C3'), 129.4 (d, C8), 129.5 (d, C2'), 134.3 (s, C4a), 135.3 (s, C8a), 138.5 (s, C1')

GC-MS:
Method: A
Retention time: 6.58
Main fragments: 247 (M^+, 25), 246 (73), 223 (34), 222 (72), 220 (69), 156 (35), 128 (92), 91 (100)

HR MS:

Calculated $[M+H]^+$: 248.1434
Found: 248.1428

Rac-1-(propyn-1-yl)-2-benzyl-1,2,3,4-tetrahydroisoquinoline (5f)



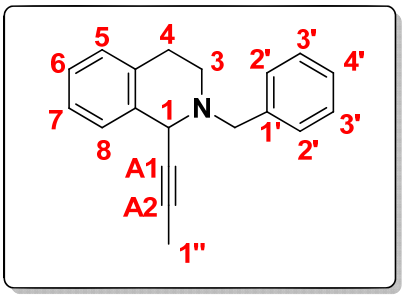
$C_{16}H_{17}N$
M = 223.31
2c

$C_{19}H_{19}N$
M = 261.36
5f

Prepared according to General Procedure **C** (p. 117).
The product was purified via preparative TLC (PE:$CHCl_3$ = 3:2).

Yield: 70% (37 mg, 0.14 mmol)
Appearance: light yellow oil
TLC: R_f= 0.61 (PE:$CHCl_3$ = 3:2)

NMR:



^{1}H-NMR (200 MHz, $CDCl_3$): δ = 1.89 (s, 3H, H1″), 2.66-3.09 (m, 4H, H4, H3), 3.86 (m, 2H, Ph-CH_2), 4.54 (s, 1H, H1), 7.05-7.50 (m, 9H, H5-H8, H2′-H4′)

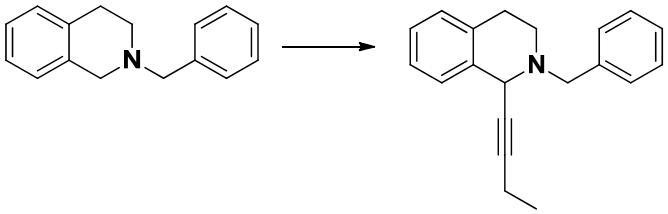
^{13}C-NMR (50 MHz, $CDCl_3$): δ = 4.06 (q, C1″), 29.3 (t, C4), 45.8 (t, C3), 54.5 (t, Ph-CH_2), 59.7 (d, C1), 77.5 (s, CA2), 82.7 (s, CA1), 126.1 (d, C7), 127.1 (d, C4′), 127.4 (d, C6), 128.0 (d, C5), 128.6 (d, C3′), 129.3 (d, C8), 129.5 (d, C2′), 134.2 (s, C4a), 136.5 (s, C8a), 138.9 (s, C1′)

GC-MS:
Method: A
Retention time: 6.20
Main fragments: 261 (M^+, 39), 260 (100), 246 (43), 234 (49), 170 (31), 142 (40), 141 (88), 129 (28), 115 (28), 105 (24), 91 (72)

HR MS:

Calculated $[M+H]^+$: 262.1590
Found: 262.1588

Rac-1-(butyn-1-yl)-2-benzyl-1,2,3,4-tetrahydroisoquinoline (5g)



$C_{16}H_{17}N$
M = 223.31

2c

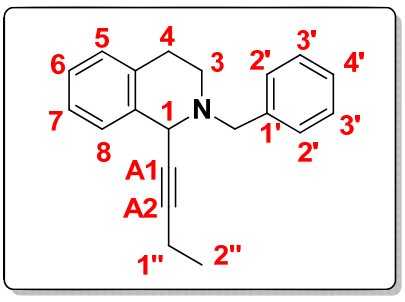
$C_{20}H_{21}N$
M = 275.39

5g

Prepared according to General Procedure **C** (p. 117).
The product was purified via preparative TLC (PE:$CHCl_3$ = 3:2).

Yield: 90% (50 mg, 0.18 mmol)
Appearance: light yellow oil
TLC: R_f= 0.61 (PE:$CHCl_3$ = 3:2)

NMR:



^{1}H-NMR (200 MHz, $CDCl_3$): δ = 1.19 (t, ^{3}J=7.4Hz, 3H, H2″), 2.18-2.35 (dq, ^{3}J=7.4Hz, ^{4}J=2.2Hz, 2H, H1″), 2.70-3.05 (m, 4H, H4, H3), 3.86 (dt, ^{3}J=17.3Hz, ^{3}J=8.4Hz, 2H, Ph-CH_2), 4.56 (s, 1H, H1), 7.08-7.50 (m, 9H, H5-H8, H2′-H4′)

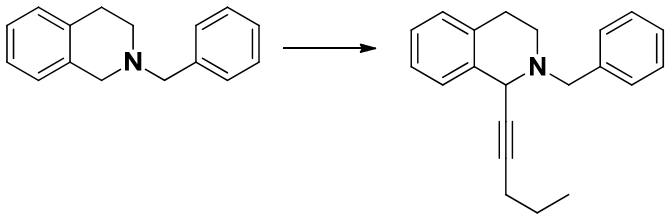
^{13}C-NMR (50 MHz, $CDCl_3$): δ = 12.9 (q, C2″), 14.7 (t, C1″), 29.3 (t, C4), 45.9 (t, C3), 54.4 (t, Ph-CH_2), 59.7 (d, C1), 77.5 (s, CA2), 88.8 (s, CA1), 126.0 (d, C7), 127.0 (d, C4′), 127.4 (d, C6), 128.0 (d, C5), 128.6 (d, C3′), 129.2 (d, C8), 129.6 (d, C2′), 134.2 (s, C4a), 136.6 (s, C8a), 138.8 (s, C1′)

GC-MS:
Method: B
Retention time: 9.19
Main fragments: 275 (M^+, 37), 274 (100), 247 (41), 246 (43), 184 (29), 155 (20), 141 (61), 115 (29), 105 (26), 91 (64)

HR MS:

Calculated $[M+H]^+$: 276.1742
Found: 276.1747

Rac-1-(pentyn-1-yl)-2-benzyl-1,2,3,4-tetrahydroisoquinoline (5h)

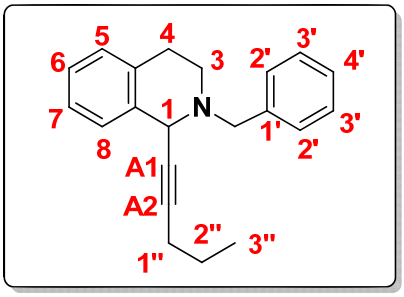


$C_{16}H_{17}N$	$C_{21}H_{23}N$
M = 223.31	M = 289.41
2c	5h

Prepared according to General Procedure **C** (p. 117).
The product was purified via preparative TLC (PE:$CHCl_3$ = 3:2).

Yield: 66% (38 mg, 0.13 mmol)
Appearance: light yellow oil
TLC: R_f= 0.67 (PE:$CHCl_3$ = 3:2)

NMR:



^{1}H-NMR (200 MHz, $CDCl_3$): δ = 0.91 (t, ^{3}J=7.2 Hz, 3H, H3″), 1.46 (sext, ^{3}J = 7.2 Hz, 2H, H2″), 2.12 (dt, ^{3}J=6.8 Hz, ^{4}J=2.1 Hz, 2H, H1″) 2.56-3.07 (m, 4H, H4, H3), 3.75 (dt, ^{3}J=16.9 Hz, ^{3}J=7.5 Hz, 2H, Ph-CH_2), 4.45 (s, 1H, H1), 6.93-7.38 (m, 9H, H5-H8, H2′-H4′)

^{13}C-NMR (50 MHz, $CDCl_3$): δ = 13.9 (q, C3″), 21.2 (t, C1″), 22.8 (t, C2″), 29.4 (t, C4), 45.9 (t, C3), 54.4 (t, Ph-CH_2), 59.8 (d, C1), 78.3 (s, CA2), 87.3 (s, CA1), 126.0 (d, C7), 127.0 (d, C4′), 127.4 (d, C6), 128.0 (d, C5), 128.6 (d, C3′), 129.2 (d, C8), 129.6 (d, C2′), 134.2 (s, C4a), 136.6 (s, C8a), 138.8 (s, C1′)

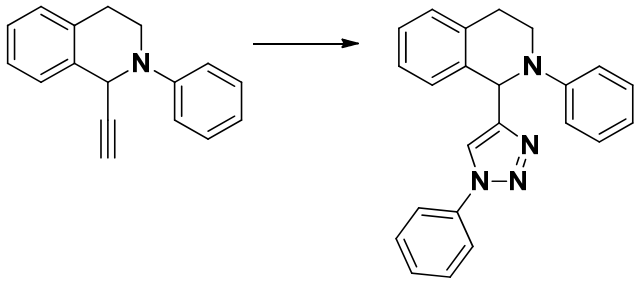
GC-MS:
Method: B
Retention time: 9.58
Main fragments: 289 (M^+, 41), 288 (100), 262 (37), 246 (45), 198 (26), 155 (34), 141 (29), 129 (20), 128 (22), 115 (25), 105 (28), 91 (67)

HR MS:

Calculated $[M+H]^+$: 290.1903
Found: 290.1892

4.3 Click reactions

2-phenyl-1-(1-phenyl-1H-1,2,3-triazol-4-yl)-1,2,3,4-tetrahydroisoquinoline (6a)



3h

$C_{17}H_{15}N$
M = 233.31

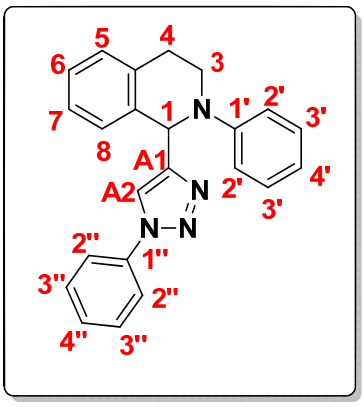
6a

$C_{23}H_{20}N_4$
M = 352.43

Alkyne **3h** (93 mg, 0.4 mmol, 1.0 equiv., in 1 ml MeCN) was put in a reaction vial. Under stirring, azidobenzene (48 mg, 0.4 mmol, 1.0 equiv.) was slowly added to the mixture via syringe. The reaction mixture was heated up to 60 °C and stirred at this temperature overnight. The reaction mixture was then diluted with ethyl acetate, washed with brine, dried over Na_2SO_4 and the solvent was evaporated. The resulting brown solid was washed with diethyl ether and filtrated.

Yield: 100% (140mg, 0.4 mmol)
Appearance: light brown solid
Mp: 146-149° C
TLC: R_f= 0.175 ($CHCl_3$)

NMR:



^{1}H NMR (200MHz, d-6-DMSO): δ = 2.95-3.12 (m, 2H, H4), 3.57-3.87 (m, 2H, H3), 6.18 (s, 1H, H1), 6.68 (t, J=3Hz, 1H, Har), 6.91-7.04 (m, 2H, Har), 7.10-7.62 (m, 10H, Har), 7.76-7.88 (m, 2H, Har), 8.66 (s, 1H, HA2)
^{13}C NMR (50 MHz, d-6-DMSO): δ = 27.7 (t, C4), 42.0 (t, C3), 54.7 (d, C1), 114.2 (d, C2′), 117.5 (d, CA2), 120.0 (d, C2″), 120.7 (d, C4′), 126.2 (d, C7), 127.0 (d, C6), 128.0 (d, C5), 128.5 (d, C8), 128.7 (d, C3″, C4″), 129.2 (d, C3″), 130.0 (d, C3′), 135.0 (s, C8a), 136.4 (s, C4a), 136.7 (s, CA1), 148.9 (s, C1″), 150.7 (s, C1‘)

HR MS:

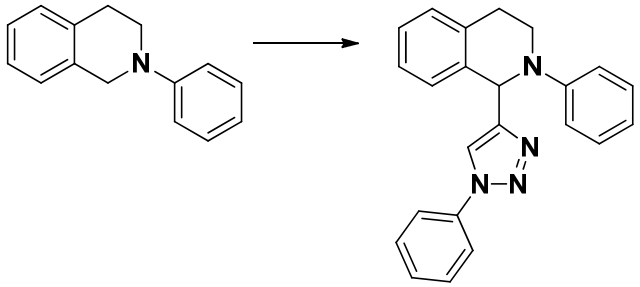
Calculated $[M+H]^+$: 353.1761
Found: 353.1749

One-pot Decarboxylation-Alkynylation-Click reactions

General Procedure E:

CuCl (5.9 mg, 0.04mmol), MeCN (1 ml) and N-Phenyl-tetrahydroisoquinoline (0.4 mmol) were put into a reaction vial and the mixture was flushed with Ar. Then *t*-BuOOH (0.04 ml, 5-6M/decane) and propinoic acid (1.6 mmol) were added via syringe. The reaction mixture was heated up to 50 °C and stirred for 2 days. Then 0.4 mmol of azide were added and the resulting mixture was stirred at 60 °C overnight.

2-phenyl-1-(1-phenyl-1H-1,2,3-triazol-4-yl)-1,2,3,4-tetrahydroisoquinoline (6a)



2a

$C_{15}H_{15}N$
M = 209.29

7a

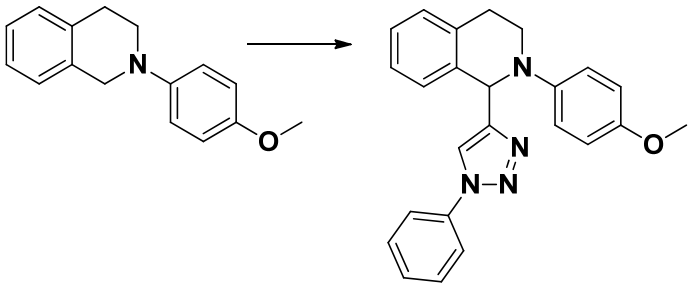
$C_{23}H_{20}N_4$
M = 352.43

Prepared according to the general procedure **E** (p. 160).

Workup: The reaction mixture was diluted with ethyl acetate, washed with brine, dried over Na_2SO_4 and the solvent was evaporated. The resulting brown solid was washed with diethyl ether and filtrated.

Yield: 90% (127 mg, 0.36 mmol)

2-(4-methoxyphenyl)-1-(1-phenyl-1H-1,2,3-triazol-4-yl)-1,2,3,4-tetrahydroisoquinoline (6b)



2b

$C_{16}H_{17}NO$
M = 239.31

6b

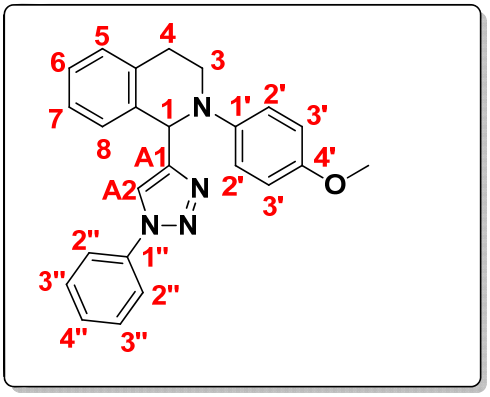
$C_{24}H_{22}N_4O$
M= 382.46

Prepared according to the general procedure **E** (p. 160).

Workup: The reaction mixture was diluted with ethyl acetate, washed with brine, dried over Na_2SO_4 and the solvent was evaporated. The resulting brown solid was washed with diethyl ether and filtrated.

Yield: 50% (191 mg, 0.2 mmol)
Appearance: light brown crystals
TLC: R_f = 0.85 (EE + 10 % Et_3N)
Mp: 150-151 °C

NMR:



^{1}H-NMR (200 MHz, $CDCl_3$): 2.80-3.10 (m, 2H, H4), 3.33-3.62 (m, 2H, H3), 3.65 (s,3H, -O-CH_3), 5.93 (s, 1H, H1), 6.73 (d, J=9Hz, 2H, Har), 6.88 (d, J=9Hz, 2H, Har), 7.06-7.43 (m, 7H, Har), 7.49-7.58 (m, 3H, Har)

^{13}C-NMR (50 MHz, APT, $CDCl_3$): δ = 28.5 (t, C4), 44.5 (t, C4), 55.6 (d or q, C1 or C6'), 57.4 (d or q, C1 or C6'), 114.6 (d, 2C), 118.4 (d, 2C), 119.8 (d, C5''), 120.4 (d, 2C), 126.3 (d), 127.0 (d), 128.2 (d), 128.5 (d), 128.7 (d), 129.6 (d), 134.8 (s), 135.0 (s), 137.0 (s), 143.9 (s, C1'), 151.1 (s), 153.4 (s, C4')

HR MS:

Calculated $[M+H]^+$: 383.1866
Found: 383.1856

5. H-D exchange reactions on Heterocycles

5.1 Deuteration on sp²-systems

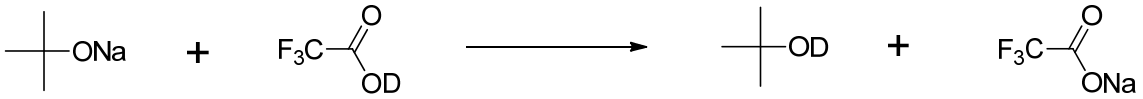
General procedure for the preparation of deuterated compounds in batch

Heteroarene (0.5 mmol, 1.0 equiv.), $Ru_3(CO)_{12}$ (16 mg, 0.01 mmol, 0.02 equiv.) and *t*-BuOD (5 equiv./deuteration position) were filled into a reaction vial with a screw cap septum. The vial was flushed with argon several times. The reaction mixture was then heated to 115°C and stirred at this temperature for 3h. After cooling to r.t. 10ml of *n*-hexane were added and the resulting solvent mixture was evaporated (azeotropic distillation of *t*-BuOH/*n*-hexane). Deuteration degrees were determined via ^{1}H-NMR.
In the case, where multiple cycles were applied, the same amount of $Ru_3(CO)_{12}$ and *t*-BuOD were added after the evaporation step again and the reaction was repeated.

General Procedure for the preparation of deuterated compounds in the microwave

Heteroarene (0.5 mmol, 1.0 equiv.), $Ru_3(CO)_{12}$ (16 mg, 0.01 mmol, 0.02 equiv.) and *t*-BuOD (10 equiv./deuteration position) were filled into a microwave vial. The vial was sealed and subsequently flushed with argon. The reaction mixture was then heated in the microwave to 115°C for 15min. After cooling to r.t. 10ml of *n*-hexane were added (azeotropic distillation of *t*-BuOH/*n*-hexane) and the resulting solvent mixture was evaporated. Deuteration degrees were determined via ^{1}H-NMR.

Synthesis of *t*-BuOD via CF_3COOD



A mixture of sodium-*t*-butoxide (480 mg, 5 mmol, 1.0 equiv.) and CF_3COOD (575 mg, 5 mmol, 1.0 equiv.) was stirred at room temperature for 1h. The product was purified via Kugelrohr distillation and obtained in 31% yield (147 mg).

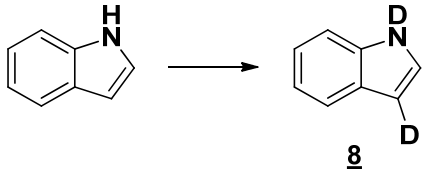
General note for ^{13}C NMR spectra of deuterated substances

Due to the existence of several isotopomers by incomplete deuteration and their interactions, signals in ^{13}C-spectra can split or decrease in intensity. Since the assignment of the split signals to the corresponding isotopomers is not trivial, only

the chemical shift of the most intense signal is reported and these signals are marked with an *.

5.1.1 Deuteration of electron-rich heteroarenes

1,3-Dideuteroindole (8)



8

C_8H_7N
M = 117.15

$C_8H_5D_2N$
M = 119.16

prep. via microwave protocol; substrate: 59 mg (0.5 mmol), amount of *t*-BuOD applied: 752 mg, 10 mmol = 10 equiv./D-position

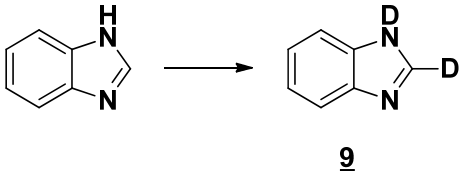
Deuteration grade: 90% (according to GC-MS, ^{1}H-NMR)

^{1}H-NMR (200 MHz, $CDCl_3$): δ = 6.53 (d, J=2.93 Hz, 0.09H, H3), 7.01-7.36 (m, 4H, H4-H7), 7.57-7.70 (m, 1H, H2), 7.81-8.0 (m, 0.11H, H1)

Deuterium NMR (400 MHz, $CHCl_3$): δ = 6.53 (s), 8.16 (s); (see Appendix A)

^{13}C-NMR (50 MHz, $CDCl_3$): δ = 102.9* (C3), 111.4* (C7), 120.1 (d, C6), 121.0*(C4), 122.2 (d, C5), 124.3* (C2), 128.0* (C4a), 136.0* (C7a)

1,2-Dideuterobenzimidazole (9)



9

$C_7H_6N_2$
M = 118.14

$C_7H_4D_2N_2$
M = 120.15

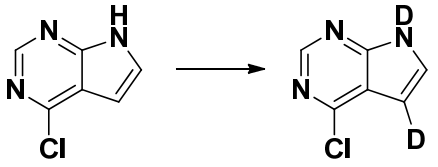
prep. via conventional heating; substrate: 60 mg (0.5 mmol), amount of *t*-BuOD applied: 376 mg, 5 mmol = 5 equiv./D-position

Deuteration grade: 71%

^{1}H-NMR (200 MHz, DMSO-d6): 7.11-7.28 (m, 2H, H5, H6), 7.52-7.66 (m, 2H, H4, H7), 8.27 (s, 0.29H, H2)

^{13}C-NMR (50 MHz, DMSO-d6): 116.0 (d, C4), 122.7 (d, C5), 142.9* (C2)

1,3-Dideutero-6-Chloro-7-deazapurine (10)



10

$C_6H_4ClN_3$ M = 153.57 → $C_6H_2D_2ClN_3$ M = 155.58

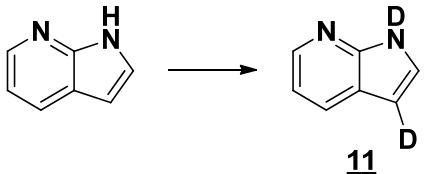
prep. via conventional heating; substrate: 77 mg (0.5 mmol), amount of *t*-BuOD applied: 376 mg, 5 mmol = 5equiv./D-position

Deuteration grade: 78%

^{1}H-NMR (200 MHz, DMSO-d6): 6.33 (d, J=3.13, 0.23H, H3), 7.42 (s, 1H, H2), 8.34 (s, 1H, H6), 12.31 (s, 1H, NH)

^{13}C-NMR (50 MHz, DMSO-d6): 99.7* (C7), 117.5* (C5), 129.2* (C8), 151.2 (s, C6), 151.4* (C2), 152.7 (s, C4)

1,3-Dideutero-7-azaindole (11)



11

$C_7H_6N_2$ M = 118.14 → $C_7H_4D_2N_2$ M = 120.15

prep. via microwave protocol; substrate: 60mg (0.5mmol), amount of *t*-BuOD applied: 752 mg, 10 mmol = 10 equiv./D-position; Purification via column chromatography (PE:EE 10:1)

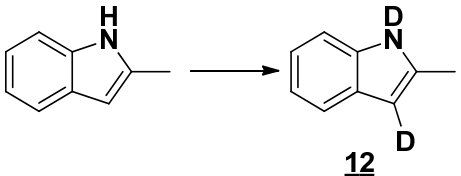
Yield: 87% (52 mg, 0.4 mmol)

Deuteration grade: 80%

^{1}H-NMR (200 MHz, $CDCl_3$): 6.49 (d, J= 3.52 Hz, 0.19H, H3), 7.01-7.17 (m, 1H, H2), 7.38 (s, 1H, H5), 7.96 (d, J= 7.83 Hz, 1H, H6), 8.35 (d, J= 3.91 Hz, 1H, H4), 12.02 (s, 0.22H, NH)

^{13}C-NMR (50 MHz, $CDCl_3$): 100.5* (C3), 115.7 (d, C5), 120.6* (C3a), 125.4* (C2), 129.1 (d, C4), 142.2 (d, C6), 148.8 (s, C7a)

1,3-Dideutero-2-methylindole (12)



12

C_9H_9N
M = 131.17

$C_9H_7D_2N$
M = 133.19

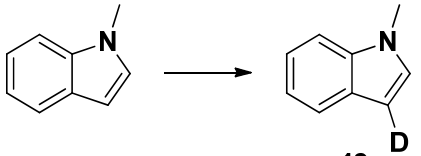
prep. via microwave protocol; substrate: 66 mg (0.5 mmol), amount of *t*-BuOD applied: 752 mg, 10 mmol = 10 equiv./D-position

Deuteration grade: 70%

^{1}H-NMR (200 MHz, $CDCl_3$): 2.44 (s, 3H, -CH_3), 6.26 (m, 0.29H, H3), 7.10-7.34 (m, 3H, H4-H6), 7.50-7.66 (m, 1H, H7)

^{13}C-NMR (50 MHz, $CDCl_3$): 14.0 (q, -CH_3), 100.7 (d, C3), 110.5 (d, C7), 119.9 (d, C5, C4), 121.2 (d, C6), 129.4 (s, C3a), 135.4 (s, C2), 136.3 (s, C7a)

3-Deutero-1-methylindole (13)



13

C_9H_9N
M = 131.17

C_9H_8DN
M = 132.18

prep. via microwave protocol; substrate: 66 mg (0.5 mmol), amount of *t*-BuOD applied: 752 mg, 10 mmol = 10 equiv./D-position

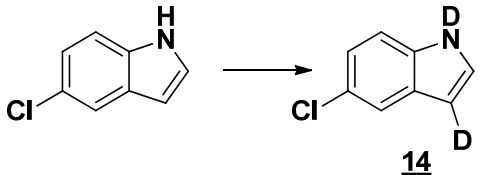
Deuteration grade: 85% (according to GC-MS, ^{1}H-NMR)

^{1}H-NMR ($CDCl_3$): 3.73 (s, 3H, CH_3), 6.44 (d, J=2.93 Hz, 0.16H, H3), 6.95-7.31 (m, 4H, H2, H5, H6, H4), 7.58 (d, J=7.43 Hz, 1H, H7)

Deuterium-NMR (400 MHz, $CHCl_3$): 6.44 (s); (see Appendix B)

^{13}C-NMR: 33.1 (q, CH_3), 101.2 (C3), 109.5 (d, C7), 119.5 (d, C5), 121.2 (d, C4), 121.8 (d, C6), 128.8 (s, C3a), 129.1* (C2), 137.0 (s, C7a)

1,3-D2-5-chloroindole (<u>14</u>)



<u>14</u>

C_8H_6ClN
M = 151.59

$C_8H_4D_2ClN$
M = 153.61

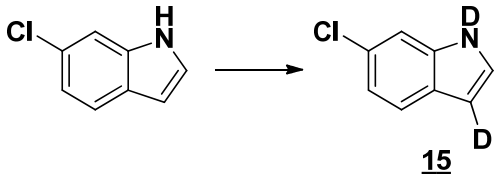
prep. via microwave protocol; substrate: 76 mg (0.5 mmol), amount of *t*-BuOD applied: 752 mg, 10 mmol = 10 equiv./D-position; Purification via column chromatography (PE:EE 5:1)

Yield: 92% (71 mg, 0.46 mmol)
Deuteration grade: 85%

^{1}H-NMR (200 MHz, $CDCl_3$): 6.47 (d, J=3.13 Hz, 0.15H, H3), 7.06- 7.24 (m, 3H, H2, H5, H6), 7.61 (d, J=1.76 Hz, 1H, H7), 8.03 (s, 0.21H, NH)

^{13}C-NMR (50 MHz, $CDCl_3$): 102.6* (C3), 112.3 (d, C7), 120.3 (d, C4), 122.5 (d, C6), 125.6* (C2), 125.8* (C5), 129.1* (C3a), 134.2* (C7a)

1,3-Dideutero-6-Chloroindole (15)



15

C_8H_6ClN
M = 151.59

$C_8H_4D_2ClN$
M = 153.61

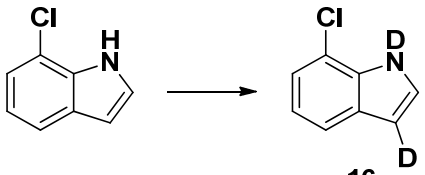
prep. via microwave protocol; substrate: 76 mg (0.5 mmol), amount of *t*-BuOD applied: 752 mg, 10 mmol = 10 equiv./D-position

Deuteration grade: 87%

^{1}H-NMR (200 MHz, $CDCl_3$): 6.56 (d, J= 2.93 Hz, 0.13H, H3), 7.07-7.23 (m, 2H, H2, H5), 7.37 (d, J= 1.76 Hz, 1H, H7), 7.58 (d, J= 8.41 Hz, 1H, H4), 8.05 (s, 0.22H, NH)

^{13}C-NMR (50 MHz, $CDCl_3$): 103.0* (C3), 111.2* (C7), 120.8* (C4), 121.8 (d, C5), 125.0* (C2), 126.6* (C3a), 128.1 (s, C6), 136.4* (C7a)

1,3-Dideutero-7-Chloroindole (16)



16

C_8H_6ClN
M = 151.59

$C_8H_4D_2ClN$
M = 153.61

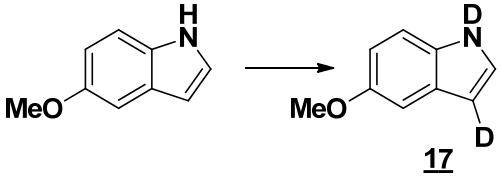
prep. via microwave protocol; substrate: 76 mg (0.5 mmol), amount of *t*-BuOD applied: 752 mg, 10 mmol = 10 equiv./D-position; Purification via column chromatography (PE:EE 5:1)

Yield: 83% (64 mg, 0.41 mmol)
Deuteration grade: 86%

^{1}H-NMR (200 MHz, $CDCl_3$): 6.62 (d, J= 3.13 Hz, 0.12H, H3), 7.01-7.32 (m, 3H, H2, H5, H6), 7.23 (d, J=3.33 Hz, 1H, H4), 8.34 (s, 0.54H, NH)

^{13}C-NMR (50 MHz, $CDCl_3$): 104.0* (C3), 116.9 (d, C4), 119.6 (d, C6), 120.9 (s, C7), 121.6 (d, C5), 125.0* (C2), 129.5* (C3a), 133.4* (C7a)

1,3-Dideutero-5-methoxyindole (<u>17</u>)



<u>17</u>

C_9H_9NO
M = 147.17

$C_9H_7D_2NO$
M = 149.19

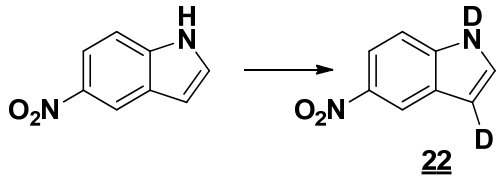
prep. via microwave protocol; substrate: 74 mg (0.5 mmol), amount of *t*-BuOD applied: 752 mg, 10 mmol = 10 equiv./D-position

Deuteration grade: 84% (according to GC-MS, ^{1}H-NMR)

^{1}H-NMR (200 MHz, $CDCl_3$): 3.99 (s, 3H, CH_3), 6.62 (d, J=2.54, 0.16H, H3), 7.01 (dd, J=8.70 Hz, J=2.45 Hz, H2), 7.20-7.42 (m 2H, H6, H7), 8.17 (s, 0.22H, NH)

^{13}C-NMR (50 MHz, $CDCl_3$): 56.1 (q, CH_3), 102.4* (C3), 102.5* (C4), 112.1* (C7), 112.5 (d, C6), 125.2* (C2), 128.4* (C3a), 131.2* (C7a), 154.3 (s, C5)

1,3-Dideutero-5-nitroindole (<u>22</u>)



<u>22</u>

$C_8H_6N_2O_2$
M = 162.15

$C_8H_4D_2N_2O_2$
M = 164.16

prep. via microwave protocol; substrate: 81 mg (0.5 mmol), amount of *t*-BuOD applied: 752 mg, 10 mmol = 10 equiv./D-position

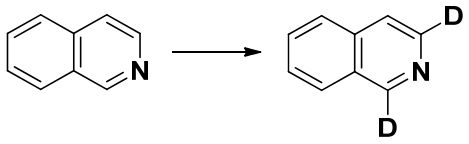
Deuteration grade: 35% (according to GC-MS, ^{1}H-NMR)

^{1}H-NMR ($CDCl_3$): 6.69-6.79 (m, 0.65H, H3), 7.31-7.52 (m, 2H, H5, H6), 8.12 (dd, J=9.00 Hz, J=2.35 Hz, 1H, H7), 8.62 (m, 1.53H, H4, NH)

^{13}C-NMR (50 MHz, $CDCl_3$): 105.5* (C3), 111.4 (d, C7), 118.1 (d, C6), 118.4* (C2), 127.6 (s, C3a), 127.7* (C5), 139.1 (C7a), 142.3* (C4)

5.1.2 Deuteration of electron-poor heteroarenes

1,3-Dideuteroisoquinoline (7)



7

C_9H_7N
M = 129.16

$C_9H_5D_2N$
M = 131.17

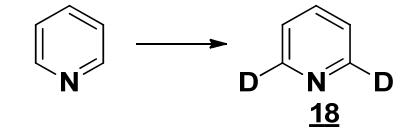
prep. via conventional heating using 2 subsequent steps; substrate: 65 mg (0.5 mmol), amount of *t*-BuOD applied: 2x 376 mg, 5 mmol, 5 equiv./D-position; Purification via column chromatography (PE:EE 10:1).

Yield: 94% (62 mg, 0.47 mmol)
Deuteration grade: 93%

^{1}H-NMR (200 MHz, $CDCl_3$): 7.38-8.18 (m, 5H, Har), 8.53 (d, J=2.74 Hz, H3, 0.08H), 9.22-9.29 (m, 0.07H, H1)

^{13}C-NMR (50 MHz, $CDCl_3$): 120.6 (d, C4), 126.2 (d, C5), 126.7* (C7), 127.7* (C8), 128.9 (s, C8a), 130.6* (C6), 136.1 (s, C4a), 143.3 (C3), 152.8 (C1)

1,5-Dideuteropyridine (18)



18

C_5H_5N
M = 79.10

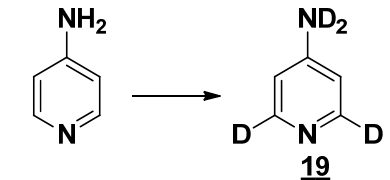
$C_5H_3D_2N$
M = 81.11

prep. via conventional heating; substrate: 158 mg (2 mmol), amount of *t*-BuOD applied: 1.5 g, 20 mmol = 5 equiv./D-position
Workup: 1 equivalent of NaH was added to the reaction mixture. After stirring for 5min 2ml of water were added. The organic phase was extracted with 2x2 ml of dichloromethane. The solvent was evaporated and deuteration grade determined.

Deuteration grade: 79%

^{1}H-NMR (200 MHz, DMSO-d6): 7.06 (d, J=3.81 Hz, 2H, H3, H5), 7.46 (t, J= 3.81 Hz, 1H, H4), 8.32 (d, J=1.91 Hz, 0.9H, H2, H6)

4-N,N-dideuteroamino-1,5-dideuteropyridine (19)



19

$C_5H_6N_2$ M = 94.11 → $C_5H_2D_4N_2$ M = 98.14

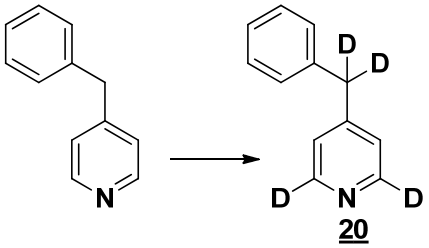
prep. via conventional heating; substrate: 94 mg (0.5 mmol), amount of *t*-BuOD applied: 752 mg, 5 mmol, 5 equiv./D-position

Deuteration grade: 50%

^{1}H-NMR (200 MHz, DMSO-d6): 6.03 (s, 0.54H, NH_2), 6.49 (s, 2H, H3, H5), 8.00 (d, J=2.74 Hz, 0.9H, H2, H6);

^{13}C-NMR (50 MHz, DMSO-d6): 110.3 (d, C3, C5), 153.0 (d, C2, C6), 156.0 (s, C4)

4-(Dideutero(phenyl)methyl)-1,5-dideuteropyridine (20)



20

$C_{12}H_{11}N$ M = 169.22 → $C_{12}H_7D_4N$ M = 173.25

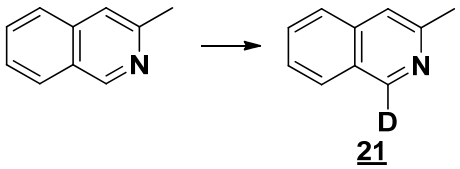
prep. via conventional heating; substrate: 85 mg (0.5 mmol), amount of *t*-BuOD applied: 376 mg, 5 mmol = 5 equiv./D-position

Deuteration grade: 50% (Pyr), 84% (Bn)

^{1}H-NMR (200 MHz, DMSO-d6): 4.00 (s, 0.29H, -CH_2), 6.89-8.00 (m, 6H, Har), 8.65-8.99 (m, 1H, Pyr-H2, Pyr-H6)

^{13}C-NMR (50 MHz, DMSO-d6): 125.0 (d, Pyr-3, Pyr-5), 127.3 (d, Ph-C4), 129.5 (d, Ph-C3), 129.8 (d, Ph-C2), 140.4 (s, Ph-C1), 150.5* (Pyr-2, Pyr-6, Pyr-4)

1-Deutero-3-methylisoquinoline (21)



21

$C_{10}H_9N$
M = 143.19

$C_{10}H_8DN$
M = 144.19

prep. via conventional heating; substrate: 143 mg (0.5 mmol), amount of *t*-BuOD applied: 188 mg, 2.5 mmol, = 5 equiv./D-position

Deuteration grade: 58%

^{1}H-NMR (200 MHz, $CDCl_3$): 2.69 (s, 3H, CH_3), 7.41-7.56 (m, 4H, H4-H7) 7.89 (d, J=8.02 Hz, 1H, H8), 9.15 (s, 0.42H, H1)

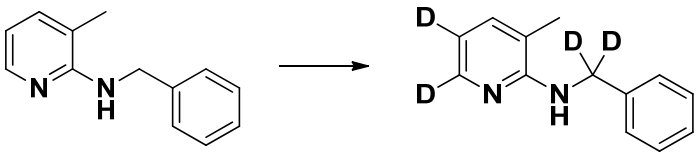
^{13}C-NMR (50 MHz, $CDCl_3$): 24.4 (q, CH_3), 118.6 (d, C7), 126.1 (d, C4), 126.4 (d, C5), 127.0 (s, C8a), 127.6 (d, C8), 130.4 (d, C6), 136.7 (s, C4a), 151.8 (s, C3), 152.1 (d, C1)

5.2 Deuteration on sp³-systems

General procedure

Substrate (0.5mmol), $Ru_3(CO)_{12}$ (16mg, 0.01mmol) and *t*-BuOD (5 equiv./deuteration position) were filled into a reaction vial with a screw cap septum. The vial was flushed with argon several times. The reaction mixture was then heated to 140°C and stirred at this temperature for 24h. After cooling to r.t. 10ml of *n*-hexane were added and the resulting solvent mixture was evaporated (azeotropic distillation of *t*-BuOH/*n*-hexane). Deuteration degrees were determined via ^{1}H-NMR.

N-(dideutero(phenyl)methyl)-N,5,6-trideutero-3-methylpyridin-2-amine (23)



23

$C_{13}H_{14}N_2$
M = 198.26

$C_{13}H_{10}D_4N_2$
M = 202.29

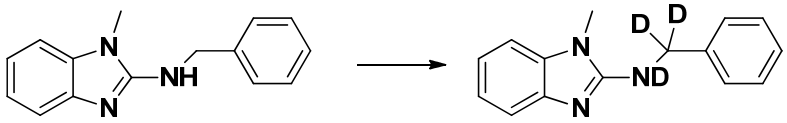
prep. via conventional heating; substrate: 92 mg (0.5 mmol), amount of *t*-BuOD applied: 752 mg, 10 mmol, = 5 equiv./D-position;

Deuteration grade: 51% (Pyr-5), 22 (Pyr-6), 89 (Bn)

^{1}H-NMR (200 MHz, $CDCl_3$): 1.96 (s, 3H, -CH_3), 4.26 (s, 0.26H, -CH_2), 4.50-4.63 (m, 0.86H, -NH), 6.41-6.55 (m, 0.49H, Pyr-5), 7.05-7.38 (m, 6H, Har), 7.83-8.02 (m, 0.78H, Pyr-6)

^{13}C-NMR (50 MHz, $CDCl_3$): 17.2 (q, CH_3), 113.1 (d, Pyr-5), 116.7 (d, Pyr-3), 127.4 (d, Ph-C4), 128.1 (d, Ph-C2), 128.8 (d, Ph-C3), 137.0* (Pyr-4), 140.2 (s, Ph-C1), 145.7* (Pyr-6), 156.9 (Pyr-2)

N-(dideutero(phenyl)methyl)-N-deutero-1-methyl-1H-benzo[d]imidazol-2-amine (24)



24

$C_{15}H_{15}N_3$
M = 237.30

$C_{15}H_{12}D_3N_3$
M = 240.32

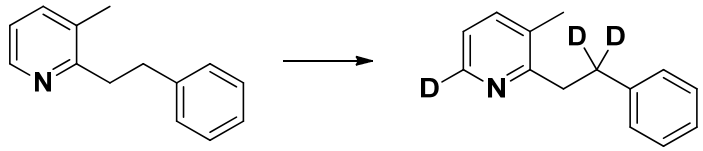
prep. via conventional heating; substrate: 119 mg (0.5 mmol), amount of *t*-BuOD applied; 564 mg, 7.5 mmol, = 5 equiv./D-position

Deuteration grade: 88%

^{1}H-NMR (200 MHz, $CDCl_3$): 3.38 (s, 3H, N-CH_3), 4.60-4.71 (m, 0.26H, -CH_2), 4.78-4.95 (m, 0.74H, -CH_2), 5.26 (s, 0.24H, -NH), 6.82-7.65 (m, 9H, Har)

^{13}C-NMR (50 MHz, $CDCl_3$): 28.4 (q, -CH_3), 107.3 (d, C4), 116.4 (d, C7), 119.8 (d, C5), 121.4 (d, Ph-C6), 127.7 (d, Ph-C3), 128.1 (d, Ph-C4), 128.8* (Ph-C2), 135.3 (s, C3a), 138.8* (Ph-C1), 142.3 (s, C7a), 154.7 (s, C2)

2-(1,1-dideutero-2-phenylethyl)-6-deutero-3-methylpyridine (25)



25

$C_{14}H_{15}N$
M = 197.28

$C_{14}H_{12}D_3N$
M = 200.29

prep. via conventional heating; substrate: 99 mg (0.5 mmol), amount of *t*-BuOD applied: 564 mg, 7.5 mmol = 5 equiv./D-position

Deuteration grade: 42% (Pyr), 87% (CH_2)

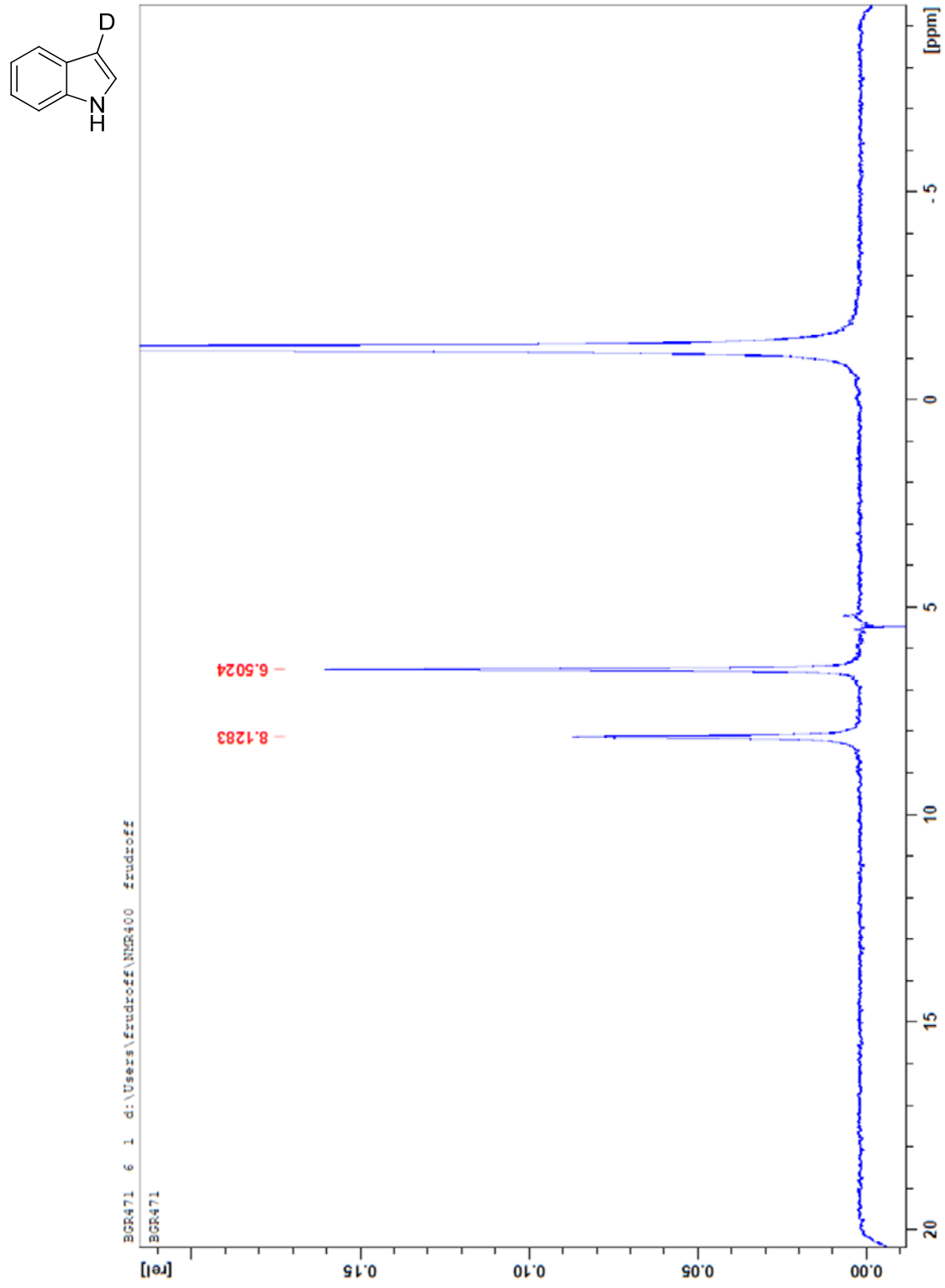
^{1}H-NMR (200 MHz, $CDCl_3$): 2.46 (s, 3H, -CH_3), 3.06 (s, 2.26H, CH_2-CH_2), 6.95-7.44 (m, 7H, Har), 8.44 (d, J=3.91 Hz, 0.58H, Pyr-H6)

^{13}C-NMR (50 MHz, $CDCl_3$): 19.0 (q, -CH_3), 35.3* (CH_2-CH_2), 121.6* (Pyr-5), 126.2 (d, Ph-C4), 128.9 (d, Ph-C2), 128.8 (d, Ph-C3), 131.5 (s, Pyr-3), 137.9 (d, Pyr-4), 142.3 (s, Ph-C1), 147.1* (Pyr-6), 159.8 (Pyr-2)

APPENDIX

APPENDIX A:

^{2}D-NMR:



APPENDIX B:

^{2}D-NMR: