Development of copper-, silver-, and rhodium-catalyzed coupling reactions

Von der Fakultät für Mathematik, Informatik und Naturwissenschaften der RWTH Aachen University zur Erlangung des akademischen Grades eines Doktors der Naturwissenschaften genehmigte Dissertation

vorgelegt von

Diplom-Chemiker (Dipl.-Chem.)

Bünyamin Özkaya

aus Homburg (Saar)

Berichter: Universitätsprofessor Dr. rer. nat. Frédéric W. Patureau

Universitätsprofessor Dr. rer. nat. Carsten Bolm

Tag der mündlichen Prüfung: 11. September 2023

Diese Dissertation ist auf den Internetseiten der Universitätsbibliothek verfügbar.

Statutory Declaration

Bünyamin Özkaya hereby declares that this thesis and the contents presented therein are his own and were generated independently, as a result of his own original research.

I hereby declare on oath:

1. This thesis was written entirely in the phase as a doctoral student of this faculty and university.
2. If any part of this thesis has been previously used for an academic degree or other qualification at this or any other institution, this has been clearly declared.
3. Whenever other own- or third-party publications were consulted, these were clearly cited.
4. If cited from other own- or third-party publications, the source was always indicated. The thesis is completely my work, except for such citations.
5. All major sources of support have been declared:
6. Whenever any part of this thesis is based on collaboration with others, I clearly labelled which work was carried out by others and which was done by myself.
7. Parts of this thesis has led to following publications, which have been previously published:

    - Step and redox efficient nitroarene to indole synthesis
      B. Özkaya, C. L. Bub, F. W. Patureau*, *Chem. Commun*. **2020**, *56*, 13185.
    - HBF_4- and $AgBF_4$-Catalyzed ortho-Alkylation of Diarylamines and Phenols
      C. K. Rank, **B. Özkaya**, and F. W. Patureau*, *Org. Lett.* **2019**, *21*, 6830-6384.
    - **B. Özkaya**, H. Kelm, F. W. Patureau, CCDC 2209643: Experimental Crystal Structure Determination, 2022, DOI: 10.5517/ccdc.csd.cc2d59tq.

Aachen, Bünyamin Özkaya

The represented work in this doctoral thesis was performed at the Institute of Organic Chemistry at RWTH Aachen University from February 2019 until September 2020 under the supervision of Prof. Dr. Frédéric W. Patureau except for Chapter 1, most parts of Chapter 2 and some parts of Chapter 3.3.1.

These exceptions correspond to results obtained from March 2017 until January 2019, that is before the transfer of the Patureau group from Technische Universität Kaiserslautern to RWTH Aachen University, also conducted under the supervision of Prof. Dr. Frédéric W. Patureau.

“İmkanın sınırını görmek için imkansızı denemek lazım.”

“To see the limits of the possible, you have to try the impossible.”

Mehmet II.

Curriculum Vitae

Personal Information

Date of birth	28 March 1991
Place of birth	Homburg (Saar)
Nationality	German

Education

02/2019 – 09/2022	**RWTH Aachen University** Completion of doctoral studies in the research group of Prof. Dr. F. W. Patureau Title: Development of copper-, silver-, and rhodium-catalyzed coupling reactions
03/2017 – 01/2019	**Technical University Kaiserslautern** Start of doctoral studies in the group of Prof. Dr. F. W. Patureau
10/2010 – 02/2017	**Technical University Kaiserslautern** Study of chemistry; focus: catalysis Diploma thesis in the group of Prof. Dr. F. W. Patureau, grade: 1.1 Title: “Synthesis of 3,5-disubstituted Phenols and their Application in Ruthenium Catalyzed C−O Bond Formation” Overall grade: Diploma: 1,3
08/2002 – 06/2010	**Saarpfalz-Gymnasium in Homburg (Saar)** Graduation from high school: Overall grade: 2,5

Publication list:

- C. Yu, **B. Özkaya**, F. W. Patureau*, *Chem. Eur. J.* **2021**, *27*, 3682-3687.
- **B. Özkaya**, C. L. Bub, F. W. Patureau*, *Chem. Commun*. **2020**, *56*, 13185.
- C. K. Rank, **B. Özkaya**, and F. W. Patureau*, *Org. Lett.* **2019**, *21*, 6830-6384.
- C. Heitz, A. W. Jones, § **B. Oezkaya**,§ C. L. Bub,§ M.-L. Louillat-Habermeyer, V. Wagner, F. W. Patureau*, *Chem. Eur. J*. **2016**, *22*, 17980. (§ these three authors contributed equally)

Abbrevations

[$RhCp^*Cl_2$] *pentamethylcyclopentadienyl rhodium (III) dichloride*

AcOH *acetic acid*

AIBN *azobisisobutyronitrile*

CDC *cross dehydrogenative coupling*

CMD *concerted metalation deprotonation*

COE *cyclooctene*

Cp* *pentamethylcyclopentadienyl anion*

DCM *dichloromethane*

DFT *density functional theory*

DMSO *dimethyl sulfoxide*, *dimethyl sulfoxide*

GC *gas chromatography*

KIE *kinetic isotopic effect*

n.d. *not detected*

nbd *norbornadien*

nm *nanometre*

NMR *nuclear magnetic resonance spectroscopy*

PPC *polypropylene carbonate*

RT *room temperature*

s.c. *standard conditions*

TCE *tetrachloroethylene*

TM *transition metal*

Table of contents

1 Nitrogen-nitrogen bond formation

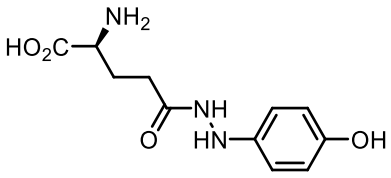
1.1 Background

1.1.1 Occurrence and significance of nitrogen-nitrogen bonds

Nitrogen-Nitrogen bonds are widely spread among natural products, organic materials and pharmaceuticals.[1–4] There were over 200 natural products known to contain N—N bonds, mostly isolated from the natural source in the mid to late 1900's.[3] Many of them show interesting properties, exemplary xanthodermine **1**, which has activity against cancer cells and dixiamycin A **2** as an antibiotic (Figure 1 a).[5,6] However, not only naturally occurring molecules with a N—N bonds are of enormous importance, but also synthetically accessible molecules are widely used since the beginning of the 20th century.[7,8] One of these is the special motif of triazole: a relatively electron rich aromatic heterocycle containing three nitrogen, which makes them easily bind to many receptors and enzymes.[1] Carboxyamidotriazoles **3** can inhibit ion channels and reduce tumor cells to proliferate and migrate (Figure 1 b).[9] A different, yet important link type of N—N bonds is in azo compounds. In 1904 Paul Ehrlich studied how azo dyes effect mice, which were infected with trypanosoma.[10] One of these tested dyes, trypan blue **4**, is still used for the assessment of tissue viability and as a dye for cotton textile (Figure 1 c).[8,11]

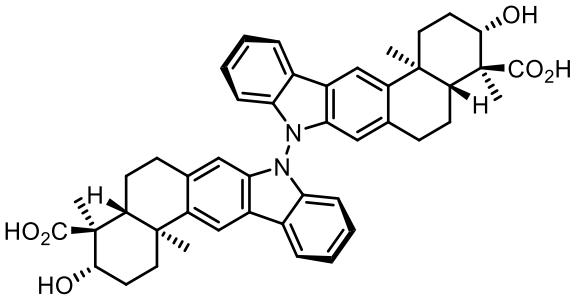
These few examples show the immense importance of nitrogen-nitrogen bonds in organic chemistry and the potential of new nitrogen-nitrogen linked molecules. Unfortunately, the number of synthetical methods forming these compounds is strongly varying, depending on the nature of the bond, which will be discussed in the next chapter.

a) Natural products:



xanthodermine
(activity on melanoma
cancer cells)

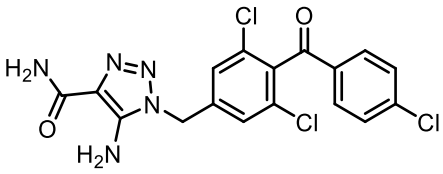
1



dixiamycin A
(antibacterial activities against
Staphylococcus aureus)

2

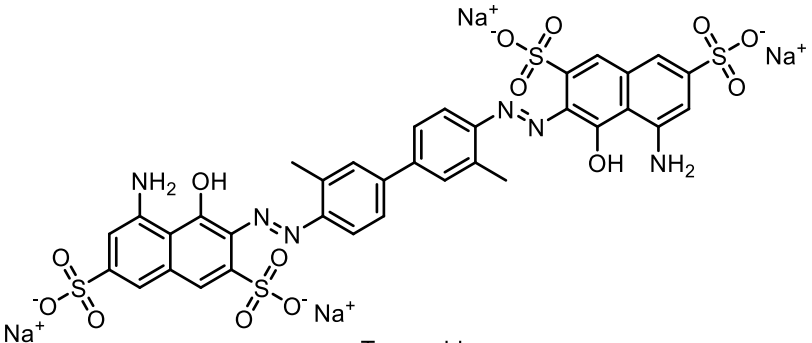
b) Pharmaceuticals:



carboxyamidotriazole
(calcium channel blocker)

3

c) Organic materials:



Trypan blue
(dye for cotton industry
used in mice for assessment
of tissue viability)

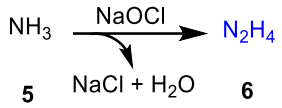
4

Figure 1: Selected molecules containing a nitrogen-nitrogen bond.[3,5,8,9,11,12]

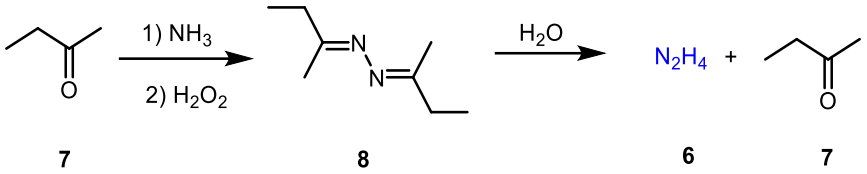
1.1.2 Synthesis of nitrogen-nitrogen bonds

Hydrazine **6** is the simplest example of a nitrogen-nitrogen double or single bond containing molecule. It is an exothermic reagent, since it will explosively decompose to nitrogen gas and ammonia depending on the conditions.[13] This makes hydrazine **6** and its derivatives to an excellent fuel for diverse applications.[14] The synthesis of the compound has been well studied.[15] One of the most known strategy is the Olin Raschig process, in which stoichiometric amounts of sodium hypochlorite is used (Scheme 1 a).[16] In the mid 1970's, the Pechiney–Ugine–Kuhlmann process was developed based on a publication by Schirmann *et al*. (Scheme 1 b).[17,18] The reaction proceeds smoothly with hydrogen peroxide as the oxidant via an oxaziridine intermediate.

a) Hydrazine synthesis by Raschig



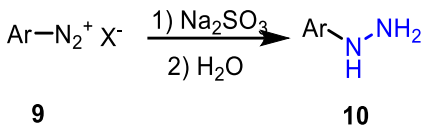
b) Pechiney–Ugine–Kuhlmann process



Scheme 1: Hydrazine processes.[16–18]

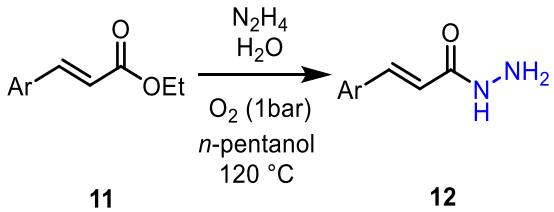
Aryl-hydrazine derivates **10** can be accessed by the reduction of diazonium salts **9**, yet the synthesis forms stoichiometric amounts of salts (Scheme 2 a).[19] In 2013, Pieber *et al*. demonstrated the transformation of cinnamic ethyl-esters **11** to the corresponding monosubstituted hydrazine derivatives **12**.[20]

a) Acces to aryl-hydrazine via diazonium salt



9 **10**

b) Synthesis of acryl-hydrazines

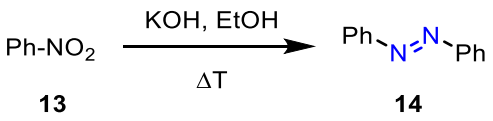


11 **12**

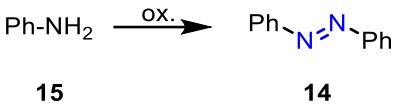
Scheme 2: Synthesis of monosubstituted hydrazine derivatives.[19,20]

Azobenzenes are one of the oldest motives in organic chemistry, since they have been described by Mitscherlich in 1835 (Scheme 3 a).[21] He isolated azobenzene **14** by reducing nitrobenzene **13** with potassium hydroxide in alcohol. 30 years later, Glaser found that it is also possible to oxidize aniline **15** to azobenzene **14** (Scheme 3 b).[22] Since then many strategies have been developed for the synthesis of azobenzenes, yet most of them generate stoichiometric amounts of waste.[4] In 2014 Wang *et al.* published an efficient protocol by using oxygen as a green oxidant and ammonium bromide as cocatalyst, addressing the demand of a sustainable process (Scheme 3 c).[23]

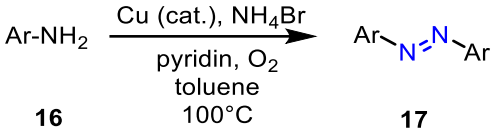
a) Discovery of azobenzene by Mitscherlich



b) oxidative route to azobenzene by Glaser



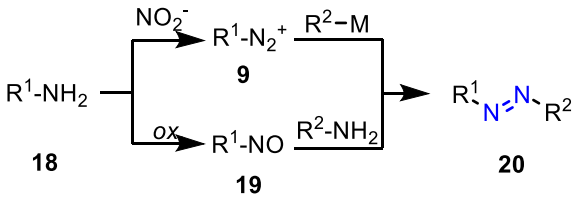
c) copper catalyzed route for azobenzenes by Wang



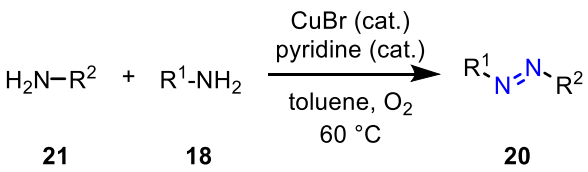
Scheme 3 Synthesis of symmetrical azobenzes.

Unsymmetrical azobenzenes **20** require traditionally a two-step synthesis via diazonium salts **9** or nitroso **19** compounds and/or a preactivated metal-carbon bond (i.e. Grignard-reagent) (Scheme 4 a).[24,25] This leads inevitably to stoichiometric amounts of inorganic waste. 2010, Zhang *et al.* reported a dehydrogenative cross coupling reaction, as a more sustainable option for these structures **20** (Scheme 4 b).[26]

a) traditional pathway to unsymm. azobenzenes



b) oxidative procedure for unsymm. azobenzenes by Hongwei

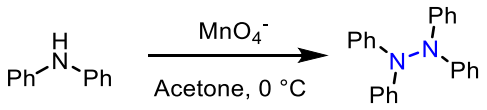


Scheme 4: Synthesis of unsymmetrical azobenzenes.[24,25]

Even though tetraphenyl hydrazine **23** was already described by Wieland and other researchers in the early 20th century, the synthesis of tetra-aryl hydrazines derivatives were rarely reported (Scheme 5 a).[27] In 2013 Zhu and Shi reported the homocoupling of anilines **24** with diaziridinone **25** as oxidant.[28] Primary anilines resulted in the corresponding azo compound, whereas secondary anilines **24** were transformed to the tetra-aryl substituted hydrazines **26** (Scheme 5 b). However, only six examples with little structural diversity are reported and the oxidant **25** is not atom economical.

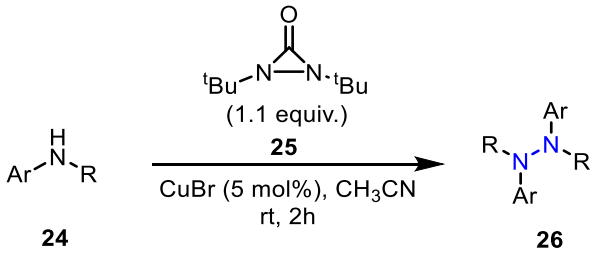
A special type of secondary amines are carbazoles **27**, which tend to usually react in a C—N bond forming fashion under oxidative conditions.[29] Nevertheless, Baran and coworkers showcased the dimerization of carbazoles **27** with a N—N linkage using electro oxidative conditions (Scheme 5 c).[30] A variety of different groups were tolerated in C2 position, as well as β-carboline derivatives (**27,** with X=N). The developed method was applied as the central step of total synthesis of dixiamycin B (enantiomer of **2**).

a) Wielands procedure for tetraphenylhyrdazine



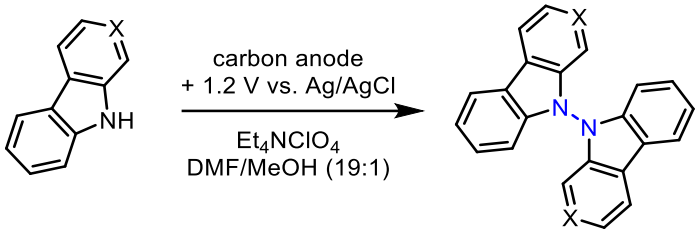
22 **23**

b) Cu(I)-Catalyzed oxidative coupling with Diaziridinone by Zhu



24 **26**

c) Electrochemical oxidative dimerization of carbazols



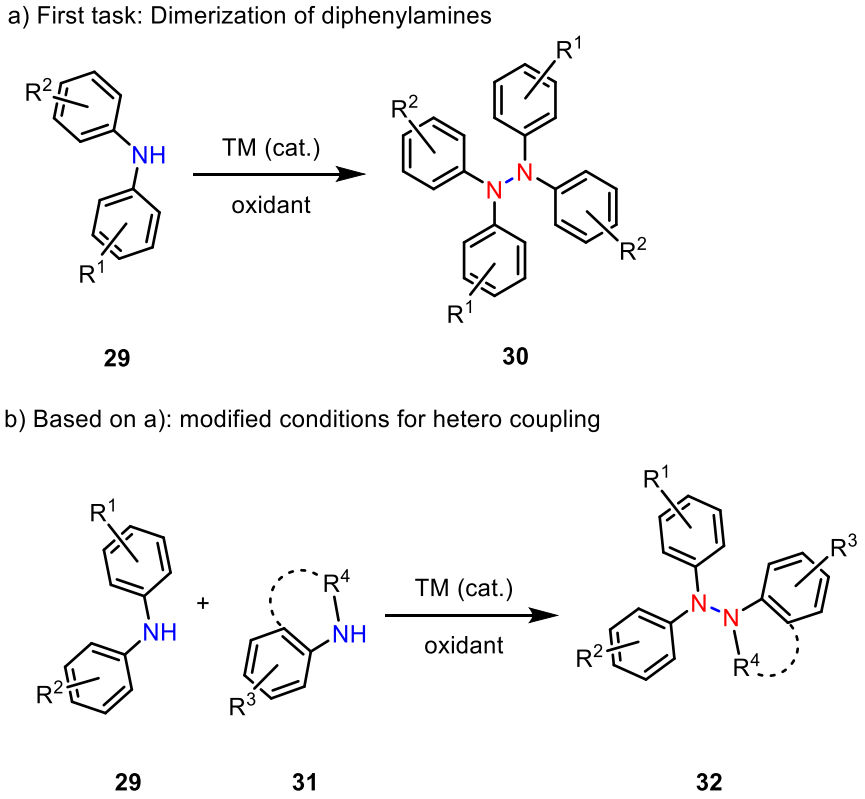
27 **28**

Scheme 5: Synthesis of tetra-aryl substituted hydrazines

The small number of methods for the synthesis of tetra aryl-substituted hydrazines show that this field is underexplored. Unsymmetrical products have not been reported till 2017 and new routes towards this scaffold are needed.

1.2 Motivation and task

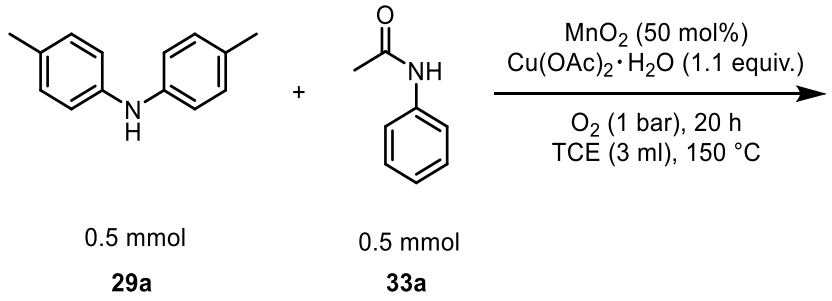
As described in chapter 1.1.2, tetra-aryl substituted hydrazines are mostly underinvestigated. The general task was to find oxidative conditions (possibly metal assisted), in which a N—N bond is formed in a CDC fashion. Secondary amines would be a great choice as substrates in view of atom economy and step efficiency. The dimerization of diphenylamines **28** should be investigated (Scheme 6 a), which is using a chemical oxidant and thus being an alternative method to Baran's work (Scheme 5 c). Based on this, it should be possible to reoptimize the conditions in a fashion that a diphenylamine **28** can couple with a secondary amine **31** to a N—N linked hetero-coupling product **32** (Scheme 6 b).



Scheme 6: General objective of N—N bond formation

1.3 Results and discussion

For the initial reactions *p,p*-ditolylamine **29a** was chosen as the nucleophilic and acetanilide **33a** as the electrophilic coupling partner (Scheme 7). The methyl-groups allow yield determination by proton NMR-spectroscopy. Manganese (IV) oxide was chosen for the reaction since it has the potential to act as oxidant and catalyst. Additionally, copper (II) acetate hydrate was chosen and tetrachloroethylene (TCE) as the solvent. Due to its coordination to metals or to *π*-systems it has an antioxidation effect, which allows the use of sensitive substrates at higher temperatures.[31]



Scheme 7: Initial conditions for N—N bond formation.

TLC analysis showed full conversion and three different products. However, only one was isolated successfully and a proton NMR-spectroscopy was measured (Figure 2).

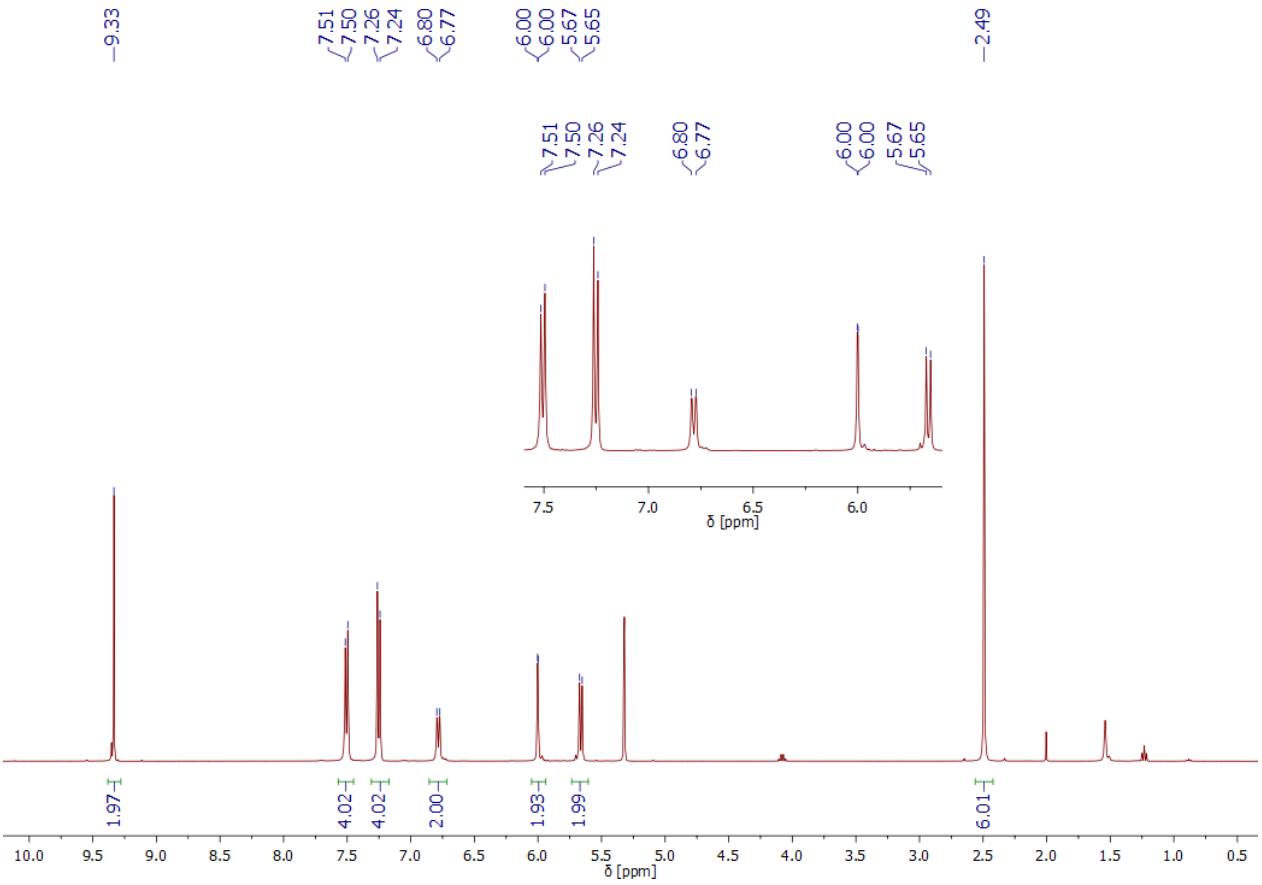


Figure 2: ^{1}H-NMR of isolated compound

Based on the AA'BB' spin system (δ ~ 7.50 & 7.25 ppm) and the methyl-signals (δ ~ 2.50 ppm), the new compound must include at least one diphenylamine scaffold. The singlet at 9.33 indicates an aldehyde group, which can be generated by oxidation of a methyl group.[32] The multiplicities of the remaining signals are rather interesting: two doublets and one singlet indicate that a new carbon—carbon has been formed. One of the doublets was identified to be *dd* (^{3}J= 8.0 and ^{4}J= 1.2), indicating that a carbazole motif might have been formed. This would be in line with a report by Jones *et al*. in 2015 in which strained C-C bonds can be formed under strong oxidative conditions in a CDC fashion.[33] With this interpretation, the following structure was originally proposed (Figure 3):

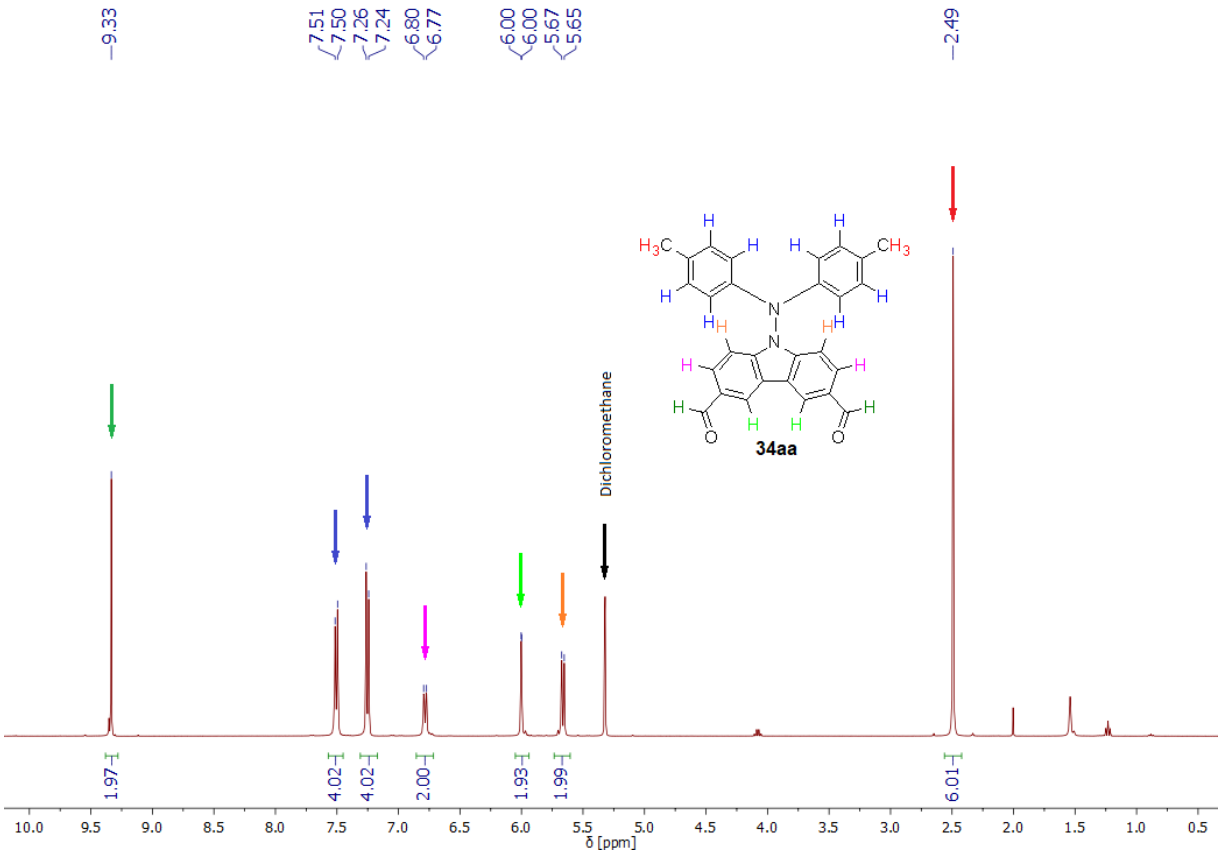
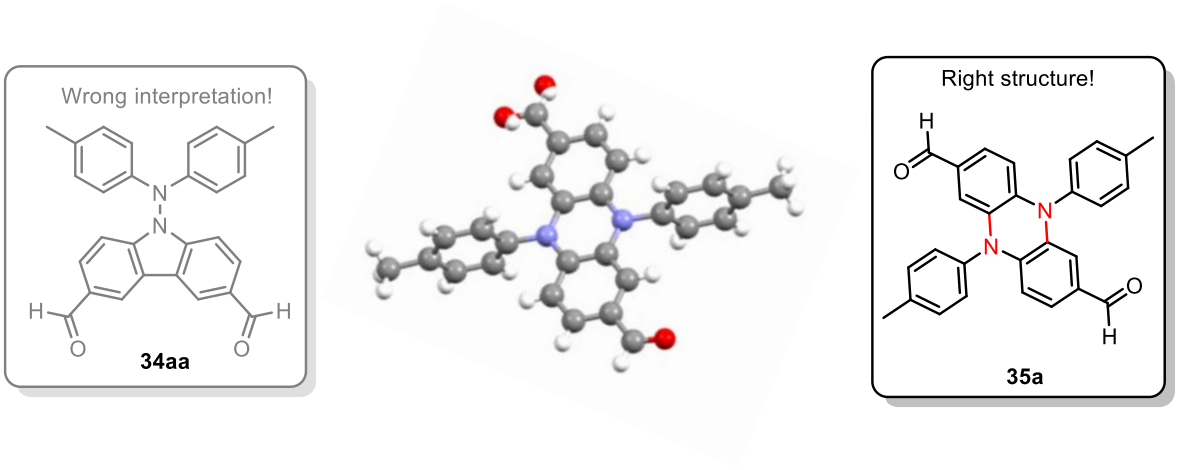


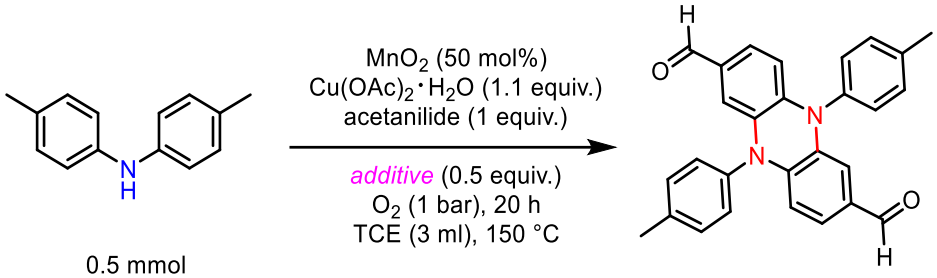
*Figure 3: Interpretated NMR- spectroscopy data and suggested structure of the new compound **34a**.*

The assumed product **34aa** was isolated with a yield of 14% (Scheme 7). Even though it was exclusively formed from the diarylamine **29a** the overoxidation led to an unsymmetrical homo-coupling product and this circumstance was accepted and the originally proposed product **34aa** was further investigated. Throughout the optimization process, crystallization attempts were repeatedly carried out to confirm the structure. In the late, course measurable crystals could be grown, from which the following structure **35a** resulted (Scheme 8). Unfortunately, all analytical data match both structures **34aa** and **35a**. Even though **35a** was not the desired structure, there is no one step synthesis for this 5,10-diphenyl-dihydrophenazine motif. It is also worth mentioning that this structure has never been synthetized before.



Scheme 8: Comparison of wrong interpretation and the actual structure.[34]

All following experiments at that time were carried out with the conviction that **34aa** was formed. However, for the sake of clarity all following schemes and tables will show the structure **35a**, which was formed in the reaction.



0.5 mmol

29a

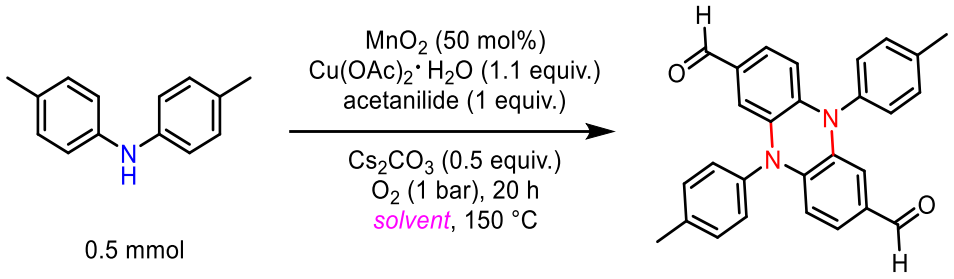
35a

Entry	Additive	NMR-Yield [%]
1[a]	-	traces
2[b]	-	traces
3[c]	AcOH	traces
4	K_2CO_3	10
5	Na_2CO_3	23
6	$CaCO_3$	6
7	Cs_2CO_3	(22)

Table 1: Additive screening for dihydrophenazine-scaffold. Isolated yields in parentheses. [a] $Cu(OAc)_2$ instead of $Cu(OAc)_2 \cdot H_2O$. [b] Acetanilide omitted. [c] 0.5 mL AcOH and 2.5 mL TCE.

Two control experiments were carried out and based on this some additives were screened (Table 1). If dry copper (II) acetate was used, only trace amounts of the product were detected (Table 1, entry 1). Without acetanilide the selectivity of the reaction dropped significantly and only trace amounts of product were detected, indicating a role as ligand (Table 1 entry 2). Different carbonates were engaged as base. Even though cesium carbonate and sodium carbonate gave similar result (Table 1, entry 5 & 7), the cesium salt was chosen since it has a better solubility in organic solvents and is widely used in organic synthesis.[35]

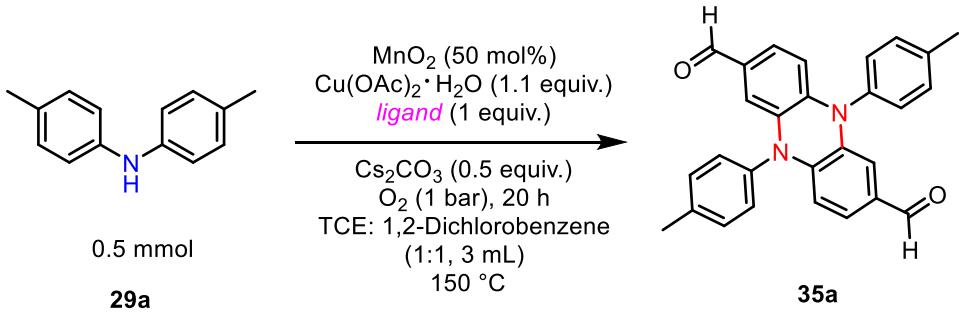
Some solvents were screened and 1,2-dichlorobenzene was chosen as the second solvent in a 1:1 ratio with TCE to increase the solubility of all components (Table 2).

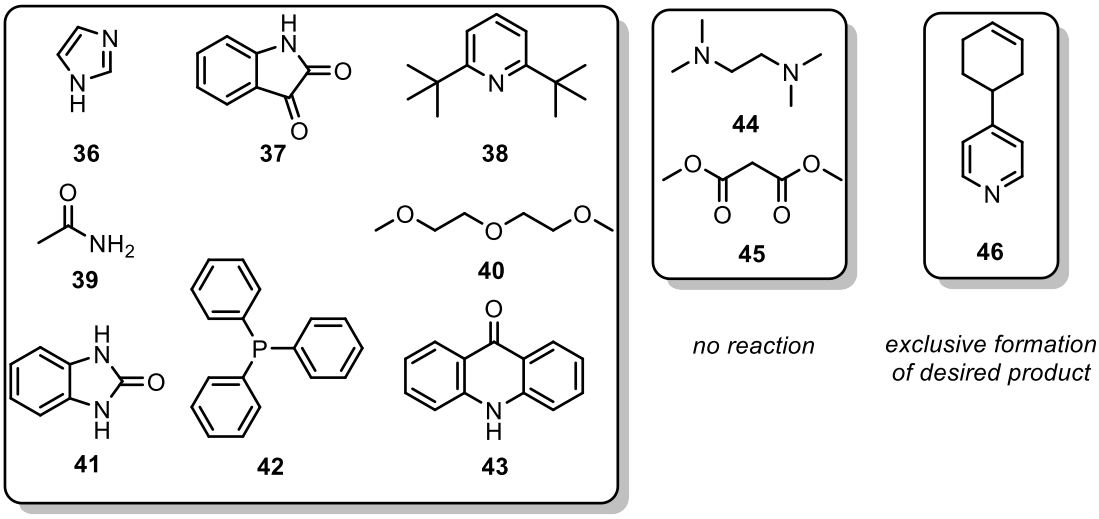


Entry	Solvent [ml]	NMR-Yield [%]
1	TCE:1,2-dichlorobenzene (1.5:1.5)	25
2	TCE:2-chlorotoluene (1.5:1.5)	21
3	TCE:chlorobenzene (1.5:1.5)	20
4	TCE: *tert*-amyl alcohol (1.5:1.5)	10

Table 2: Screening of different solvent mixtures with tetrachloroethylene.

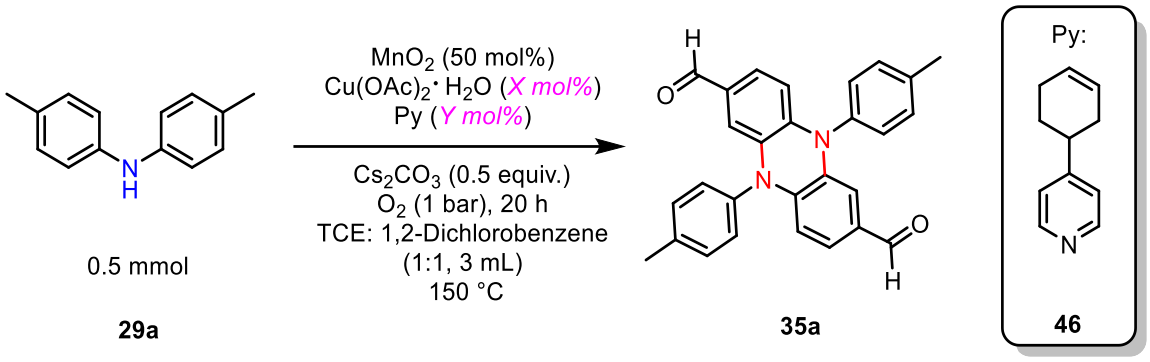
Next, different amides and heterocycles were tested and the reaction mixtures were qualitatively evaluated by TLC control (Scheme 9). Most ligands had mostly no impact on the reaction. In case of dimethylmalonate **45** and *N,N,N'N'*-tetramethylethyldiamine **44** no reaction was observed. This might be caused by irreversible coordination to the copper (II). However, 4-(3-cyclohexen-1-yl)pyridine **46** was able to exclusively deliver the product.





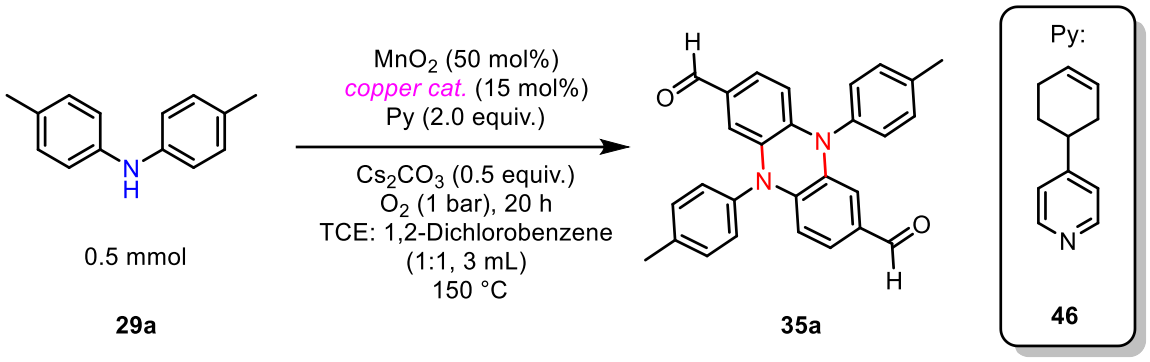
Scheme 9: Ligand screening for oxidative phenazine formation.

With this new ligand **46** in hand, the idea was to reduce the copper amount to a catalytic loading and different amounts of copper (II) acetate hydrate and the ligand were screened (Table 3). Different copper sources were tested and qualitatively controlled by TLC (Table 4).



Entry	X [mol%]	Y [mol%]	NMR-Yield [%]
1	15	15	Trace
2	15	30	Trace
3	15	200	trace
4	10	10	Trace
5	10	20	Trace
6	10	200	n.d.
7	5	5	n.d.
8	5	10	n.d.
9	5	200	n.d.

Table 3: Screening of catalytic loading with copper (II) acetate hydrate and pyridine-ligand.

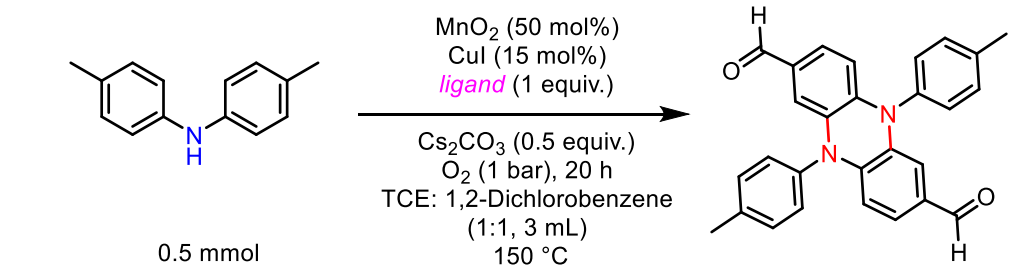


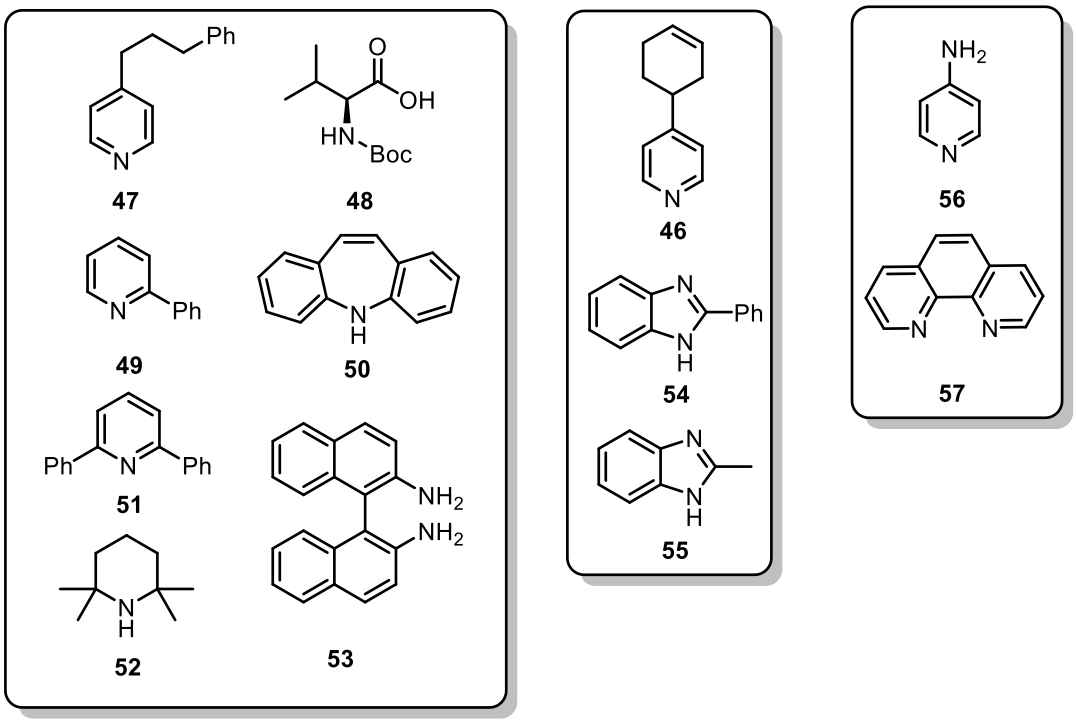
Entry	Copper cat.	TLC-control
1	$CuCl_2$	Product and byproducts detected
2	CuCl	No reaction
3	CuO	No reaction
4	$CuCO_3 \cdot Cu(OH)_2$	No reaction
5	CuI	Product detected
6	$Cu(OTf)_2$	Product and byproducts detected

Table 4: Different copper sources tested with 4-(3-cyclohexen-1-yl)pyridine as ligand.

In general, the reactions were not catalyzed by copper (I) species and basic copper (II) carbonate (Table 4, entry 2-4). Yet, copper(I) iodide was able to deliver the product with only one byproduct. (Table 4, entry 5). Copper (II) was able to catalyze the reaction, but byproducts were also detected (Table 4, entry 1 & 6). However, the difference between copper (II) chloride and copper (I) iodide was marginal.

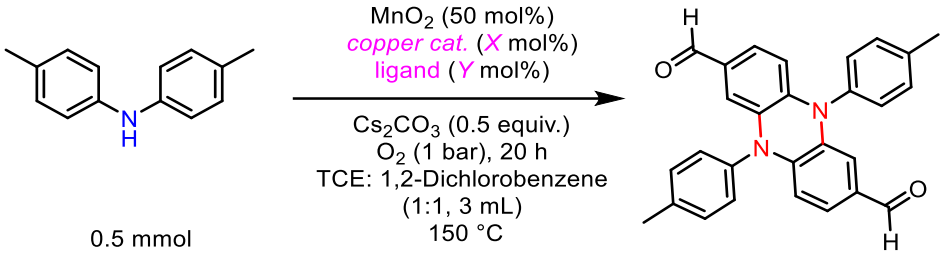
At first copper (I) iodide was chosen and various ligands were tested (Scheme 10). The ligand amount was kept at one equivalent to compare previous results. Pyridine and secondary amines as ligands generally performed poorly (**47**-**53**). Benzimidazoles **54** & **55** behaved similar to 4-(3-cyclohexen-1-yl)pyridine **45** and trace amounts of product were detected. The best qualitative results were obtained when 1,10-phenanthroline **57** or 4-aminopyridine **56** were engaged as ligands. The latter one led to more decomposition. Therefore 1,10-phenanthroline **57** was used in the further experiments.





Scheme 10: Second ligand screening with copper (I) iodide as catalyst.

With the new ligand **57** in hand, different catalytic loadings with copper (I) iodide and copper (II) chloride were tested (Table 5) since previous results were not completely conclusive (Table 4, entry 1 & 5). Additionally, 2,2'-bipyridine was tested with the same copper catalysts. The only synthetically relevant results were obtained for a catalytic loading of 15 mol% for both catalyst and ligand (Table 5, entry 1, 4, 5 and 8), with a marginal difference in yield, whereby copper (II) chloride was usually better then copper (I) iodide. Therefore, copper (II) chloride and 1,10-phenanthroline **56** was chosen as the catalytic system giving 41% of the product **35a** (Table 5, entry 5).



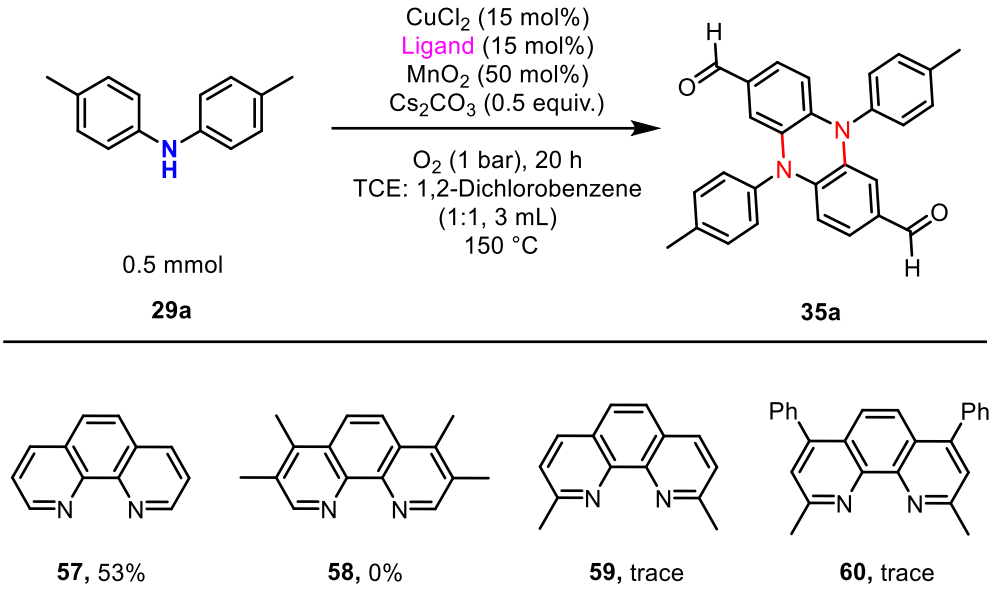
Entry	Copper cat.	Loading [X mol%]	Ligand	Loading [Y mol%]	NMR-Yield
1	CuI	15	Phenanthroline	15	37
2	CuI	7.5	Phenanthroline	7.5	11
3	CuI	1.0	Phenanthroline	1.0	6
4	CuI	15	2,2'-Bipyridin	15	39
5	$CuCl_2$	15	Phenanthroline	15	41
6	$CuCl_2$	7.5	Phenanthroline	7.5	13
7	$CuCl_2$	1.0	Phenanthroline	1.0	9
8	$CuCl_2$	15	2,2'-Bipyridin	15	40

Table 5: Test of different catalytic loadings of catalyst and ligand.

The influence of the atmosphere was investigated next. When air was used only trace amounts of the product were detected, whereas no conversion was observed when nitrogen was used. This indicates that oxygen has a decisive role as oxidant in the reaction.

Considering the general oxidation ability of manganese (IV) oxide, it was tested as the sole oxidant. Mangenese (IV) oxide was not capable of delivering the product without pure oxygen. However, if oxygen was added and the reactor size was increased from 70 mL to 170 mL, an improved yield was observed. Even though the yield was increased to 53%, both unidentified side products were still detected. Despite all efforts, the side products could not be isolated nor identified by mass analysis of the reaction mixture.

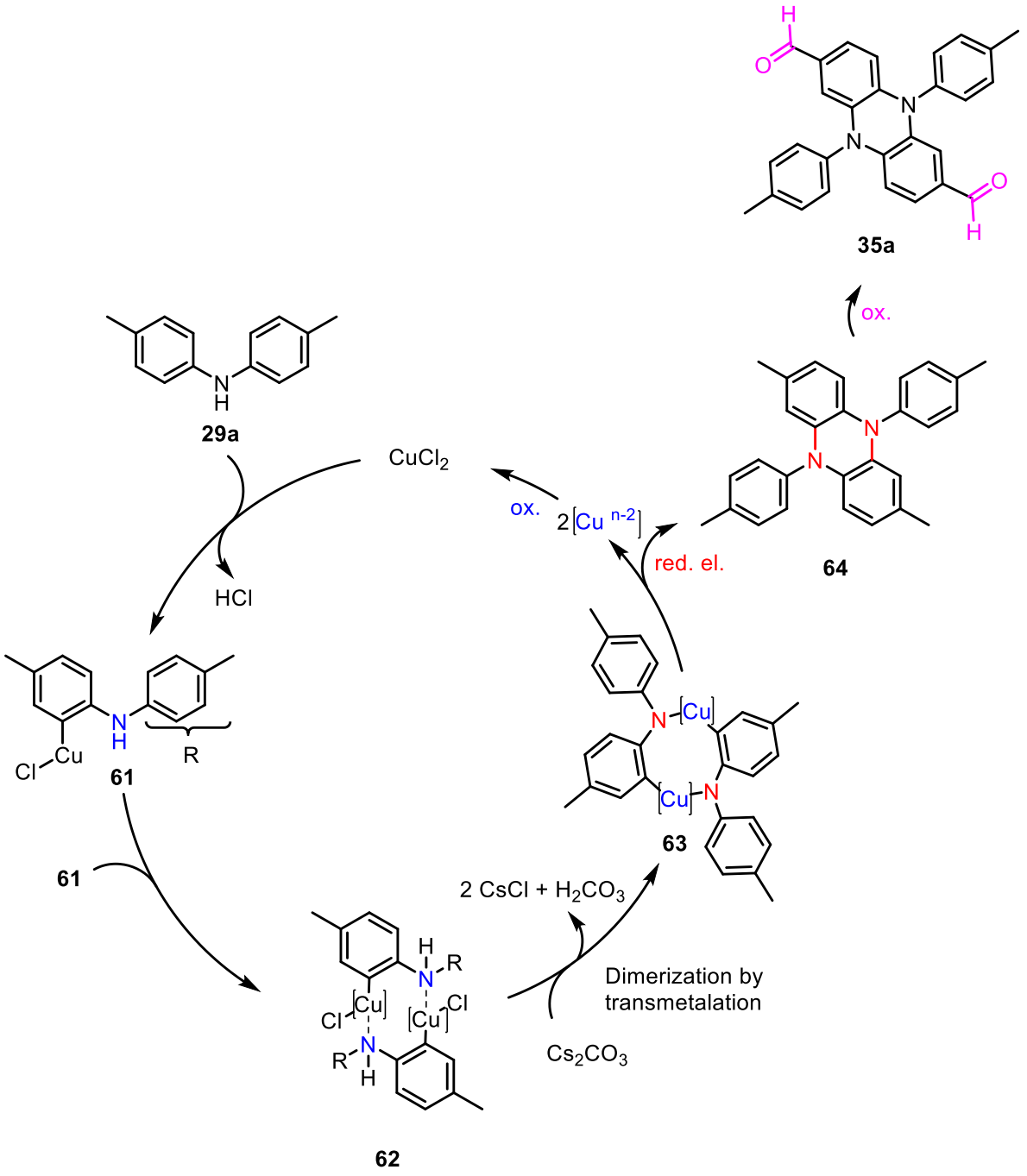
Therefore, different sterically hindered phenanthroline ligands **58**-**60** were tested, to improve the selectivity (Scheme 11). All tested variations lowered the conversion drastically and were not suited for the reaction.



Scheme 11: Test of different phenanthroline derivatives as ligands. Reactions were carried out in a 170 mL reactor. Yields determined by proton NMR spectroscopy.

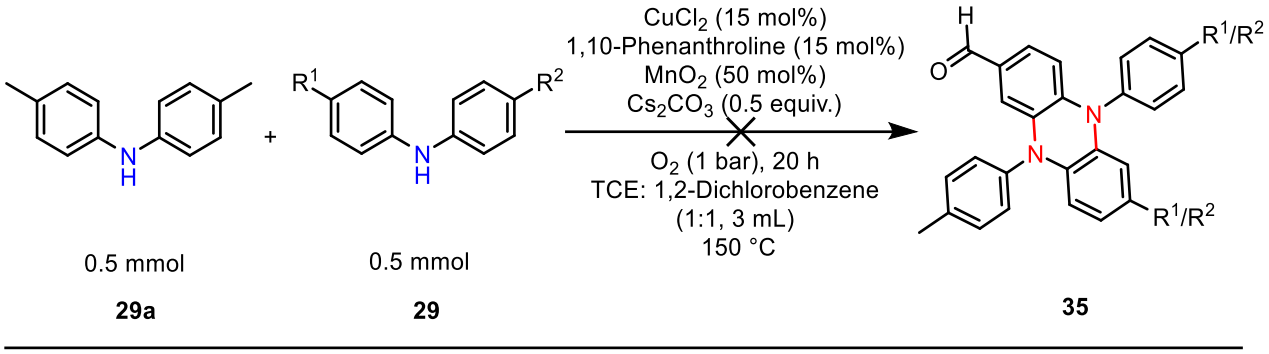
Based on the observations while optimizing, a possible mechanism is proposed (Scheme 12,). First the ortho C-H bond to the amine in **29a** might be activated and a C-Cu bond may be formed. The high electrophilic nature of the copper in **61** may lead to an arrangement (**62**), which might lead to **63** by a dimerization by transmetalation. After a reductive elimination step, the intermediate **64** might be formed and should be oxidized on the most electron-rich positions to form the product **35a**.

Another possible scenario could be that one of the methyl-groups of **29a** is oxidized in an Étard fashion and the corresponding aldehyde follows the same pathway as described above.[36]



Scheme 12: Proposed mechanism for the oxidative N-N bond formation.

To evaluate the scope of the reaction, cross coupling reactions were tested with different diphenylamines **29** and *p,p'*-ditolylamine **29a** (Scheme 13). All tested substrates led to decomposition. Therefore, isolation attempts were not carried out.

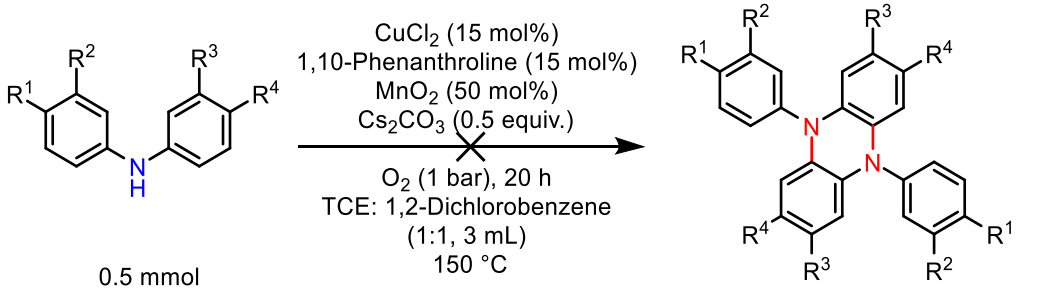


29b: R^1= R^2= H
29c: R^1= OMe, R^2= H
29d: R^1= Me, R^2= H

35ba: n.d.
35ca: n.d.
35da: n.d.

*Scheme 13: Engaged hetero-coupling attempts for the formation of 5,10-diphenyl-dihydrophenazine motifs **35.***

Additionally, three diphenylamines **29d, 29f, & 29g** were tested under the best conditions to form the homocoupling product (Scheme 14). None of the tested amines worked under these conditions.



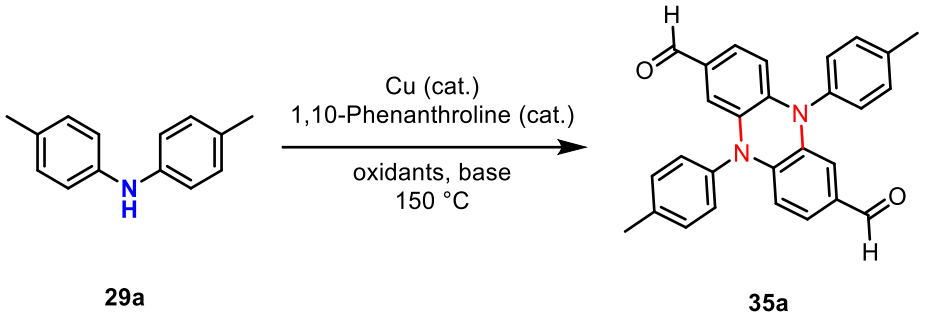
29b: R^1= OMe, R^2= R^3= R^4= H
29d: R^1= R^2= Me; R^3= R^4= Cl
29e: R^1= R^2= Me; R^3= R^4= H

35b: R^1= OMe, R^2= R^3= R^4= H
35c: R^1= R^2= Me; R^3= R^4= Cl
35d: R^1= R^2= Me; R^3= R^4= H

*Scheme 14: Test of diphenylamines for the homo-coupling to form 5,10-diphenyl-dihydrophenazines **35**.*

1.4 Conclusion

The development of a general method for the formation of tetra-aryl substituted hydrazines was unsuccessful and a 5,10-diphenyl-dihydrophenazine (**35a**) was formed instead. Due to misinterpretation of the analytical data, the conditions were optimized for an undesired product **35a** (Scheme 15).

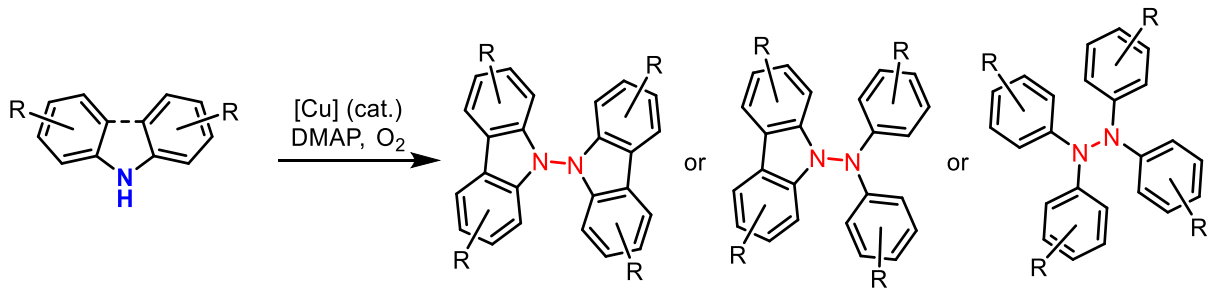


29a **35a**

*Scheme 15: Oxidative conditions developed for the formation of 5,10-diphenyl-dihydrophenazine **66a**.*

The generated 5,10-diphenyl-dihydrophenazine derivative **35a** was synthetized for the very first time. Unfortunately, even electron-rich substrates were not converted to the corresponding products under the optimized conditions. Accordingly, other substrates were not tested and the project was no longer pursued.

In 2018 Ryan *et al.* developed a catalytic method for the N—N homocoupling of carbazoles and diarylamines (Scheme 16).[37] The reaction uses oxygen as a green oxidant and copper as the catalyst. Moreover, the cross-coupling reaction between diraylamines and carbazoles was achieved in a N—N bond formation fashion, addressing the problem of the access to different tetraphenylhydrazines **30**, 9,9'-biscarbazoles **28** and carbazole-diarylamines **34**.



27 and/or 29 **28** **34** **30**

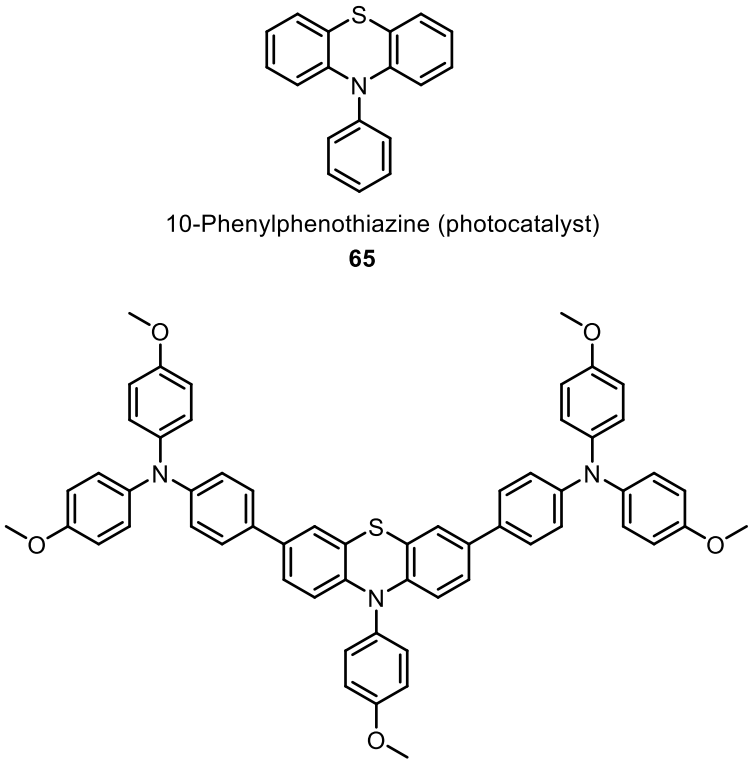
Scheme 16: General copper catalyzed reaction for N-N coupling between carbazoles and diarylamines by Stahl and coworkers.[37]

2 *Ortho*-Alkylation of phenols and diarylamines

2.1 Background

2.1.1 Phenothiazine: a special diarylamine

Phenothiazines are a particularly important scaffold for medicinal chemistry and material science.[38,39] Depending on the substitution pattern, the applicability can change a lot. The functionalization at the nitrogen has the greatest influence on the applicability of the phenothiazine. *N*-arylated phenothiazines have been studied intensively over the last few years, utilizing for example 10-phenylphenothiazine **65** as a photo-catalyst; other derivatives **66** & **67** were examined in the development of potential materials for solar energy collection and the development of OLEDs (Figure 4).[40–46]

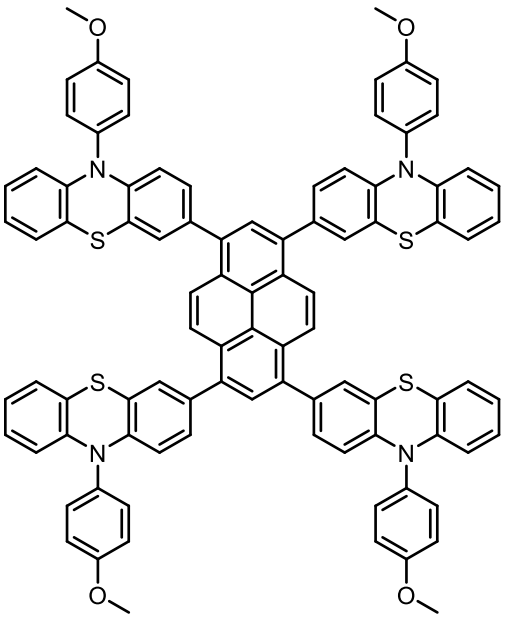


10-Phenylphenothiazine (photocatalyst)

65

PTZ2 (potential solar cell material based on phenothiazine)

66



Py-PH (green emmiter)

67

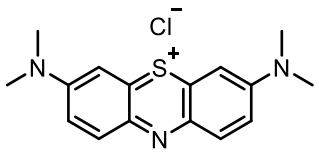
Figure 4: Phenothiazine derived structures in material science and catalysis. [40–46]

In 2016 Salunke *et al.* showcased that carbazole and phenothiazine derived structures are promising candidates for the further development of organic light emitters.[44] Their synthetized

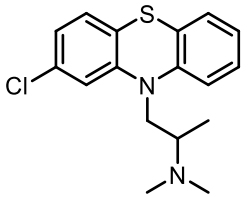
1,3,6,8-tetrakis(10-(4-methoxyphenyl)-10*H*-phenothiazin-3-yl)pyrene (PY-PH) **67** is a green emitter (Figure 4), which has an electroluminescence peak at 540 nm. The maximum brightness at around 2116 cd m^{-2} and the power efficiency of 0.45 lm W^{-1} shows the potential of such structures as cheap alternative for organic light emitters. Another recent accomplishment is particularly impressive, in which Grisorio *et al.* showed in 2017 that the synthetized phenothiazine derivative **66** has a conversion efficiency for sunlight energy of 17.6% (Figure 4), a value which can compete with state-of-the-art Spiro-OMeTAD (17.7%) solar cells.[46]

Due to the biological activity of phenothiazines, methylene blue **68** has been already studied in the late 19th century by Paul Ehrlich for the treatment of malaria.[47] With the synthesis of promethazine **69**, the rise of phenothiazine in medicinal chemistry started (Figure 5 a)).[39] Today some phenothiazine based drugs (**70** & **71**) are indispensable and are on the WHO list of essential drugs, which are used as neuroleptic drugs (Figure 5 b)).[48]

a) Examples of early studied phenothiazines

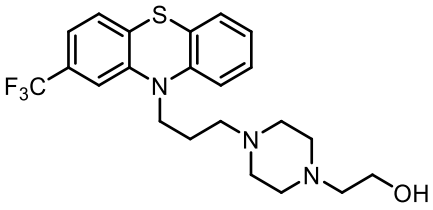


Methylene blue
68

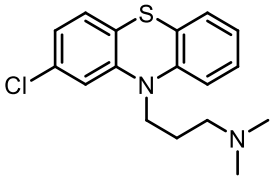


Promethazine
69

b) Two examples of phenothiazine based neuroleptic drugs



Fluphenazine
70



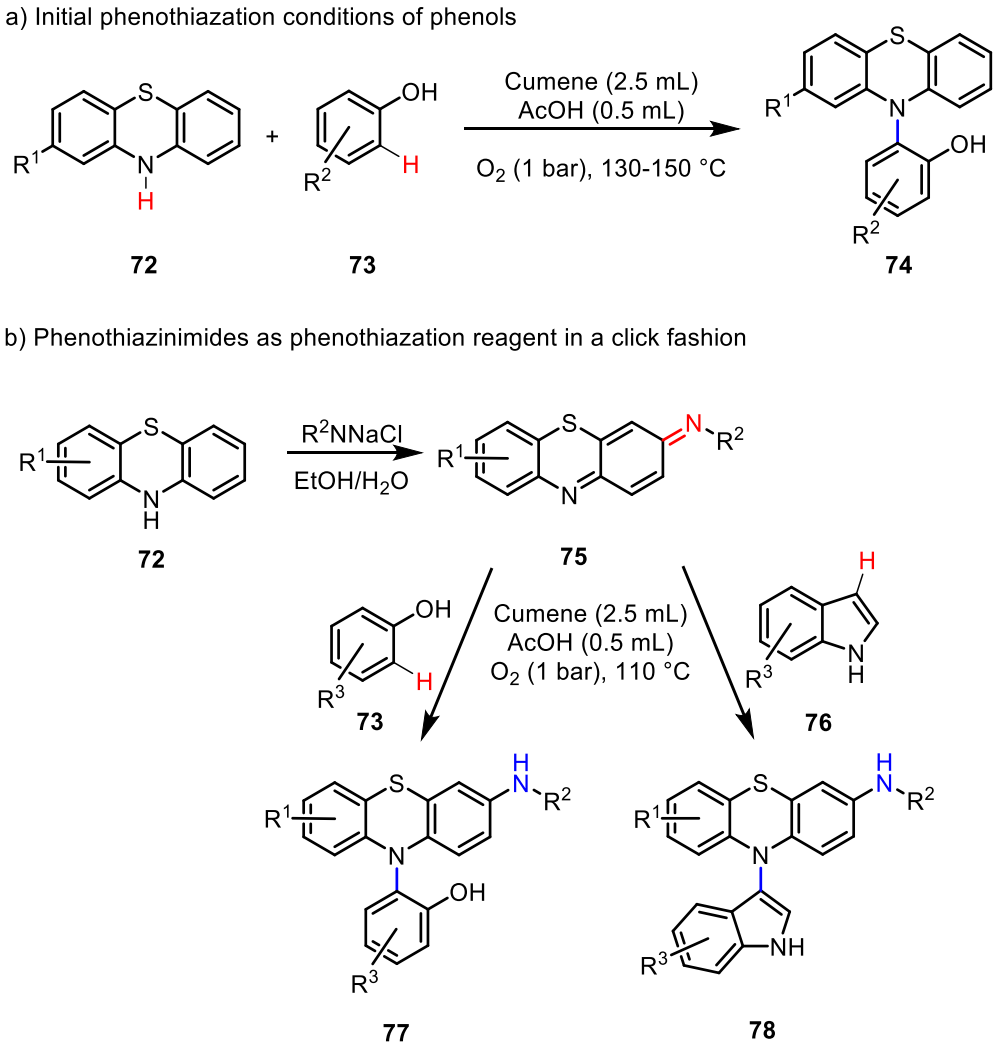
Chlorpromazine
71

Figure 5: Two examples of phenothiazine based neuroleptic drugs.[39,48]

All these examples showcase the significance of *N*-functionalized phenothiazine in different research fields for future applications.

The Patureau group saw the potential of phenothiazine **72** as radical coupling reagent, as it served as amination source for phenols **73** in a CDC reaction using oxidative methods (Scheme 17).[49,50]

One of these methods was a cumene/ acetic acid/ oxygen system, which was able to deliver a C-N cross coupled product **74** with phenols **74** (Scheme 17 a)).[49] By modifying the phenothiazine to **75**, it was also possible to obtain the phenothiazinated indole in three position **78** at slightly lower temperatures.[51]

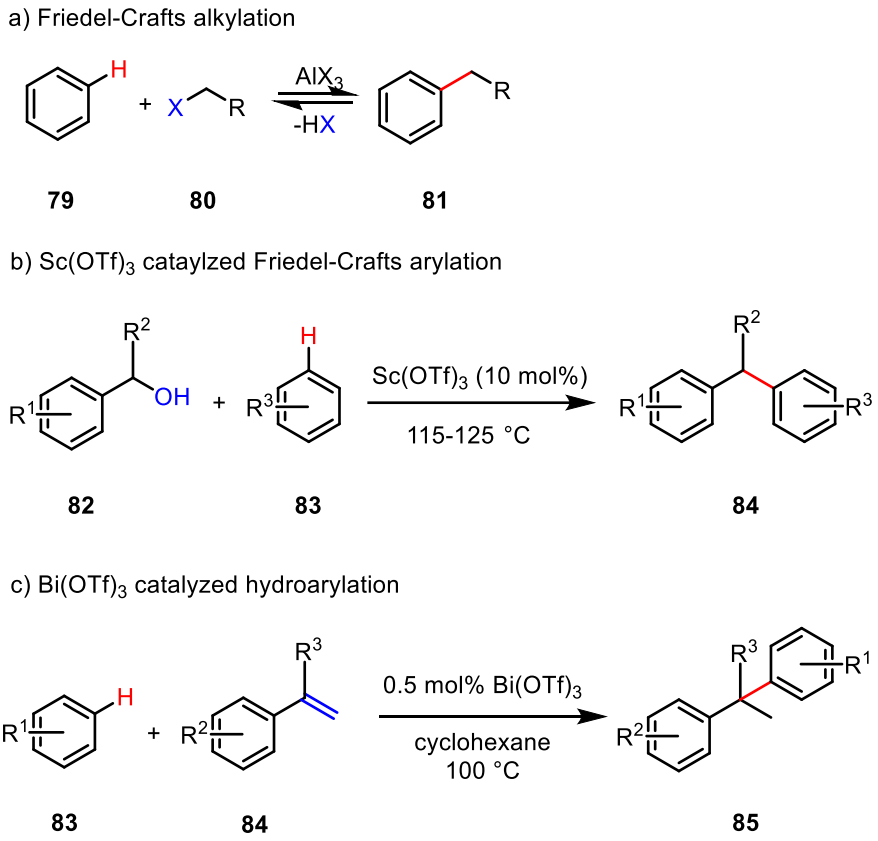


Scheme 17: Amination reactions developed by the Patureau group.[49,50]

2.1.2 Hydroarylation methods

One of the oldest methods to construct C-C bonds with arenes is Friedel-Crafts-Alkylation, where an alkyl halide **80** undergoes a S_eAr with an arene **79** with the help of a Lewis acid (e.g. iron)

(Scheme 18 a).[52] Although this reaction is still used to construct C-C bonds with arenes **79** it has downsides, such as stoichiometric amounts of Lewis acids, functional group tolerance or regioselectivity. Because the product is more nucleophilic, multiple alkylation reactions might occur.[53] All this and the need of more environmental and economical friendly methods lead to the development of many Lewis acid catalyzed alkylation protocols with greener leaving groups and/ or different catalysts.[54]

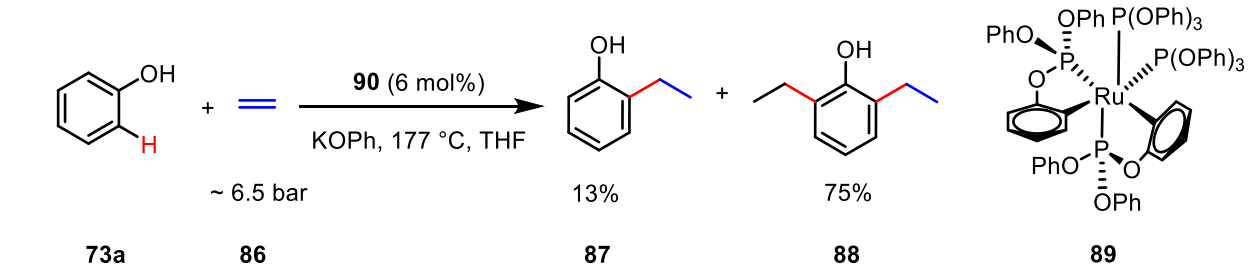


Scheme 18: Traditional Friedel-Crafts-Alkylation and scandium catalyzed alkylation by Fukuzawa.[54,55]

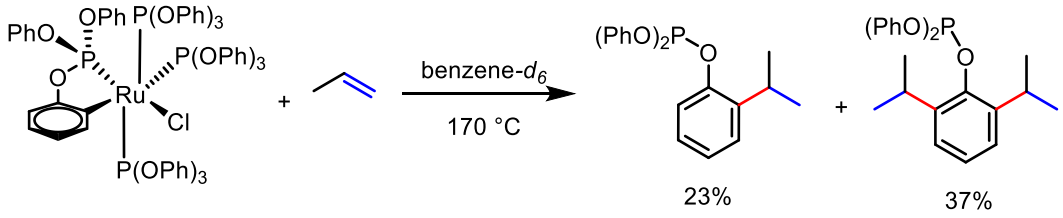
In the late 90s Tsuchimoto *et al.* developed as one of the first a scandium catalyzed arylation of benzyl alcohols **82**, addressing some issues of Friedel-Craft (Scheme 18 b). Even though the Lewis acid was used in catalytic amounts and the side product was only water, the selectivity issue could not be solved, giving a mixture of *ortho*, *para* and *meta* substitution for certain compounds (e.g. toluene).[55,56] A different strategy to avoid pre-activation of one coupling partner would be to use double bonds as reactive sites, such as in styrene (e.g. **84**, if R^3= H). Rueping and coworkers showcased that 1 mol% bismuth(III) triflate is able to catalyze the reaction of benzyl alcohols with arenes. They were able to use the same catalyst for styrene derivatives **84** with only 0.5 mol%

catalyst (Scheme 18, c).[57] Even though the catalytic loading is low and the yields are generally good, the authors observe mixtures in terms of regioselectivity (*ortho*, *para* and *meta*)

a) first catalytic *ortho*-selective C-H alkylation of phenols by Lewis and Smith

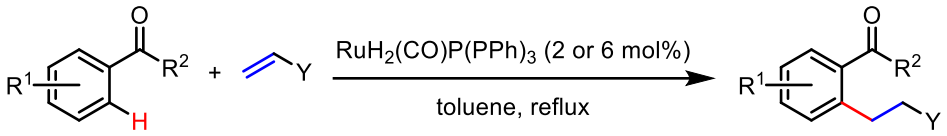


73a **86** **87** **88** **89**



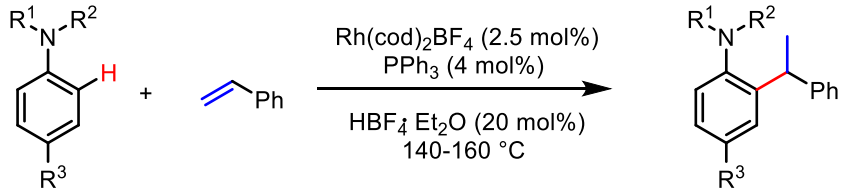
90 **91** **92** **93**

b) Murai's ruthenium catalyzed hydroarylation of olefins



94 **95** **96**

c) first practical hydroalkylation of anilines by Beller

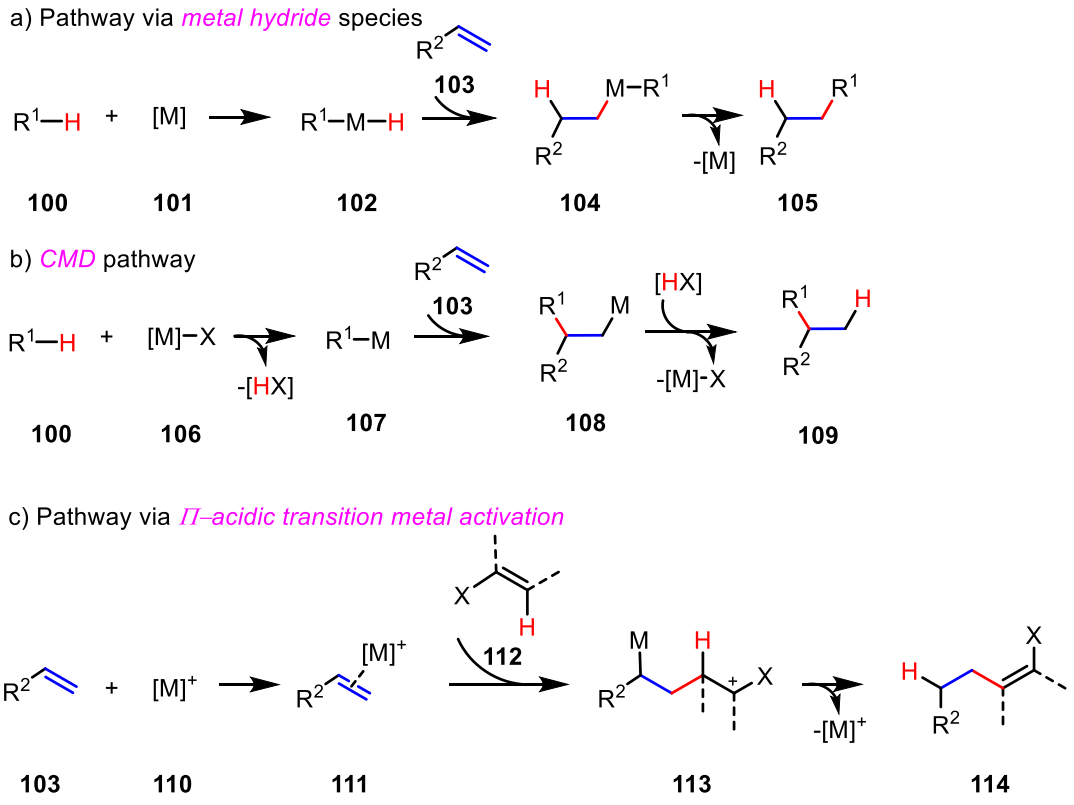


97 **98** **99**

Scheme 19: Pioneer work in the field of hydro arylation.[58,59]

This regioselectivity issue was solved by the rise of transition metal catalyzed reactions. The first *ortho*-selective reaction was developed by Lewis and Smith in 1986, despite di-functionalization occurred (Scheme 19, a)).[58] The ruthenium complex **89** had triphenyl phosphite as ligand, generating a directing group *in situ*. However, the reaction only worked with ethylene **86** and

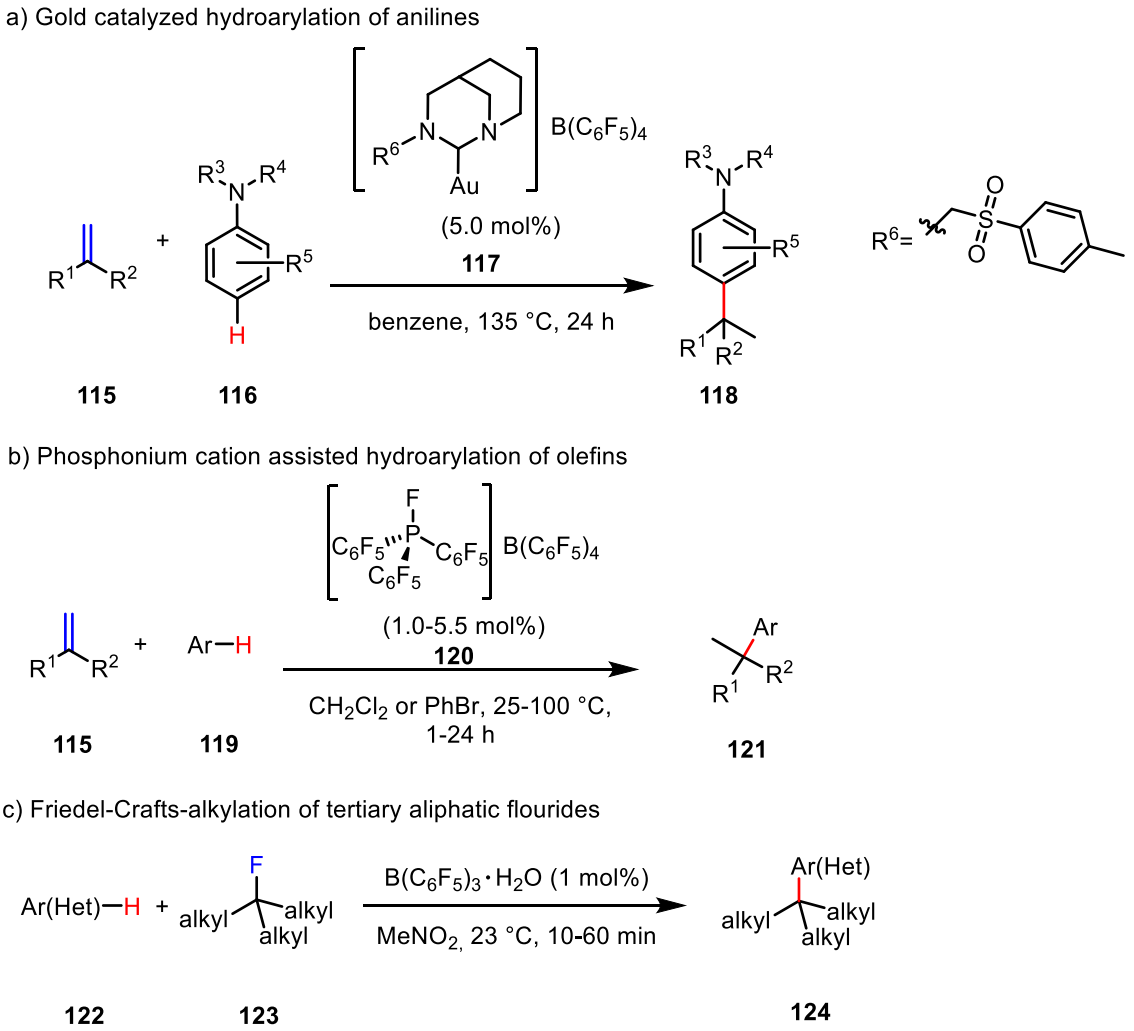
styrene, giving di-functionalization in case of ethylene **88** and a polymeric product for styrene. When propylene **92** was engaged with **90**, branched products **92** & **93** were detected. Another particularly important contribution to this field is the work of Murai *et al.*, in which the reaction of aromatic ketones **94** was described with olefins **95** (Scheme 19 b).[59] The method gives good yields for a variety of linear anti-Markovnikov products **96**. In 1992, Brunet *et al.* discovered the first *ortho*-alkylation of aniline with norbornene, which he studied extensively later.[60] The authors expected the hydroamination product, which was described before, but made this unpredictable discovery.[61] Amines are challenging for *(pseudo)ortho*-alkylation reactions due to their potential coordination to the metal thus deactivating the catalyst.[62] Despite these problems, Beller and coworkers were able to develop a rhodium catalyzed *ortho*-hydro alkylation of anilines **97** with styrene **98** (Scheme 19 c)).[63] It should be noted, that the reaction is Brønsted acid assisted and was applicable to electron rich anilines (high *N*-basicity). Since the development of these methods, many transition metal catalyzed alkylations have been developed, which can proceed via three different main mechanistic pathways (Scheme 20).[64–66]



Scheme 20: Major mechanistic pathways for TM catalyzed alkylations.[64,65]

If a low valent metal is used as the catalyst, the pathway is usually mediated by a metal-hydride intermediate **102** (Scheme 20 a)). The metal inserts to the C-H bond (oxidative addition), followed by a migratory insertion of the olefin. A reductive elimination gives the alkylated product **105**. The last step is considered to be rate limiting and controls the regioselectivity of the olefin insertion in consequence.[65] The reaction of Murai is a very good example of this mechanistic scenario (see Scheme 19 b)).[67] The second possibility is a carbon-metal bond, which is generated by an electrophilic metalation of the C-H bond (Scheme 20 b)).[64] Migratory insertion gives a new carbon-metal bond, which is protonated and gives a Markovnikov product **109**. This is illustrated by the reaction of Lewis and Smith, which gives only branched products **92** & **93** and has no evidence of metal-hydride species **102** (see Scheme 19 a)).[58] The last major mechanistic scenario which will be discussed, is the activation of the olefin **103** by a Lewis acidic transition metal (Scheme 20 c)). This allows a nucleophilic attack by an electron rich coupling partner **112**. After a [1,3] proton shift, the product **114** is formed.[68] The hydro alkylation of anilines **97** by Beller (Scheme 19 c)) is a good example for this type of pathway. The authors state that rhodium is activating the styrene **98** and is then attacked by the protonated aniline.[63]

Although transition metal catalyzed reactions are versatile and widely applicable, the discovery of of frustrated Lewis pair catalysis (independent or in combination with a strong Lewis acid) merged as an alternative for C-C bond formation.[56,69,70]



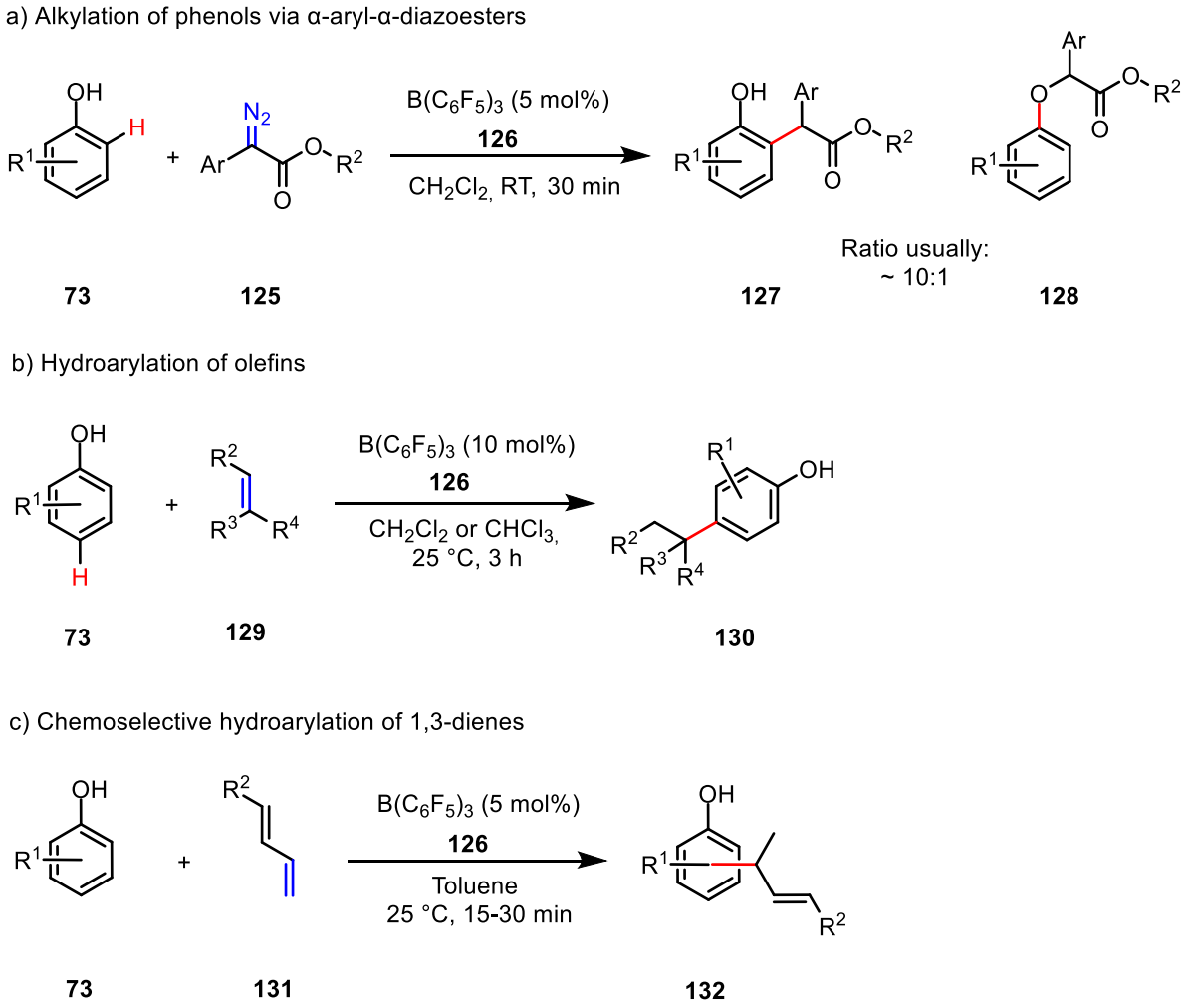
Scheme 21: Selection of $B(C_6F_5)_3$ based catalyzed reactions.[71]

Tris(pentafluorophenyl)boranes (e.g. **117** & **120**) attracted special attention as a versatile catalyst (Scheme 21).[69,71] Especially regarding alkylation of amines, it was a new alternative to transition metal catalyzed reactions and to classical Friedel-Crafts reactions, which are not suitable for this functional group.[71] Hu *et al.* discovered that the shown gold catalyst **117** was able to alkylate amines **116** in *para* with good yields (Scheme 21 a)).[71] Albeit *ortho*-functionalization was detected in some cases, the method can be considered a pioneer work for the hydro arylation of (*N,*)*N*-alkylated anilines **116** due to the lack of examples.[63,72]

Stephan and coworkers used the same borane with a phosphonium cation **120** as catalyst for the hydro arylation of aromatic compounds **119**, such as amines, phenols, indoles (Scheme 21 b).[73] The authors proposed an electrophilic phosphonium catalyzed (EPC) cycle, in which the olefin **115** (e.g. styrene) gets activated by the phosphor compound. After an initial publication for the synthesis of azides, Moran and coworkers used the tris(pentafluorophenyl)borane water adduct

for the cross-coupling reaction of tertiary aliphatic fluorides **123** with aromatic compounds **122** (Scheme 21 c)).[74]

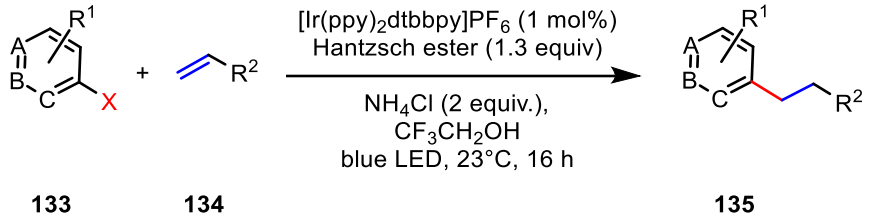
Due to the ubiquity of phenols **73** in natural products and synthetic chemistry, many methods were developed in terms of functionalization in different position.[75][76] Although, frustrated Lewis pair catalysis with phenols **73** has been less studied, some example have been developed over the past couple years (Scheme 22).[77–79]



Scheme 22: Different $B(C_6F_5)_3$ catalyzed hydroarylation methods.[77–79]

One early example was developed in 2016 by Zhang and coworkers, in which *α*-aryl *α*-diazoesters **125** react *ortho*-selectively with phenols **73** (Scheme 22 a)).[78] This was the first tris(pentafluorophenyl)-borane **126** catalyzed *ortho*-selective C−H substitution of unprotected phenols **73**. The authors had observed good chemo selectivity for the *ortho*-substituted product **127** rather than the favored X-H insertion **128** (10:1), which is known for diazo compounds in

transition metal catalyzed reactions.[80] The *ortho*-selectivity arises from the hydrogen bonding between a fluorine and the hydroxy group, enabling the boron to activate the *ortho* C-H position. One year later Bentley *et al.* developed a hydro arylation of unprotected phenols **73** with olefins **129** with almost the same conditions (Scheme 22 b)). Interestingly in this case, only *para*-substituted products **130** were detected for unprotected phenols **73**.[79] With a lower catalytic loading and toluene as solvent, 1,3 dienes **131** were transformed chemo selectively to *ortho*-allyl phenols **132** (Scheme 22 c).[77] The authors showed via DFT that the reaction undergoes a borane promoted protonation/Friedel-Crafts pathway, which involves a π- complex.



Scheme 23: Hydroarylation of unactivated olefins.[81]

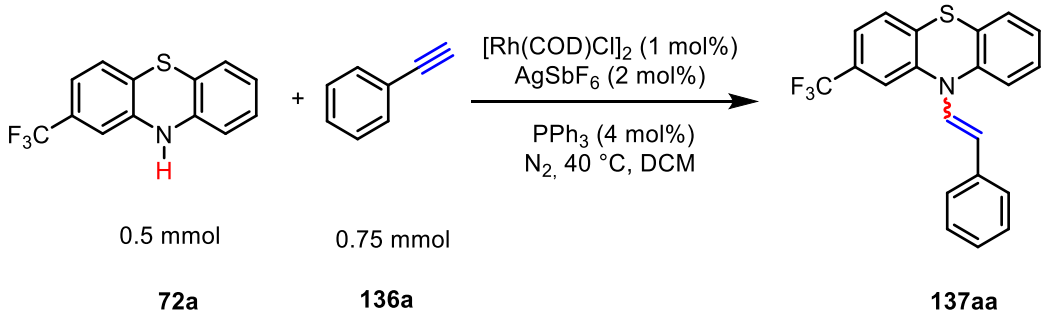
With the resurrection of radical chemistry more and more organic chemists focused on light driven/catalyzed reactions, which can access open shell reactivity.[82] Many different cross coupling reactions have been developed over the last decades, including (hydro) alkylation and arylation methods.[82,83] The working group of Jui had contributed in this field over the last few years.[84] Particularly, the selective anti-Markovnikov hydro arylation of pyridines **133** at any position is remarkable (Scheme 23).[81] The reaction was enabled by the 2,2,2-trifluoroethanol system imparting an electrophilic radical on the pyridine species **133**.

2.2 Motivation and task

Based on previous transition metal catalyzed hydroaminations, Christian Rank (PhD student in the Patureau group) was investigating phenothiazine **72** as an amination reagent for alkynes **136** (Scheme 24).[85,86]

Indeed, the desired product **137aa** was detected by Rank under the initial conditions shown in Scheme 24 a). Even though the conditions were adjusted, the product **137aa** could never be isolated in an applicable yield (Scheme 24 b)). The products may have decomposed on the acidic silica of the column.[87]

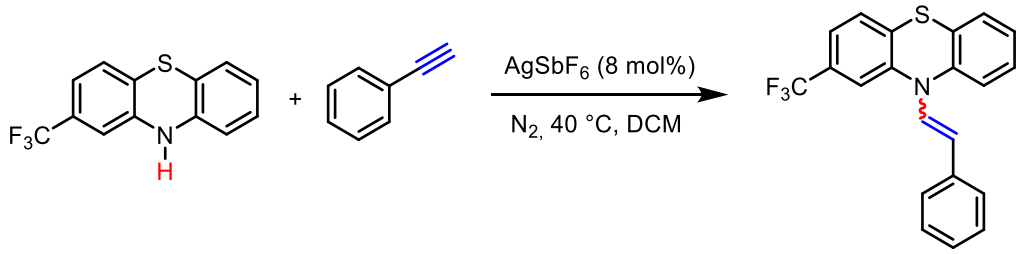
a) Initial hydro amination conditions of phenylacetylen by Rank



0.5 mmol 0.75 mmol

72a **136a** **137aa**

b) Adjusted hydro amination conditions of phenylacetylen by Rank

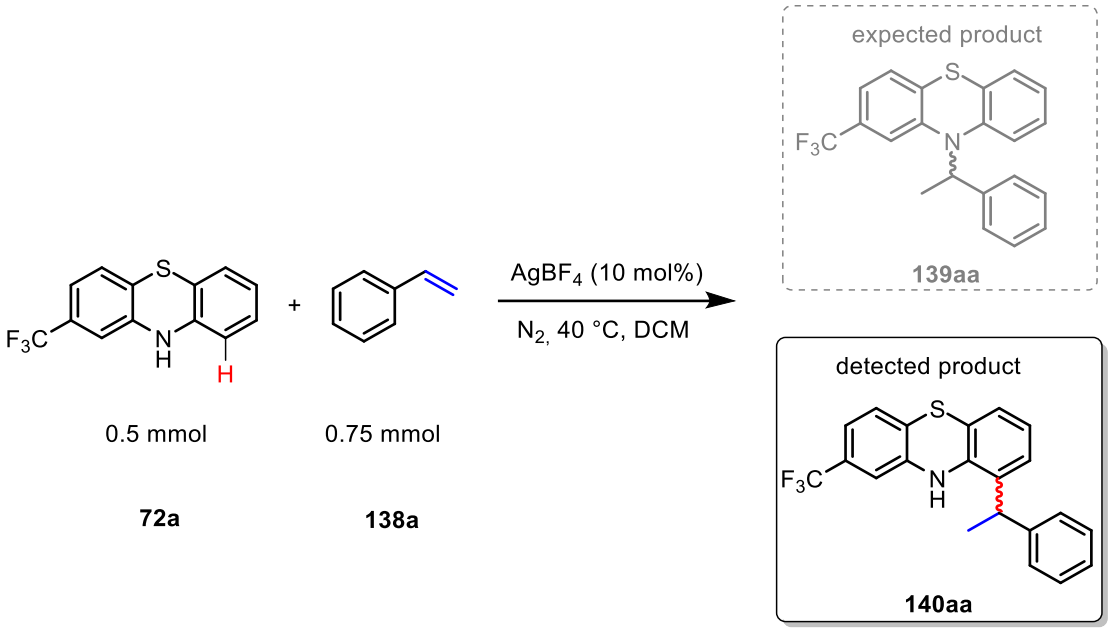


0.5 mmol 0.75 mmol

72a **136a** **137aa**

Scheme 24: First hydroamination reactions by Rank.[86]

To avoid complex purification methods of the enamine **137aa**, styrene **138a** was engaged in this reaction and later optimized by Rank (Scheme 25).[86] Unexpectedly, Rank observed an alkylation of phenothiazines in C1 position **140aa** and the desired hydro aminated product **139aa** was not detected.



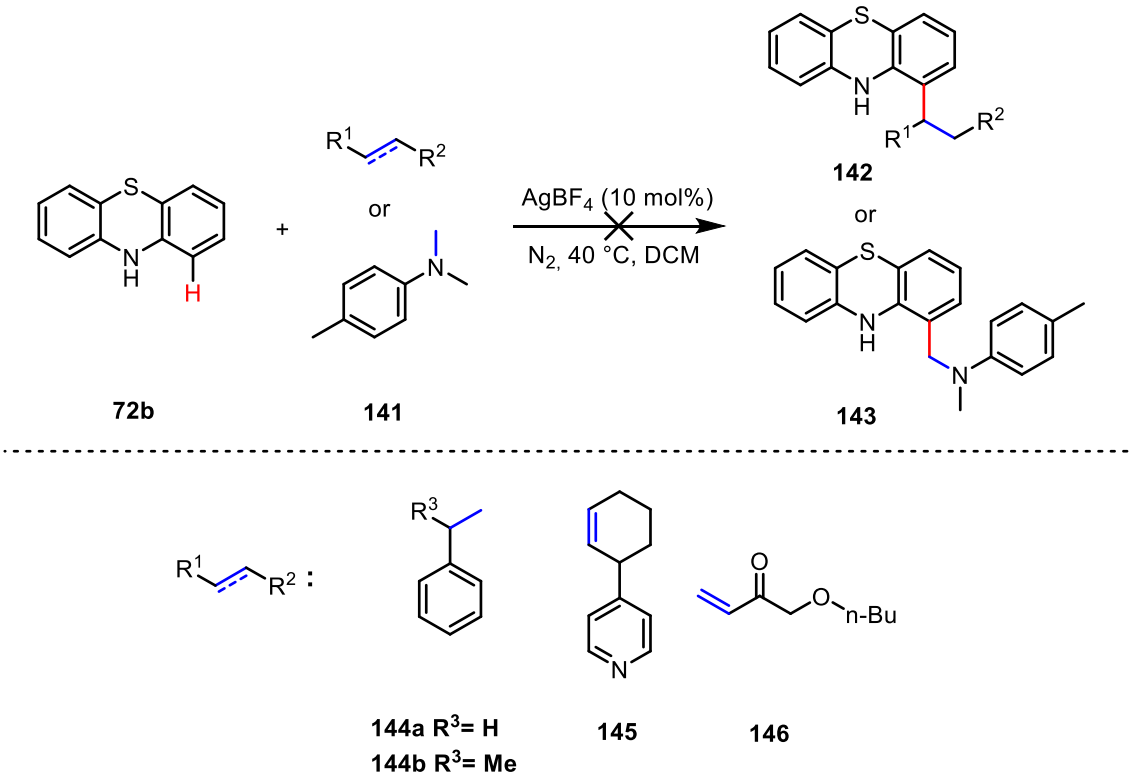
Scheme 25: Optimized reaction conditions for hydroarylation of phenothiazine by Rank.[86,88]

With this result and optimized conditions in hand, the scope should be investigated, if necessary reoptimized and mechanistic experiments should be carried out to propose a plausible mechanistic scenario.

2.3 Results and discussion

2.3.1 Diversity of the method

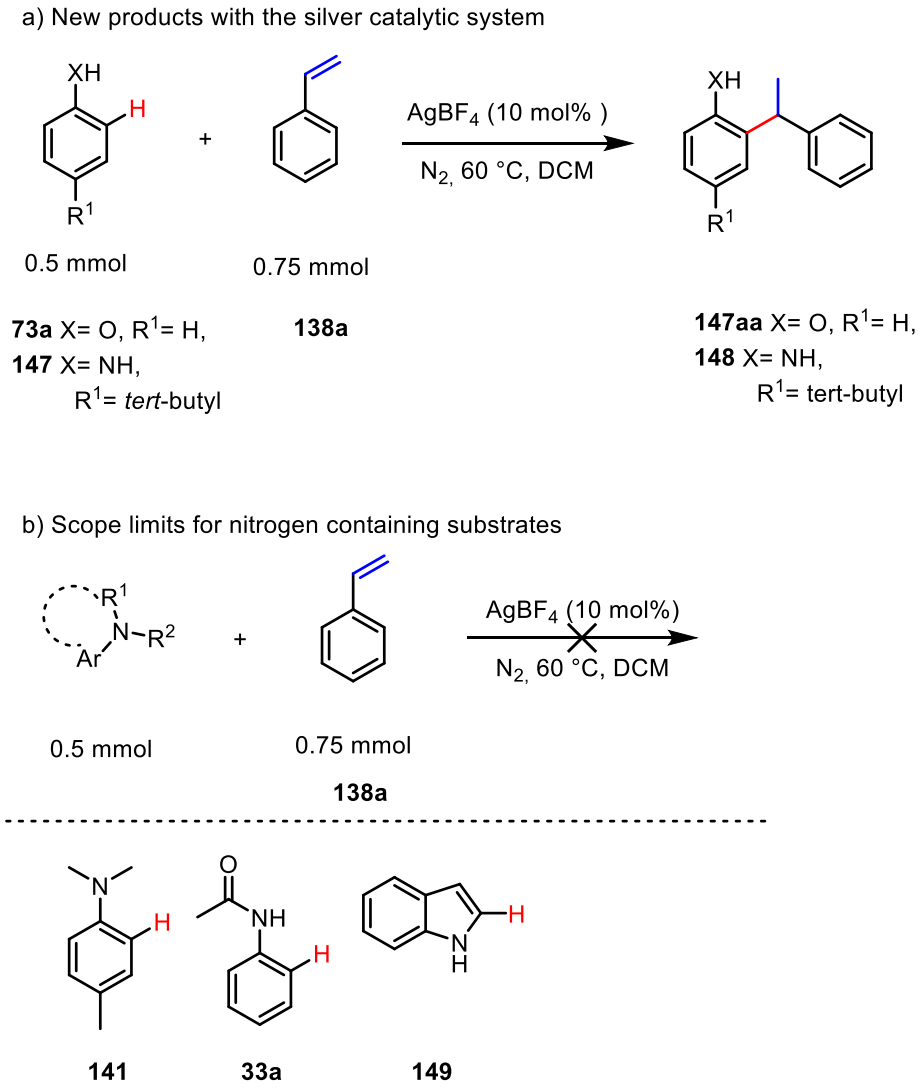
Since many (hydro)arylation processes are one electron processes, different substrates, in which a radical species might be plausible, were engaged under the conditions optimized by Rank to evaluate the range of the developed method (Scheme 26).[89]



Scheme 26: Various substrates, which were engaged in the silver catalytic system.

The reaction with ethyl- and isopropyl benzene **144a** & **144b** was not able to give any desired product **142**, even though a radical at the reactive carbon should be stabilized by electronic effects. The engaged pyridine derivative **145** was not successfully functionalized, neither at the pyridine ring nor the cyclohexenyl part. Michael-acceptors such as acrylates **146** or *N,N*-dimethyl aniline **141** were also inefficient as coupling partners under these conditions (Scheme 26).

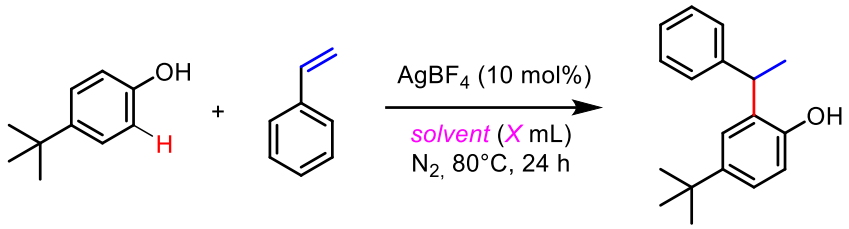
Since an one-electron process would be conceivable not only at styrene **138a** but also at phenothiazine **72**, phenothiazine **72** was also replaced by potential coupling partners and tested with a little elevated temperature to adjust for higher activation barriers (Scheme 27).[90]



Scheme 27: Engaged substrates with the modified conditions.

Although the hydro arylation of *N,N*-dimethylaniline **141**, indole **149** or acetanilide **33a** was not successful (Scheme 27 b), new products **147aa** & **148** were detected with styrene **138a** as coupling partner for phenol **73a** and aniline **147** (Scheme 27 a). **148** was only detected in traces and was not pursued anymore. The initial reaction with phenol **73a** at 60 °C was not purified since a lot of starting material was detected by TLC. Only a few parameters were changed to have a high yield of the desired product (Table 6). The *ortho*-hydro arylated phenol **147ba** was observed with 99% by GC and isolated in 88% yield (Table 6, entry 10).

Additionally, diarylated amines were found to be compatible and investigated by C. Rank.[86]



X mmol **73b** | *Y* mmol **138a** | **147ba**

Entry	X [mmol]	Y [mmol]	solvent [mL]	Yield [%]
1	0.5	0.75	CH_2Cl_2 (1)	68
2	0.5	0.75	CH_2Cl_2 (2)	59
3	0.5	0.75	CH_2Cl_2 (3)	42
4	0.5	1.0	CH_2Cl_2 (1)	63
5	0.5	1.5	CH_2Cl_2 (1)	50
6	0.75	0.5	CH_2Cl_2 (1)	84
7	1.0	0.5	CH_2Cl_2 (1)	85
8	1.5	0.5	CH_2Cl_2 (1)	96 (71)
9[a]	1.5	0.5	$C_2H_4Cl_2$ (1)	89
10[b]	1.5	0.5	$C_2H_4Cl_2$ (1)	99 (88)

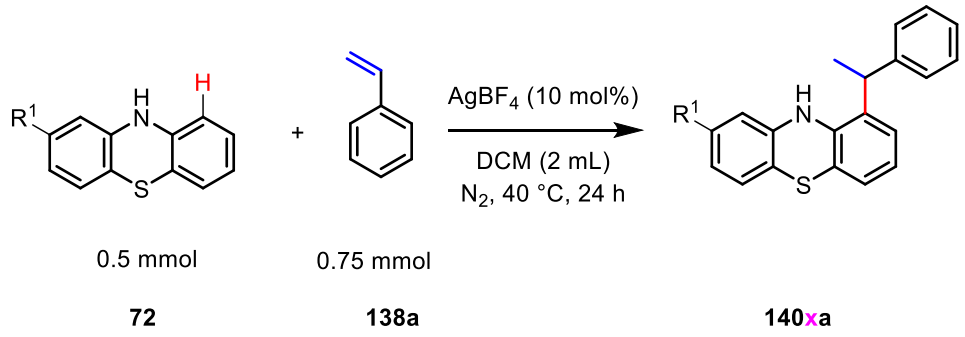
Table 6: Yields were determined by GC. Isolated yields in parenthesis. [a]Reaction was carried out at 90 °C, [b]reaction was carried out at 100 °C.

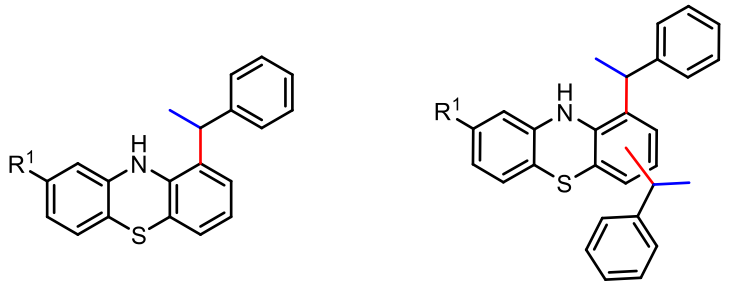
2.3.2 Examination of the substrate scope

With the optimized conditions by Rank (Scheme 25), additional phenothiazine derivatives **72** were tested (Scheme 28). With strong electron withdrawing groups in two position, double functionalization **140'** was observed (acetyl **140ca'** or CF_3 **140aa'**). As shown by Rank, only 2-chlorophenothiazine was able to deliver the product in 50% yield without detection of double functionalization.[86] Electron donating groups in two position were found to be not reactive enough (methoxy-group **72g**) or only deliver a low yield (methyl thiol **72d**). Special phenothiazine

derivatives (e.g. 10*H*-benzo[*b*]pyrido[2,3-*e*][1,4]thiazine **72e**) were tested additionally, but no conversion was observed.

In general, the phenothiazine scope was found to be limited, since most of them were converted into double functionalized product or no product at all. However, styrene derivatives were tolerated well in the reaction.[88]

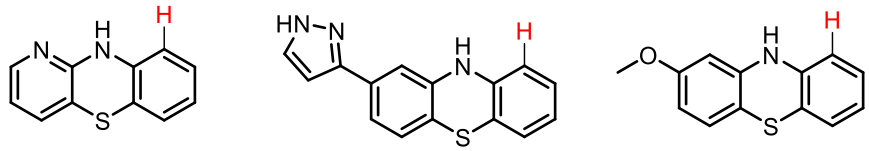




140aa: R^1 = CF_3, 42%
140ca: R^1 = acetyl, 72%
140da: R^1 = SMe, 26%

140aa': R^1 = CF_3, 55%
140ca': R^1 = acetyl, 2%
140da': R^1 = SMe, n.d.

No reaction:

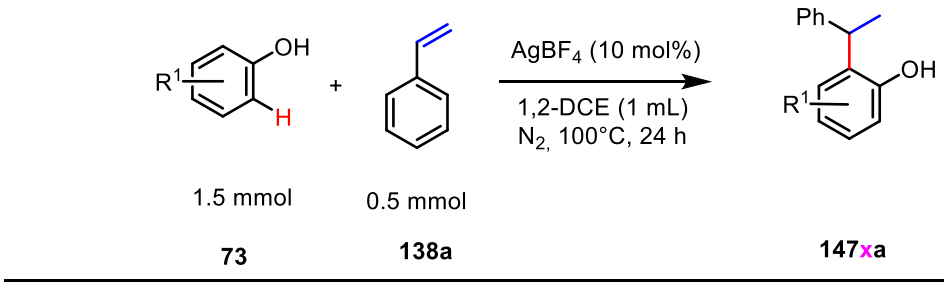


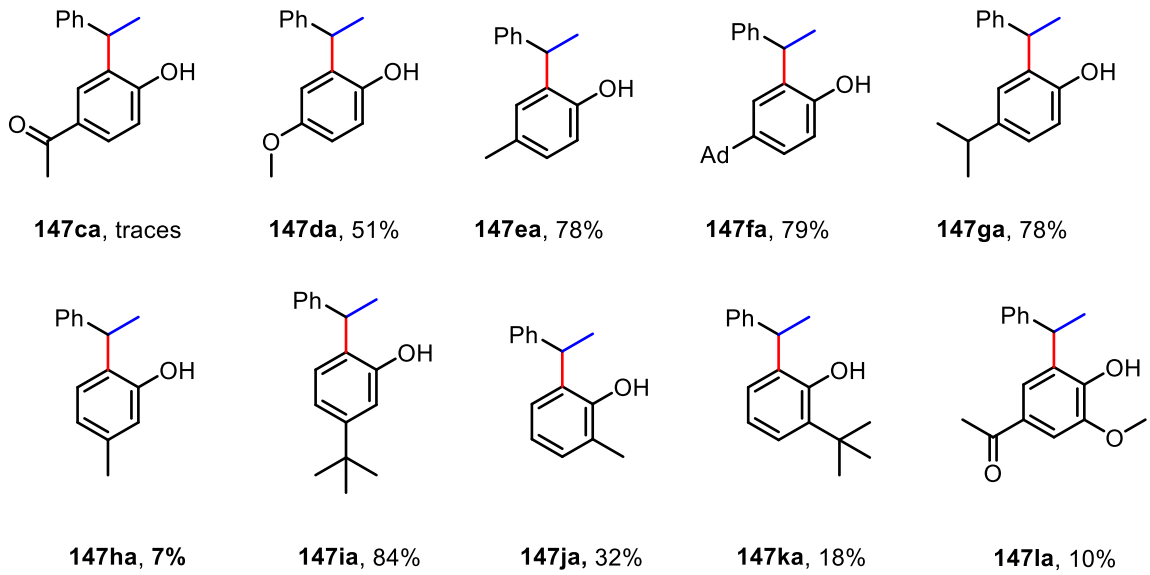
72e **72f** **72g**

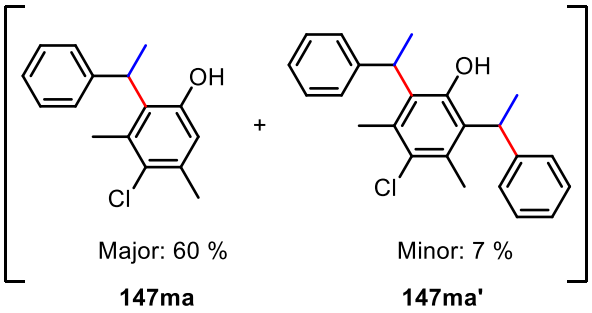
Scheme 28: Part of phenothiazine scope.

Different phenols **73** were examined next (Scheme 29). Generally, electron donating groups on phenols (**147da**-**147ga**) deliver good yields. Especially in *para*-position, phenols with an alkyl substituent were transformed with a high yield to the desired product (**147ea**-**147ga)**. Additionally, *tert*-butyl and methyl group were tested in *meta* and *ortho* positions. In contrast to electronic

effects, steric effects can be almost neglected in *meta*, in terms of influence on the yield. *Ortho*-substituted phenols, however, were less well transformed to the desired product with increasing steric effects. Thus, only 18% was obtained for *ortho*-*tert*-butyl- **147ka** whereas *meta*-substitution delivers an excellent yield of 84% for **147ia**. An electron withdrawing group only gave the product **147ca** in trace amounts. Compensating this effect with an electron donating group in *ortho* was not effective (**147ia**). However, for the example of 3,5-dimethyl-4-chlorophenol, the product was isolated in a good yield although dialkylation was observed (**147ma** & 1**47ma'**).







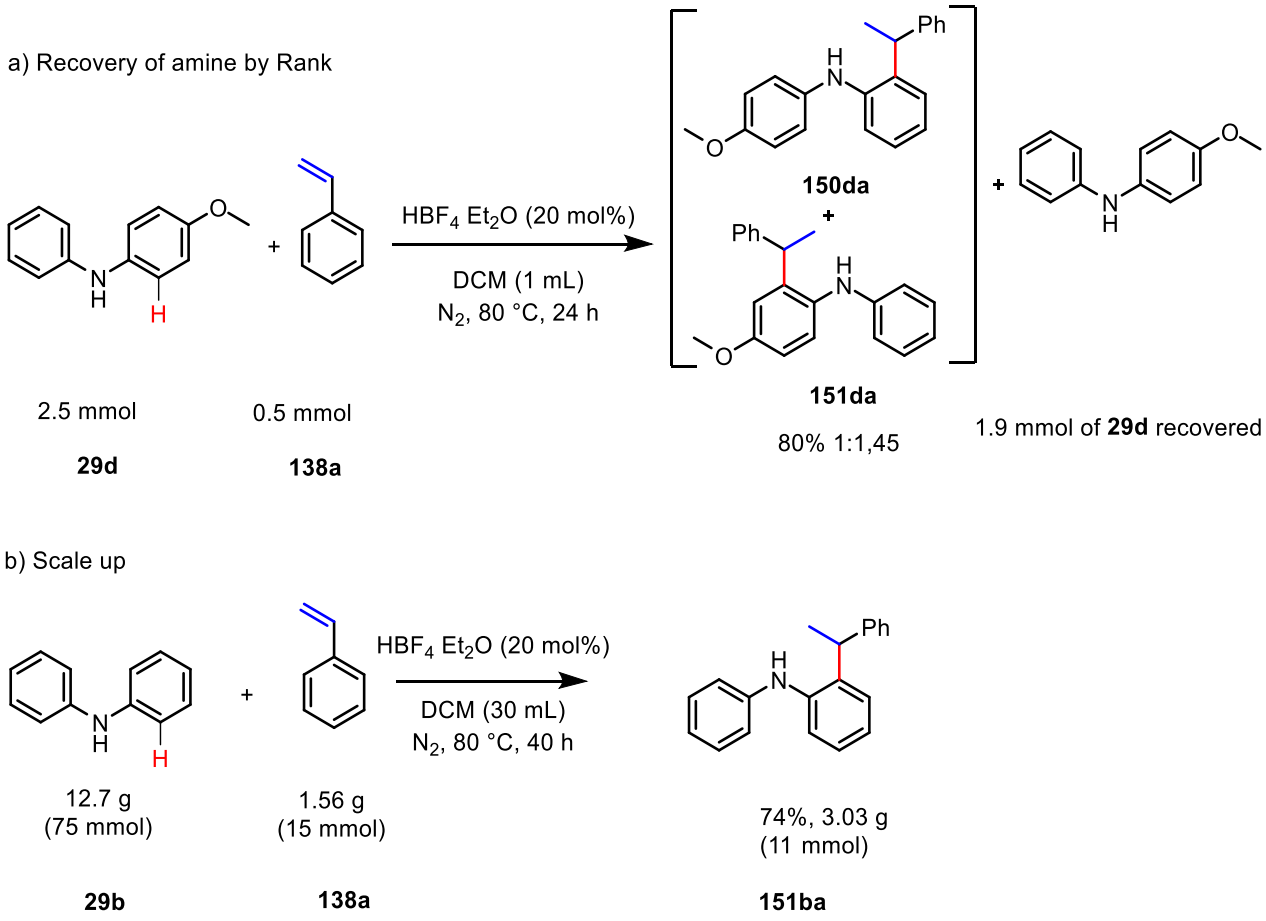
Scheme 29: Phenol scope for catalytic hydroarylation.

2.3.3 Synthetic utility

The silver(I) catalyzed reaction was found to be useful in terms of synthetic applicability. The first alkylation was always identified in *ortho*-position to the hetero atom for all cases (phenothiazine, phenol, diarylamine).[88] This is surprising since phenothiazine tends to be functionalized in *para* to the N-H (C3) by electrophilic aromatic substitution.[51,91]

For unsubstituted phenols and diarylamines alkylation at *para*-position was never found, making this method superior regioselective wise to other alkylation strategies (e.g. for phenol with $B(C_6F_5)_3$).[77,79]

As it was found out in the parallel mechanistic studies, tetrafluoroboric acid diethyl ether complex was also able to catalyze the reaction in case of phenols and diarylamines (see 2.3.4). With 20 mol% catalytic loading, the Brønsted acid was able to deliver higher yields for all diarylamine cases compared to the silver(I) catalyst.[86,88] Also for the case of 4-methoxy-*N*-phenylaniline **29d**, which was not detected in the reaction catalyzed by the silver (I) species, was isolated in a good yield with 80% by Rank (Scheme 30 a)).[86] However, the optimized conditions require five equivalents of amine. Therefore, it was demonstrated that the excess amine can be recovered (~4 equivalents).[86]



Scheme 30: a) Recovery of amine.[86] b) Scale up with diarylamine.

To demonstrate the utility of the here described method, a scale up was conducted with diphenylamine **29b** (Scheme 30 b)). With the tetrafluoroboric acid diethyl ether complex, the alkylated diphenylamine product **151ba** was also isolated in good yield for a scale up. The same product **151ba** was first synthetized by Zhu *et al.* in 2018 (Table 7).[92] The authors used a frustrated Lewis pair catalyst which is readily available but rather expensive. As shown in Table 7 both catalysts (silver and fluoroboric acid), which were used in cooperation with Rank, are considerably cheaper, more atom economical and easily scalable.[86,88] This makes both systems to modern, practical and cost-effective methods, which can be conducted in gram scale (comparison of the medium size containers, see Table 7).

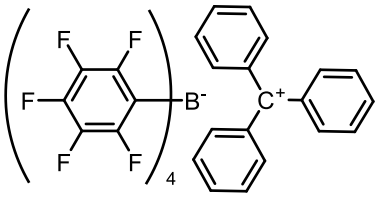
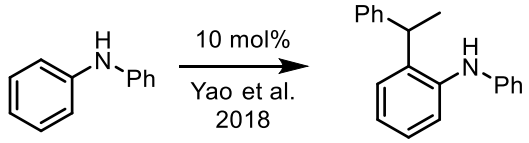
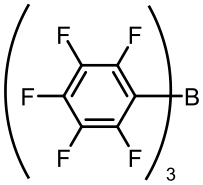
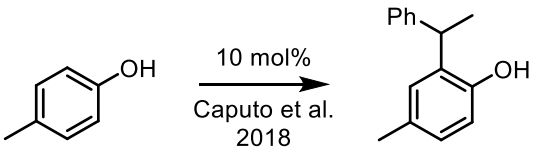
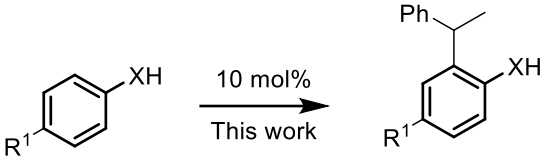
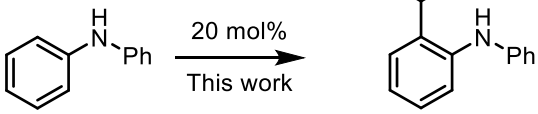
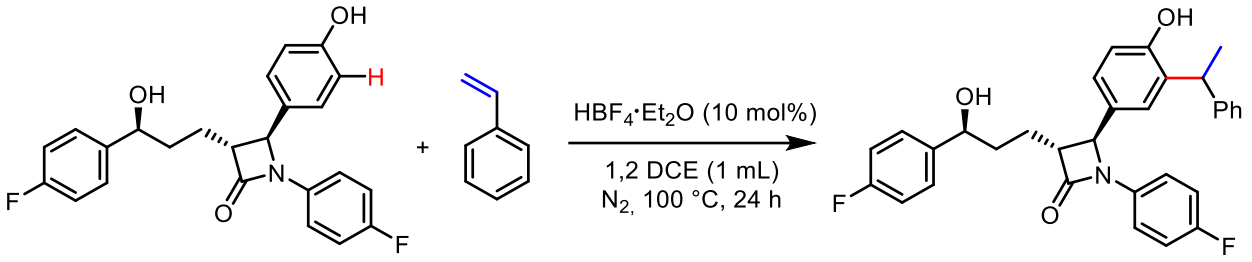
Catalyst	Cat. Price [€/mmol]	reaction and catalytic loading	Scale up reported
	112.17	 **29b** 10 mol% Yao et al. 2018 **151ba,** 38%	✗
	82.80	 **73e** 10 mol% Caputo et al. 2018 **147ea**, 61%	✗
$AgBF_4$	2.59	 10 mol% This work **29b**: R^1 =H; X= NHPh, 65% **73e**: R^1= Me; X= OH, 78% **151ba,** 65% **147ea,** 78%	✗
$HBF_4 \cdot Et_2O$	0.12	 20 mol% This work **29b** **151ba** Scale: 0.5 mmol 80% Scale: 15 mmol 74%	✓

Table 7: Comparison of the economic efficiency of the different catalytic systems for hydroarylation.[79,88,92,93]

Last, the functionalization of a drug ezetimibe **73n**, which is used for high blood cholesterol, was engaged (Scheme 31).[94]



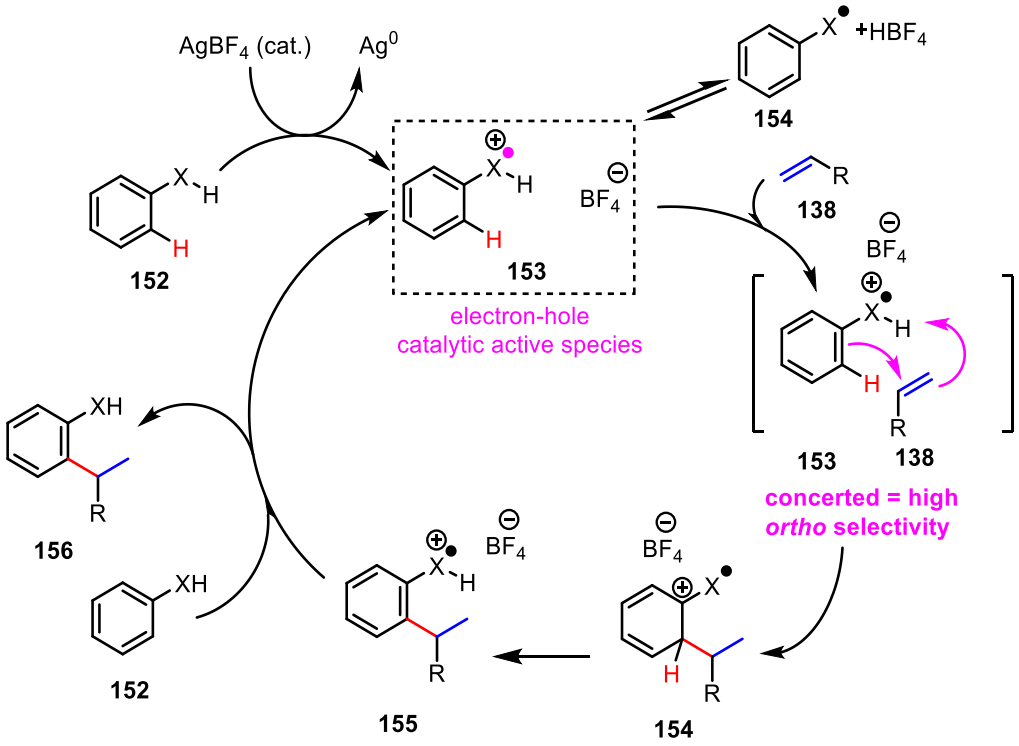
1.5 mmol **73n** | 0.5 mmol **138a** | Traces **147na**

Scheme 31: Hydroarylation attempt of ezetimibe.

The desired product **147na** was detected by TLC but only trace amounts were isolated. However, two fluorine signals and the desired quartet for the benzylic carbon of the styrene-unit were identified in the corresponding NMR-spectroscopy-data, indicating the formation of the right structure.

2.3.4 Mechanistic investigations

To have a clear understanding of the method, mechanistic experiments were performed by both authors.[88] Based on the observations for the high *ortho*-selectivity (see 2.3.3) an electron-hole catalyzed mechanism was initially proposed for the silver catalyzed reaction (Scheme 32).
Through abstracting one electron from the hetero atom of **152** by the used silver (I) compound, the acidity of the corresponding $N^{\bullet+}$—H or $O^{\bullet+}$—H acidities of **153** should be increased in such a way, that a concerted protonation and C-C bond formation is considered feasible. The catalytic cycle is closed by the reaction of the formed radical cation **155** with a starting material molecule.



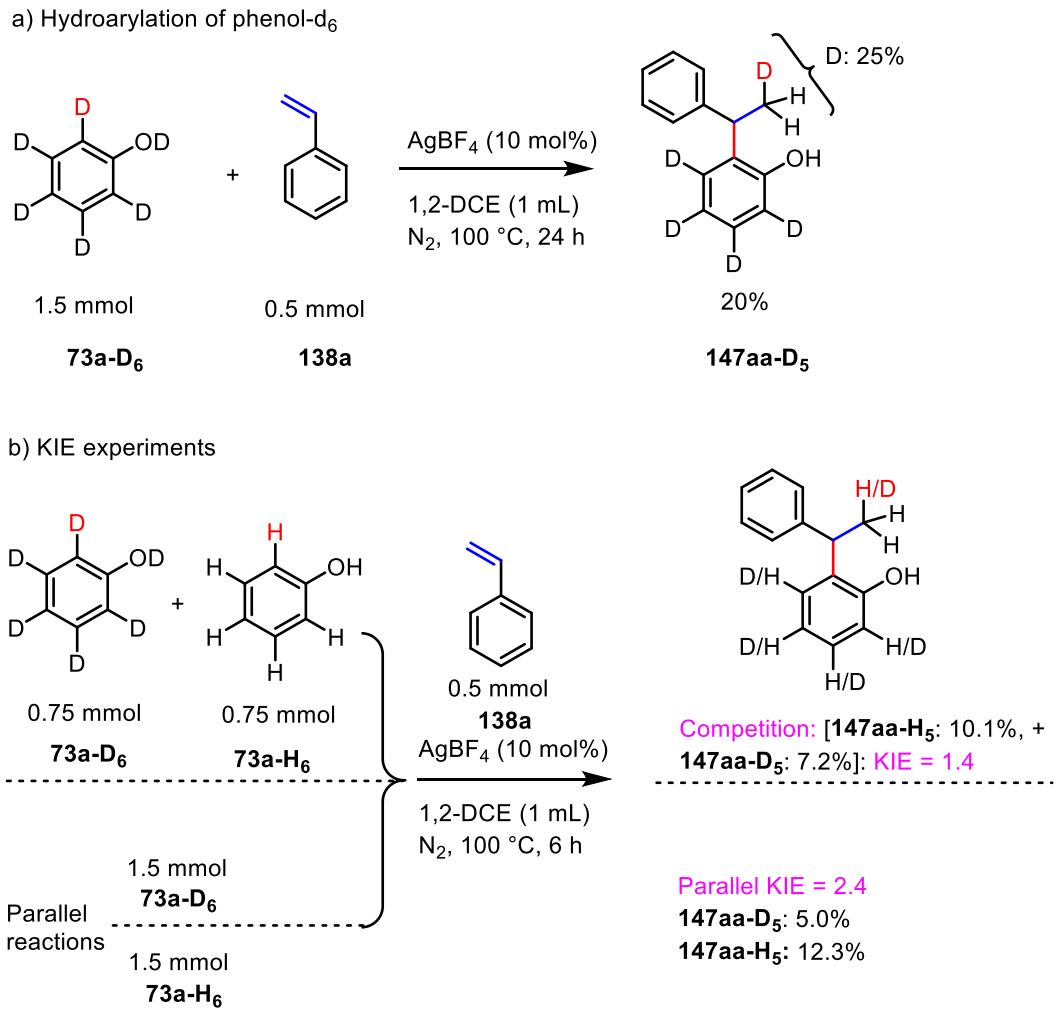
Scheme 32: First proposal: electron-hole catalysis for diarylamine and phenols.[88]

First test reactions were run by Rank, in which *N*-methyl phenothiazine was engaged under optimized conditions.[88] As expected, the *N*-protected phenothiazine gave no product, indicating the need of a hetero-proton in *ortho* to the functionalized bond. Thus, a Lewis acid mechanism seems unlikely (detection of C1 or C3 coupling product).

A typical radical scavenger, TEMPO was tested by Rank.[88] The reaction with phenothiazine did not occur, hinting a radical mechanism. This could be explained by the reduction of silver (I) to elemental silver by the radical scavenger and the formation of the corresponding oxoammonium tetrafluoroborate salt, interrupting the initial step of the catalytic cycle. To check if an electron hole is generated, a control experiment was carried out in which the speculated catalytic electron hole is generated by a nonmetallic single electron oxidant by Rank.[88] Therefore, $NOBF_4$ was selected as a nonmetallic salt to generate the catalytic electron hole. Since it possesses the same counterion as the silver precatalyst and reputed to possess a similar (slightly higher) redox potential as well, it was the ideal candidate for this purpose. Diphenylamine was chosen for the test and the hydroarylated product was obtained in a similar yield as with the silver tetrafluoroborate by Rank (Ag: 65% NO: 66%).[88]

Both experiments with TEMPO and $NOBF_4$ support the electron-hole catalysis for the silver(I) catalyzed system.

One of the last test reactions was carried out with tetrafluoroboric acid diethyl ether complex by Rank, since it should not be able to deliver the product, if an electron-hole is necessary for the reaction.[88] Surprisingly, all products were detected in relatively good or better yields compared to the silver catalyst. Additionally, it was found during the optimization that a cationic gold (I) compound (Bis-(trifluormethansulfonyl)-imidat-(triphenylphosphin)-gold(I)) also delivers the alkylated phenothiazine product.[88] These observations suggest that different mechanistic scenarios are possible for different types of catalysts.



Scheme 33: Deuteration experiments for hydroarylation of phenol.

Phenol-d_6 **73a-D$_6$** was engaged in the reaction yielding a 25% D-enriched methyl group (in **147aa-D$_5$**), which corresponds to 75% deuterium transfer, supporting a concerted transition state while the cross-coupling event (Scheme 33 a). The deviation from full deuterium transfer (33%) can be explained by integration errors in the proton NMR-spectroscopy or water traces, which

contaminated the reaction leading to a fast OH/ OD scrambling event. Finally, KIE experiments were carried out (Scheme 33 b): On the one hand the competition reaction showed a KIE of 1.4, which might indicate that the C-H cleavage is not involved in the rate limiting step. On the other hand, a KIE of 2.4 was detected when the reactions were carried out parallel, suggesting that the concerted C-C bond formation and proton/deuterium transfer are rate limiting.

All the conducted experiments by both authors suggest that various mechanistic scenarios are possible and are not mutually exclusive (Figure 6).[86,88] Considering that hydrolysis is always a possibility, the engaged silver (I) tetrafluoroborate might generate active tetrafluoroboric acid. Additionally to the electron-hole catalysis transition state, two other possibilities are suggested: Friedel-Crafts type and the activation of the proton assisted olefin by a transition metal (Figure 6), which were discussed before.

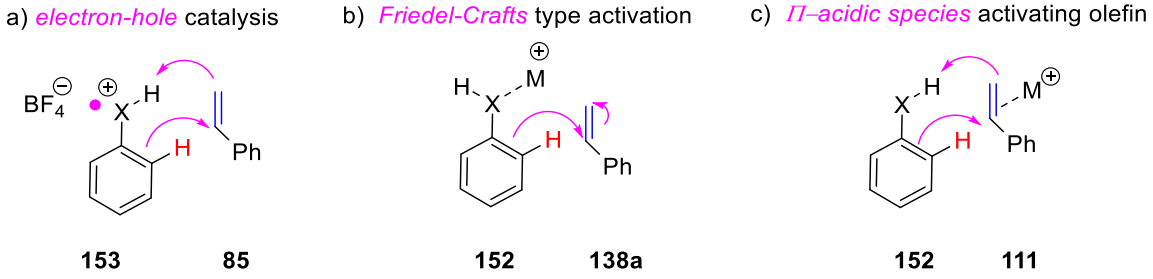
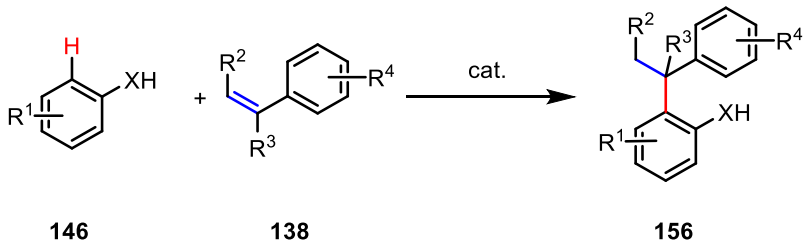


Figure 6: Possible transition states for the developed hydroarylation method.

2.3.5 Conclusion

A part of the scope of the first reported *ortho*-alkylation of phenothiazine **72** was investigated and found to be limited, since it resulted mostly in double functionalized products **140'** or low yields. Furthermore, the developed method was expanded by phenols **73**: with optimized conditions, excellent yields for phenols with electron donating groups were reported (Scheme 34). Even diarylamines **29** were found to be suitable substrates with slightly modified conditions by Rank.[86,88]



Scheme 34: General scheme for hydroarylations of phenols and phenothiazines.

In all cases a high *ortho*-selectivity was observed, making the developed method to a powerful strategy in terms of synthetic utility, especially in the light of functionalization of phenothiazines in C1 position. The applicability is further demonstrated by the development of a very cost-effective and selective method to alkylate phenols or diarylamines compared to the previously described organoboron catalysts and the successful gram scale synthesis.

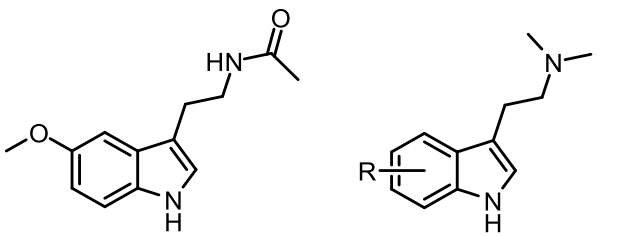
Three possible mechanistic scenarios were identified depending on the reaction conditions: Brønsted acid catalysis, Lewis acid catalysis and electron hole catalysis. The proximal X-H functional group to *ortho* was essential for reactivity and *ortho* regioselectivity, undergoing a typical concerted protonation/C−C bond-formation pathway.

3 Redox efficient indole synthesis

3.1 Background

3.1.1 Indoles and their synthesis

Due to their biological activity, as well as their frequent occurrence of indoles in drugs and natural products, indoles are considered to have an immense significance in organic chemistry.[95] One prominent example is melatonin **157**, which is a hormone regulating the sleep-wake cycle in the human body.[96] *N,N*-dimethyltryptamine and its derivatives **158** have been discovered widely in different animals and plants, being used by different cultures for rituals in South America over centuries (Figure 7).[97]



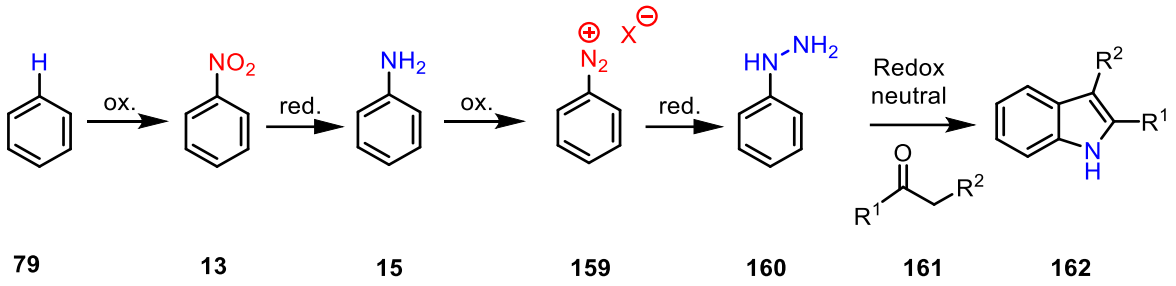
Melatonin **157**

Base structure of *N,N*-dimethyltryptamine **158**

Figure 7:Structures of two important alkaloids.

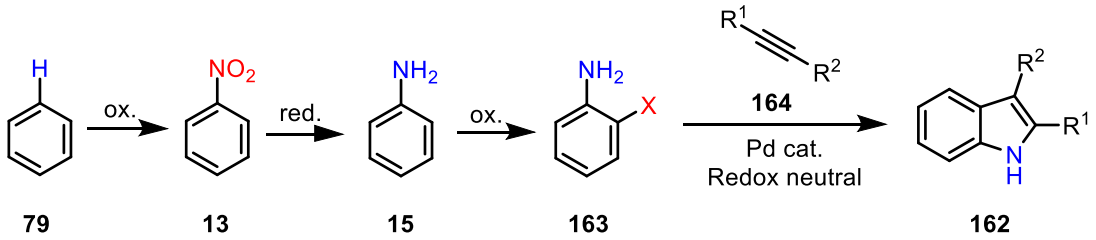
These are just two examples, which led to the development of many synthetic strategies for the indole scaffold **162** over the past years.[98,99] One of the earliest methods was discovered by Fischer in 1883, utilizing hydrazines **160** and enolizable ketones **161** .[100,101] Since then, many synthetic approaches have been developed using a similar strategy.[98,102]

A little-noticed problem of early organic chemistry was that the functional groups were usually designed using multiple pre-activation steps, that the desired reactivity would take place. This occurs also in the Fischer indole synthesis, in which the hydrazine starting material **160** must be pre-synthesized usually with reducing and oxidizing back and forth (Scheme 35). After this, the hydrazine **160** reacts with the ketone **161** in a redox neutral step.



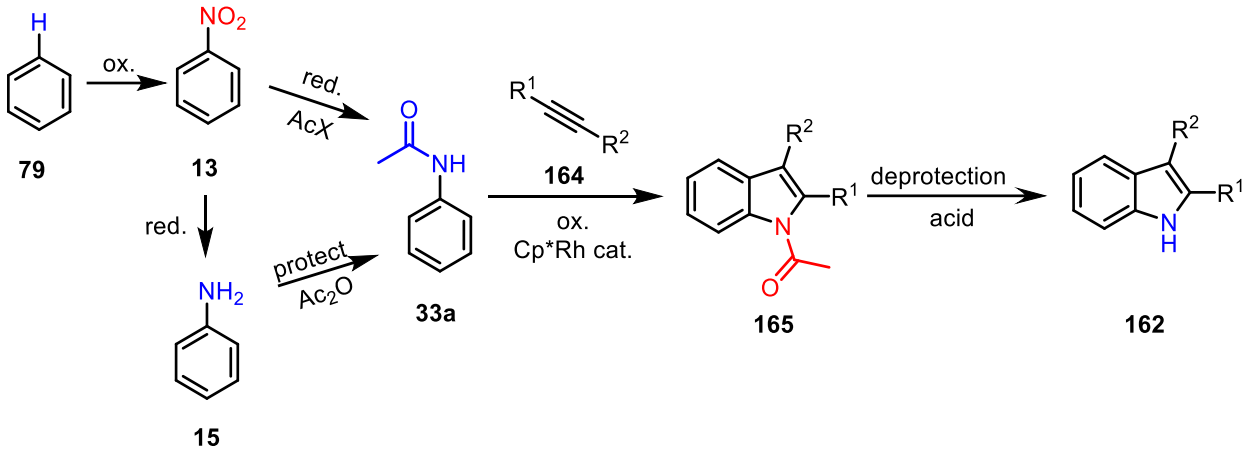
Scheme 35: Indole synthesis developed by Fischer starting from benzene.[101]

With people's increasing awareness of the environment and resource consumption, developing more sustainable and step efficient synthetic strategies has risen in the last years. A simple way to achieve a more sustainable route would be to reduce redox operations and the resulting chemical waste. In 1991, a shorter route was developed with anilines **15** by Larock *et al*..[103,104] Palladium was utilized as the catalyst, in a redox neutral cross coupling reaction with alkynes **164** as coupling partner (Scheme 36). The *ortho*-halogenated aniline **163** was required as the preactivated carbon bond for the oxidative addition to occur.



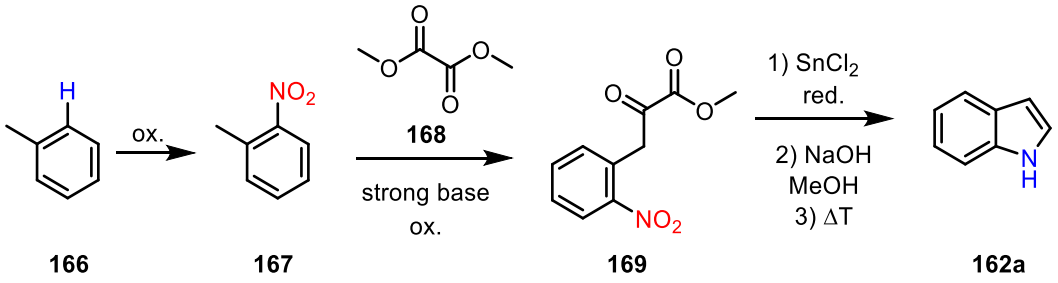
Scheme 36: Indole synthesis developed by Larock. [103]

Inspired by the developments in rhodium C-H activation, protected anilines **33** were utilized as a directing group by Fagnou *et al*. (Scheme 37).[105,106,107] In general, the broad substrate scope makes this method a particular important tool in synthetic chemistry. In terms of step and atom efficiency, additional protection/deprotection are a major drawback, especially considering the use of stoichiometric amounts of copper (II) acetate as the oxidant in the cross-coupling reaction.



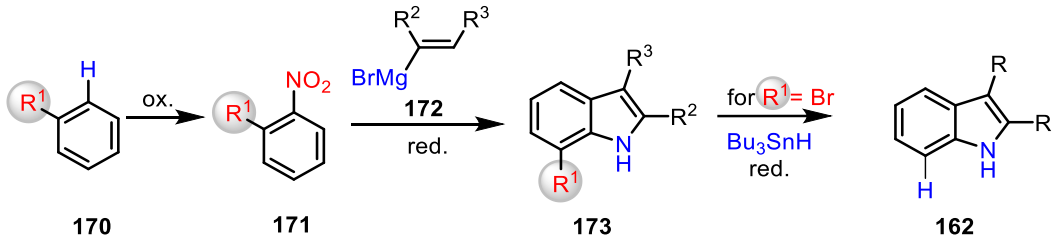
Scheme 37: General approach for Rh-catalyzed oxidative indole synthesis.[105,106,108]

A more straightforward approach would be the use of nitroaromatic compounds (e.g. **13**), which would require one less redox operation. Nitro groups are extremely stable towards degradation processes or functionalization in oxidative cross-coupling reactions.[109,110] Additionally, the resonance with the benzene ring lowers the electronic density in *ortho* position, thus reducing the directing group potential of the nitro group, making the utilization in cross coupling reactions of this compounds quite challenging.[110]



Scheme 38: Indole synthesis by Reissert.[111]

However, Reissert took advantage of the electron withdrawing character already in 1897 and used *ortho*-nitrotoluene **167** for the synthesis of indole **162a** (Scheme 38).[111] The acidified methyl group is deprotonated by a strong base and reacts with diethyl oxalate **168** in a condensation reaction. The reaction is generally carried out with tin(II) chloride for the ring closure step and is very depending on the acidic character of the methyl group, limiting the reactions applicability.[112] Yet the reaction starts from the nitro group, reducing the required redox operations to two.



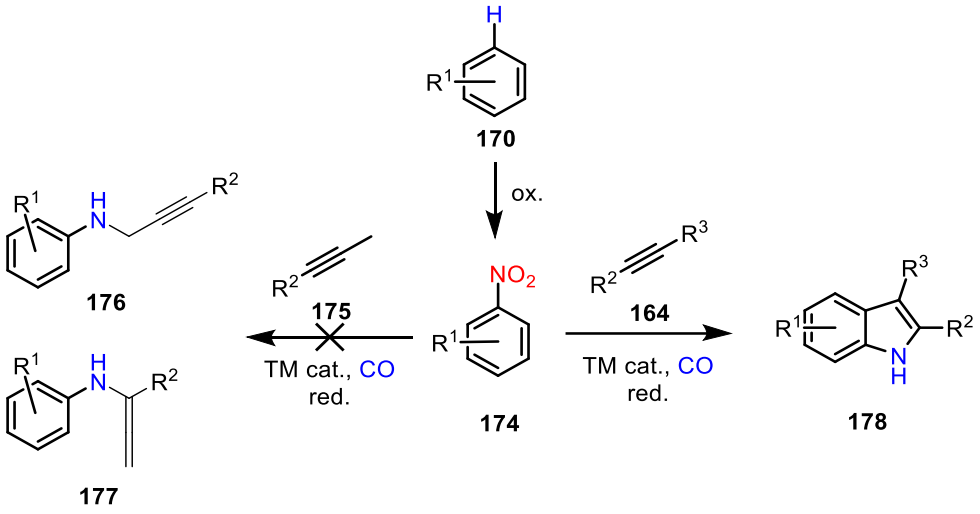
Scheme 39: Bartoli indole synthesis and deprotection strategy by Dobbs.[113,114]

In the end of the 80s, the reaction of vinyl- Grignards **172** with nitroaromatic compounds **171** was developed by Bartoli, (Scheme 39).[113] Even though the indole scaffold **173** is reached also in two redox steps, there are major drawbacks for this reaction:

1) Grignard reagents must be prepared freshly and three equivalents are required.[113] This involves a time-consuming synthesis and inorganic waste.
2) If the *ortho*-positions remain free, only low product amounts are detected. The reaction requires an *ortho*-group to give moderate yields of the corresponding indole. This implies that the reaction depends on steric effects, since the same group in *para* gives also low yields of the desired indole.[115]

The latter limitation was solved in 2001 by Dobbs *et al.* (Scheme 39).[114] The authors were able to utilize bromine in the *ortho*-position, which was enough to get promising yields. At the same time, the bromine can be easily removed through a radical reaction, using a radical starter (most cases AIBN) and tributyltin hydride, giving almost quantitative yields of the desired unsubstituted indole **162**. However, tin organo compounds are very toxic and not easy to handle, making this method an unfeasible choice.[116]

In other studies, nitroaromatic compounds **174** were reduced by CO gas by transition metal catalysis (Scheme 40), which represents probably the most redox efficient way in literature to reach the indole scaffold **178**. At the initial discovery, the authors expected a route towards propargyl- and/or allenylamines (**176** & **177**) but found the indole as the product. However, long reaction times, high pressure of toxic CO and high temperatures are needed to generate moderate yields of the indole **178**, making these methods rather impracticable.[117,118]

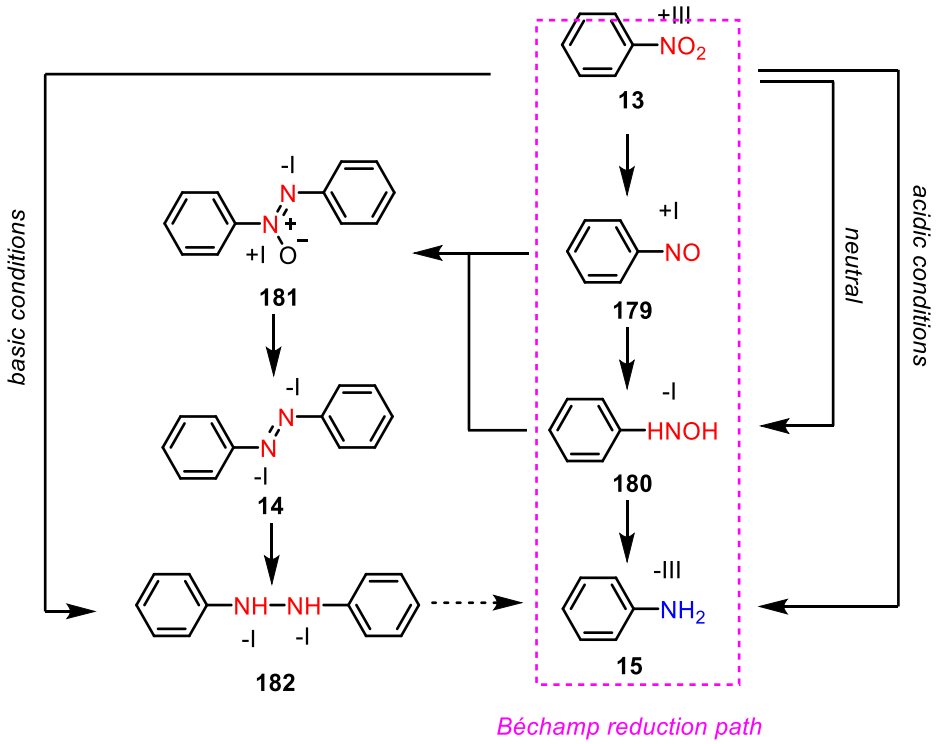


Scheme 40: Transition metal catalyzed indole synthesis with CO as reductant.[117,118]

In the last few years, several other methods were developed using transition metal catalysis to form indoles. Nonetheless, all of them do not employ the nitroarene but a derivative with a lower oxidation state (e.g. nitroso).[119]

3.1.2 Reductive coupling of nitro compounds

Nitro aromatics have an immense importance in organic chemistry by being precursors for explosives and azo dyes and the occurrence in natural products with wide range of biological activity.[120] This is illustrated by the fact that the reduction of nitrobenzene **13** to aniline **15** is one of the first industrial processes.[121] This was possible because already in the 19th century, the reduction of aniline **15** was studied by chemists in Europe.[122] The reaction developed by Béchamp is cheap, since iron was used as reductant and the resulting iron(II;II) oxide as a pigment.[121] The reduction scheme by Haber illustrates the different pathways that nitrobenzene **13** can take in the reduction to aniline **15** (Scheme 41).[123,124]

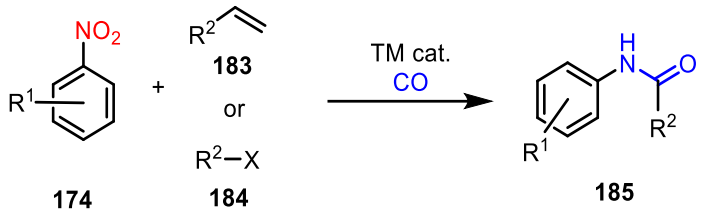


Scheme 41: Reduction paths of nitrobenzene depending on conditions by Haber.[123,124]

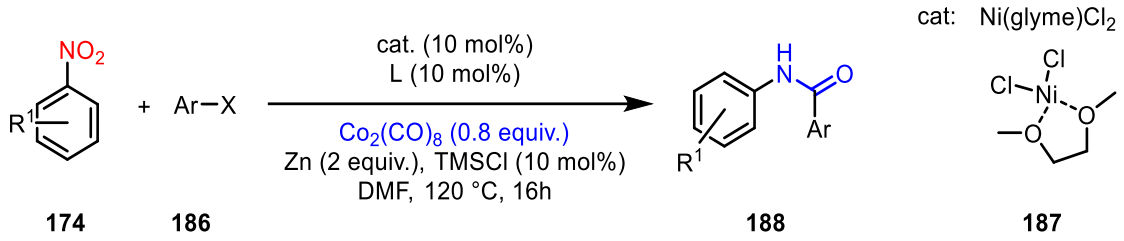
The role as a precursor is undoubtedly important since amino groups are usually utilized for amination reactions and the nitrogen is introduced by nitration. For time and step economy reasons, more interest was rising in nitro groups as starting materials, since the Bartoli indole synthesis was developed.[113]

One extensively investigated example in the last years was aminocarbonylation reactions (Scheme 42 a)). Inspired by traditional carbonylation reactions, a carbon monoxide source is utilized as CO building block in an usually transition metal catalyzed reaction.[125–127] Hu and coworkers were able to use a nickel catalyzed system with dicobalt octacarbonyl as CO source in combination with there earlier developed Zn/ TMSCl reductive conditions (Scheme 42 b)). Depending on the leaving group (X= I , Br) a different ligand was used, giving access to a broad amide scope **188** (yields: 41-91 %).

a) General reaction for aminocarbonylations

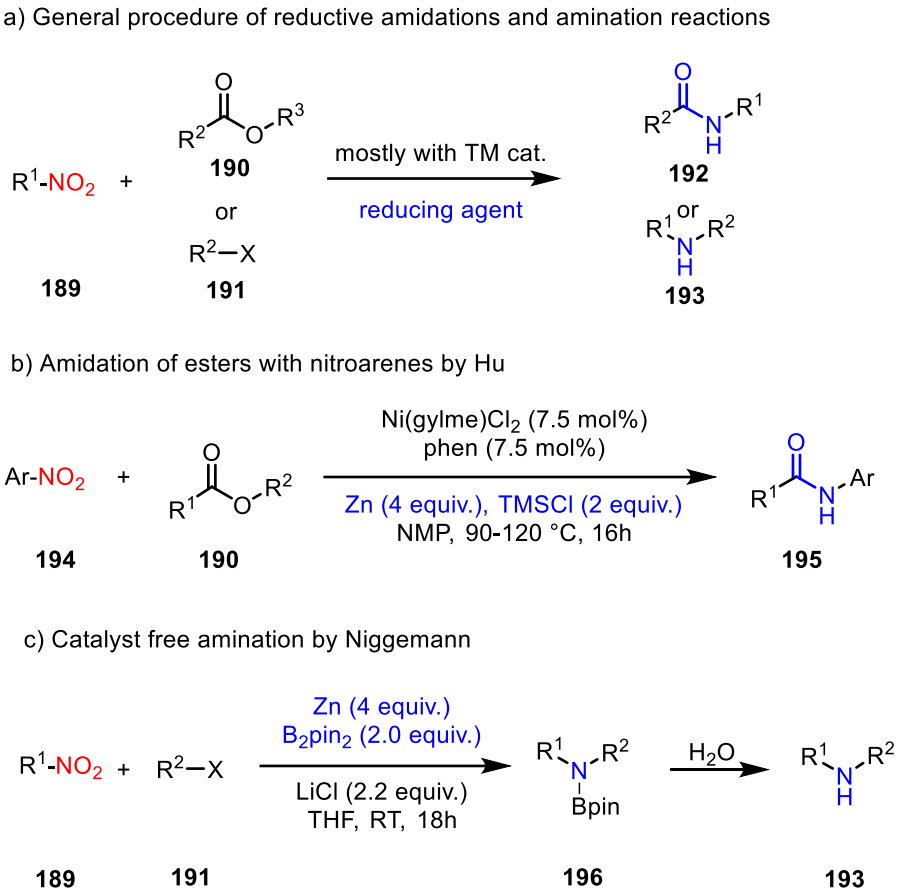


b) Nickel catalyzed reductive aminocarbonylation by Hu



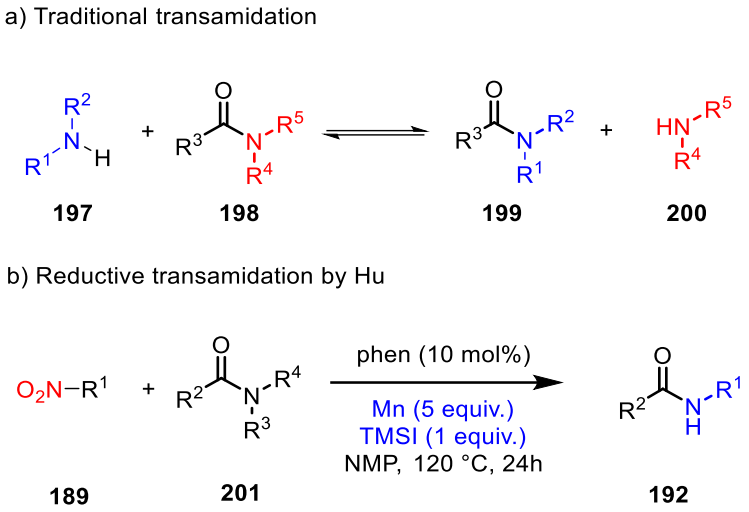
Scheme 42: TM catalyzed amino carbonylation with CO.[125–127]

Additionally amination or amidation reactions have drawn attention using different leaving groups or activated compounds such as esters **190** (Scheme 43 a)).[128–134] Especially esters **190** being particularly important for the transformation to amides **192**, which are a key component for peptides and proteins.[135] Hu and coworkers were able to apply similar conditions as in Scheme 42 b) to transform these building blocks into amides **192** with nitro aromatics **189** (Scheme 43 b)). For amination reactions, carbon halogen compounds were utilized in reductive conditions.[130] One particularly impressive protocol was developed by Niggemann and coworkers, in which a electrophilic amination reaction of carbon halides **191** occur with nitro compounds **189** as amination reagent (Scheme 43 c)). The reaction takes places by a nitrenoid species as intermediate, giving the pinacolborono protected amine **196**. Deprotection can be achieved by a quick aqueous work up.



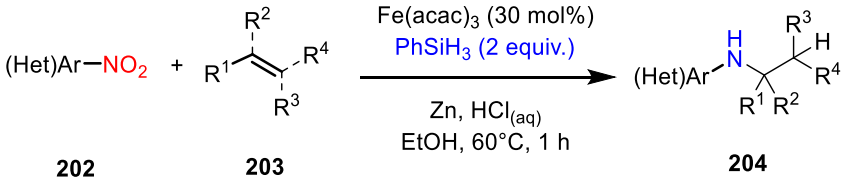
Scheme 43: Amination and Amidation of activated bonds.[128–134]

When it comes to reactions of amides **198**, one cannot search the literature without stumbling over the concept of transamidation, in which an amide **198** is transformed into another **199** (Scheme 44 a)).[136] Especially for secondary and tertiary amines, traditional transamination methods must fight with limited scope.[137] The lack of a free N-H in tertiary amides changes the reactivity drastically.[138] Additionally, transamidations are thermoneutral processes, leading to an equilibrium and a resulting mixture of products and reactants.[137] Initially the Hu group discovered a nickel catalyzed transamidation for secondary amines.[139] Only one year later, the concept was applicable on tertiary amides **201** without nickel as a transition metal catalyst (Scheme 44 b)).[140] Once again the Hu group was able to utilize their concept (cheap metal and silyl source) to a useful reaction. They showed 50 different examples with a yield up to 91%



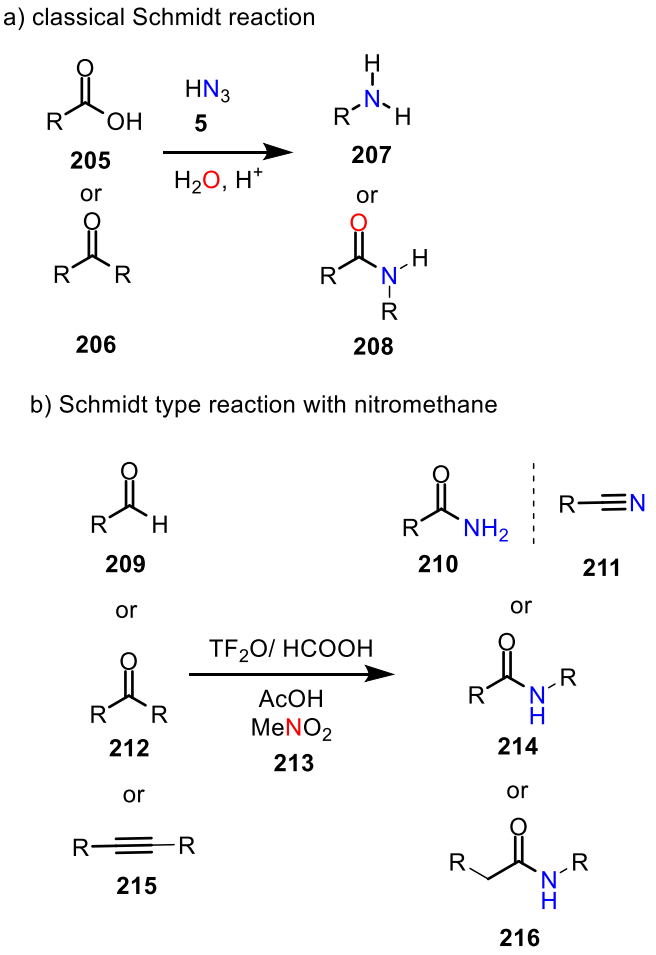
Scheme 44: Transamidation reactions.[136,139,140]

Several other groups were able to use nitro aromatics in different coupling reactions.[141,142] In 2015, Gui *et al.* developed a practical hydroamination of olefins. This was the first example for the transformation of nitro aromatic compounds **202** to secondary amines **204** (Scheme 45).[141] The reaction tolerates a wide range of functional groups (e.g. alcohols, boronic acids, diamines). Medicinal targets were synthetized exemplary with improved yields and more step efficient than the conventional routes.



Scheme 45: Hydroaminations of olefins with nitroarenes by Baran and coworkers.[141]

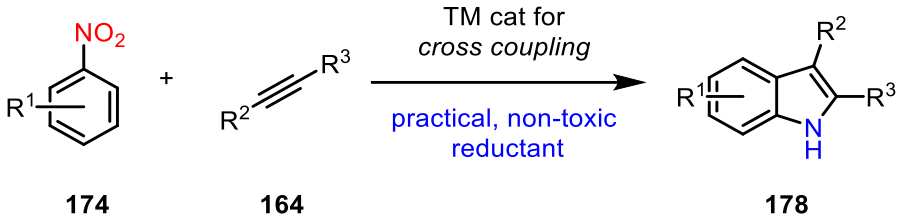
A very outstanding and recent use of nitromethane **213** was published recently by Liu *et al.* (Scheme 46).[143] The bulk chemical was used as the nitrogen donor in a Schmidt-type reaction, opening a new safer route to the same compounds without the use of dangerous azides (explosive, toxic).



Scheme 46: Classical Schmidt reaction and the developed method by Liu et al. using nitromethane.[143]

3.2 Motivation and task

As useful and versatile the previous discussed methods for the synthesis of indoles **178** are (see 3.1.1), there is still no direct synthesis from readily accessible nitro aromatic compounds **174** without limitations in the substitution pattern. Thus, a new strategy is needed in perspective to step- and redox efficiency, especially for non-*ortho* substituted nitro aromatics **174** (Bartoli).[113]
To overcome the above-mentioned limitations., a one-step reductive cross-coupling reaction of nitro aromatics **174** with alkynes **164** should be developed.



Scheme 47: General approach for reductive indole synthesis.

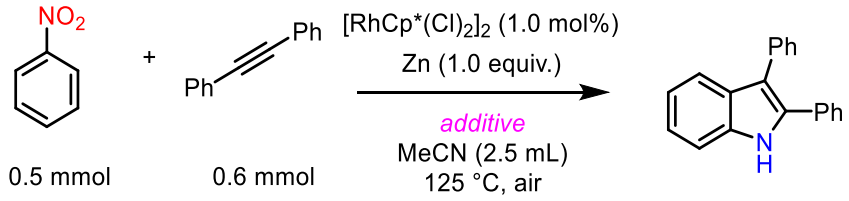
Nitro-groups have been rarely utilized as an *ortho*-directing C-H activation group (Fagnou with pioneer work in 2008), which might be caused by the lack of a free electron pair on the nitrogen and its electron deficient nature.[144] The idea was to develop conditions in which a reduced intermediate of the nitroarene interacts with a transition metal, capable of C-H activating and inducing a cross coupling reaction (Scheme 47).
With optimal conditions in hand, the substrate scope should be examined and mechanistic experiments should be carried out.

3.3 Results and discussion

3.3.1 Condition optimization

For the initial reactions, nitrobenzene **174a** and diphenylacetylene **164a** were chosen as model substrates. In perspective of a broad substrate scope, the nitro aromatic compounds should have no limitations for electron withdrawing or donating groups. Zinc was chosen to be terminal reductant, a well-known reducing agent for nitro compounds.[145]

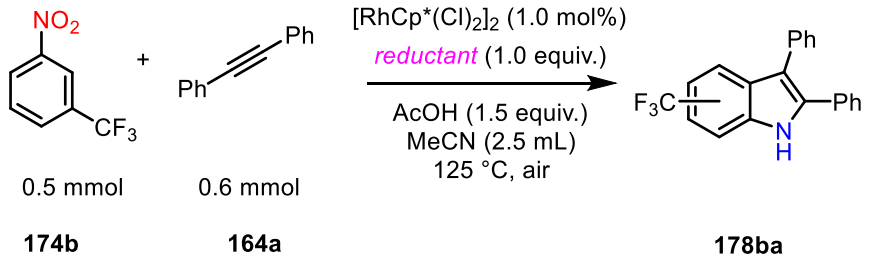
Pentamethylcyclopentadienyl rhodium (III) dichloride dimer was engaged as the catalyst. In general, the nature of additives has a huge impact on the deprotonation and the formation of the cross coupling product (see for example CMD-mechanism).[146] For this reason, the reaction was carried out with a Brønsted acid (acetic acid),a lewis acid (silver hexafluoroantimonate) and a base (potassium phosphate) (Table 8).



Entry	Additive [equiv.]	TLC control
1	K_3PO_4 (1.5)	No conversion
2	AcOH (1.5)	Desired product, isolated: 7%
3	$AgSbF_6$ (0.02)	No conversion

Table 8: Discovery of reductive nitro to indole synthesis

With acetic acid as additive, the desired product **178aa** was isolated with 7% (Table 8, entry 2).



0.5 mmol 0.6 mmol

174b **164a** **178ba**

Reductant	**TLC control**
$NaBH_4$	No conversion
Formic acid	Only corresponding aniline[a]
B_2pin_2	no conversion
Fe	Traces of product
Zn	Isolation: 2%
Mn	No conversion

Table 9: Reducing agent screening. [a] Identified by TLC-control.

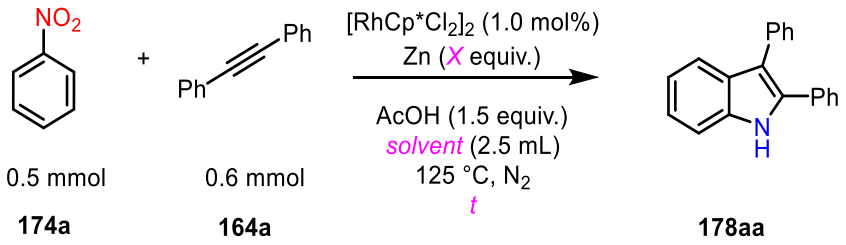
Since the product **178aa** is formed by reduction of a nitro group different reductants were tested. Compared to other reducing agents, such as common reducing agents in organic chemistry (e.g., sodium borohydride) or other base metals (e.g., manganese), zinc turned out to be the only efficient one (Table 9).

Additionally, the reaction was carried out under a nitrogen atmosphere and in dry acetonitrile. A difference in yield was not detected, however due to the reductive nature of the reaction, nitrogen was chosen as atmosphere to avoid undesired effects by oxygen in the air and dry acetonitrile was used from now on.

Since base metals, which includes zinc, generally dissolve poorly in organic non-protic solvents, the next step was to screen solvents. None of the tested solvents, such as mono or multi-halogenated (chlorobenzene, bromobenzene, dichlorobenzenes, perchloroethylene, chlorotoluenes), heterocyclic or normal aromatics (pyridine, 2,4,6-collidine, toluene, cumene, xylenes, 1,3-diisopropylbenzene, *tert*-butylbenzene) or non-aromatics (1,4-dioxane, PPC, 2-pyrrolidone, *N*-methyl-2-pyrrolidone), were able to deliver any product. Only nitrile containing solvents gave the desired indole **178ba** in trace amounts, leaving acetonitrile still as the superior solvent. Even combinations with water, ethanol, or acetic acid as a cosolvent instead of additive shut down the product formation completely. This might be caused by coordination effects of

nitriles, changing the reactivity of the catalyst drastically. Noteworthy is here that all reactions were controlled by TLC and yield determination was very difficult due to low yield of the corresponding indole. For this reason, nitrobenzene **174a** was chosen as the substrate to optimize the yield by gas chromatography.

With the new quantification method, some promising reactions were repeated with nitrobenzene **174a** (Table 10).

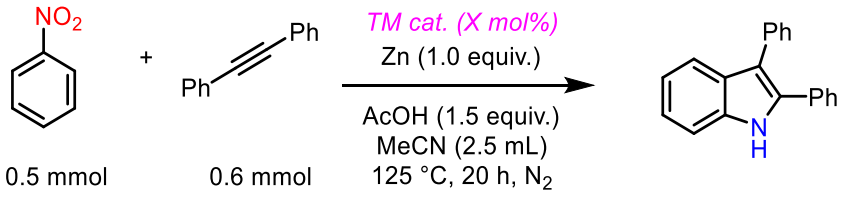


0.5 mmol **174a** | 0.6 mmol **164a** | **178aa**

Entry	Zn [X equiv.]	Solvent	Time [h]	GC-Yield [%]
1	1.0	MeCN	20	8
2	1.0	*i*PrCN	20	trace
3	1.0	PhCN	20	n.d.
4	2.0	MeCN	20	10
5	5.0	MeCN	20	6
6	8.0	MeCN	20	2
7	1.0	MeCN	24	8
8	1.0	MeCN	16	6
9	1.0	MeCN	8	4

Table 10: Repetition of most promising reactions.

Since the desired indole **178aa** was only formed with the engaged pentamethylcyclopentadienyl rhodium (III) dichloride dimer, the nature of catalyst must play a decisive role. For this reason, different catalysts were tested (Table 11).



0.5 mmol **174a** | 0.6 mmol **164a** | **178aa**

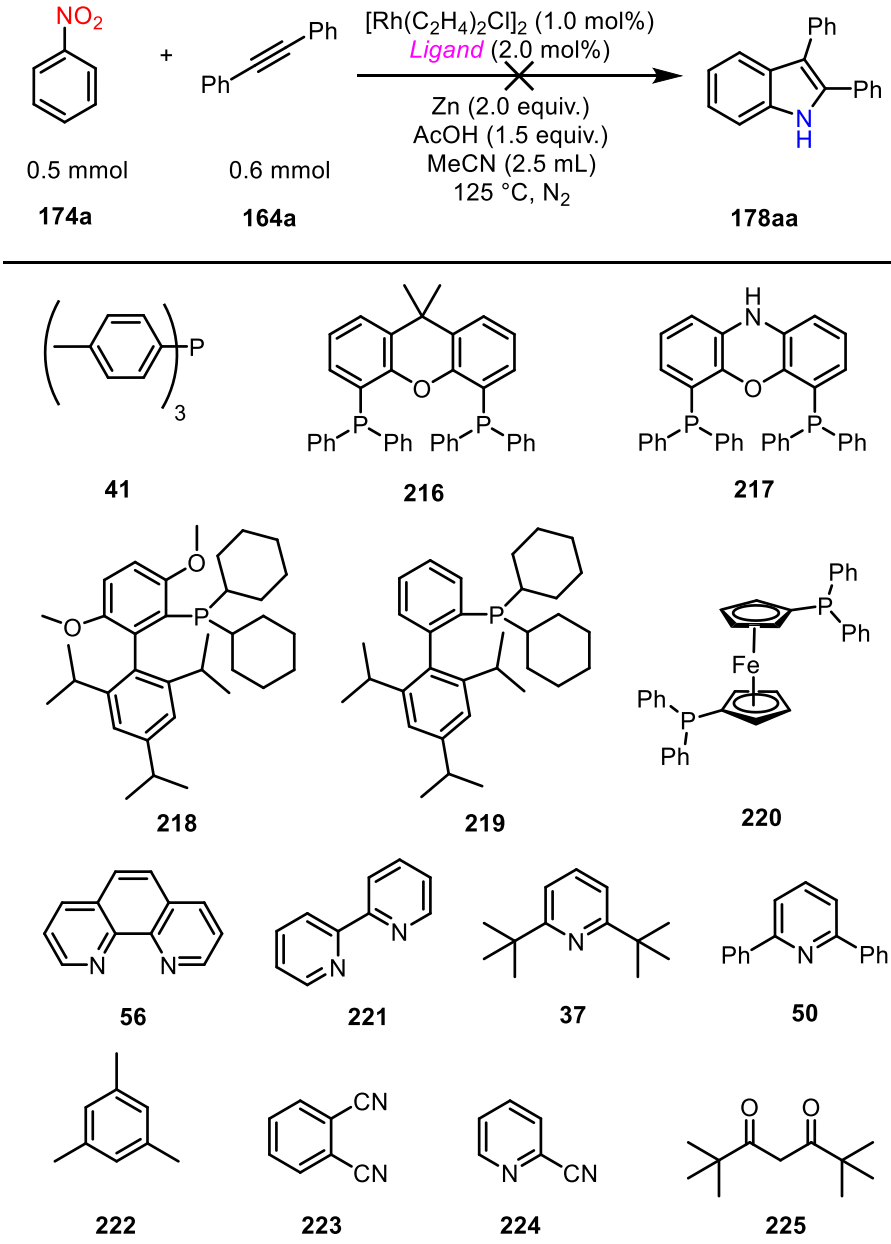
Entry	Catalyst	Loading [X mol%]	Yield [%]
1	$[RhCp^*Cl_2]_2$	1.0	7
2	$[Rh(C_2H_4)_2Cl]_2$	1.0	0
3	$[RhCp^*(MeCN)_3](SbF_6)_2$	2.0	6
4	$[Rh(C_2H_4)_2Cl]_2$ + HCp*	1.0+2.0	5
5	(Pyridine) $AuCl_3$	2.0	0
6	$Rh(nbd)_2\ BF_4$	2.0	0
7	$(Rh(nbd)Cl)_2$	1.0	0
8	$AuCl_3$	2.0	0

Table 11: Catalyst screening.

Even though the chlorobis(ethylene)rhodium dimer was not yielding any product by itself (Table 11, entry 2), addition of pentamethylcyclopentadiene to the reaction delivered the desired indole **178aa** albeit with lower yield (Table 11, entry 4).

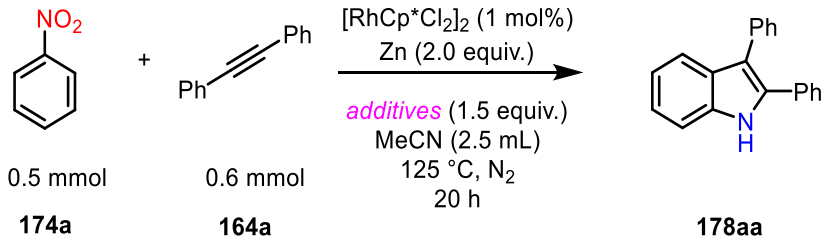
With this interesting new result, different types of ligands were tested in combination with the rhodium precursor (Scheme 48).

A variety of phosphine (**41**, **216**-**220**) and pyridine ligands (**37**, **50** & **56**) were tested, since they have a wide range of application in cross coupling reactions.[147] However, none of them were able to deliver any product. In the solvent screening, it was observed that only nitrile containing solvents were suited for the reaction. Therefore, two nitrile containing ligands (**223** & **224**) were engaged. To cover 1,3 diketones, an acetylacetonate derivative **225** was also tested. None of the tested ligands were able to produce the desired indole **178aa**.



Scheme 48: Different types of ligands tested in reaction.

During the first experiments, only acetic acid was a successful additive (Table 8, entry 2). A variety of different additives were engaged next (Table 12): copper species as Lewis acidic compounds, sodium acetate as corresponding base and a variety of organic acids were tested. Based on the Hu group's work, trimethylsilyl chloride was also tested in the reaction.[127,130,132] Since acetic acid seemed crucial for the reaction, the additive screening was done with and without acetic acid, respectively, for every additive.



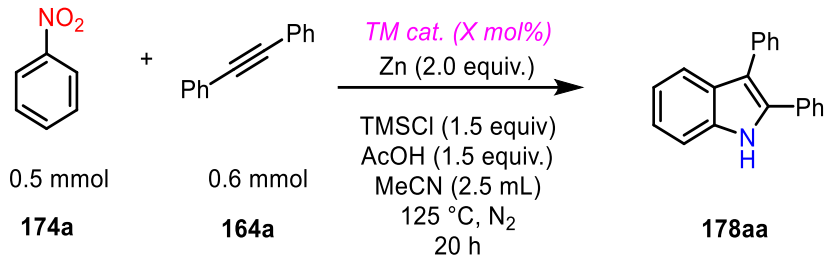
0.5 mmol **174a** + 0.6 mmol **164a** → **178aa**

Entry	Additive 1	Additive 2	GC-Yield [%]
1	$Cu(OAc)_2$ H_2O	AcOH	0
2	$Cu(OAc)_2$ H_2O	-	0
3	$CuCl_2$	AcOH	9
4	$CuCl_2$	-	0
5	$Cu(OAc)_2$	AcOH	0
6	$Cu(OAc)_2$	-	0
7	NaOAc	AcOH	3
8	NaOAc	-	0
9	TFA	AcOH	12
10	TFA	-	6
11	PivOH	AcOH	6
12	PivOH	-	1
13	PhCOOH	AcOH	7
14	PhCOOH	-	5
15	HFIP	AcOH	11
16	HFIP	-	0
17	MS 3Å	AcOH	15
18	MS 3Å	-	13
19	TMSCl	AcOH	21
20	TMSCl	-	2

Table 12: Additive screening with and without acetic acid.

Interestingly, all additives perform better with acetic acid as a second additive (Table 12, uneven entry numbers). None of the organic acids were able to perform as good as acetic acid. Molsieves in combination with the acid were slightly better, than without (Table 12, entry 17 and 18). However, trimethylsilyl chloride was almost able to triple the yield (Table 12, entry 19) in respect to the best conditions so far (Table 10, entry 1: 8 %).

With this improved condition promising catalysts were tested (Table 13).



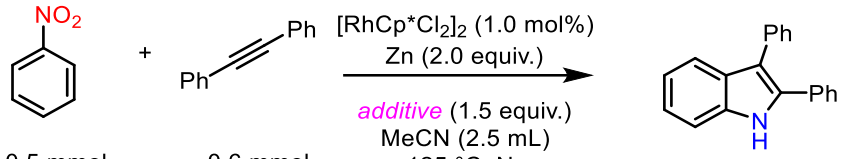
0.5 mmol **174a** | 0.6 mmol **164a** | **178aa**

Entry	Catalyst	Loading [X mol%]	GC-Yield [%]
1	$[RhCp^*Cl_2]_2$	1	21
2	$Pd(CH_3CN)_2Cl_2$	5	0
3	$[Rh(COE)_2Cl]_2$	1	2
4	[Rh(octanoate)]$_2$	1	2
5	$[Rh(MeCN)_3Cp^*)(SbF_6)_2]$	2	18

Table 13: Catalyst screening with other potential candidates.

Only a different pentamethylcyclopentadiene containing rhodium species was competitive in the reaction, with a slightly lower yield (Table 13, entry 5).

Therefore $[RhCp^*Cl_2]$ dimer was kept as the catalyst for this system and more additives were screened. A variety of different additives were tested (Table 14) based on other works for reducing nitro groups.[148]



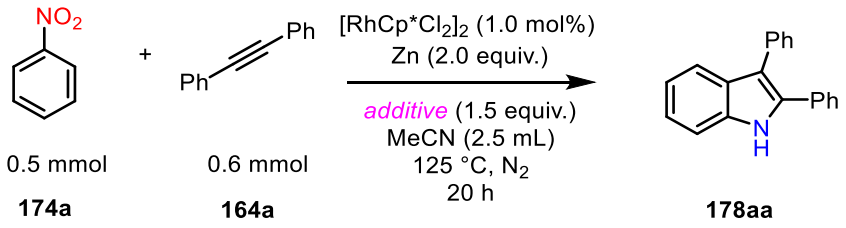
0.5 mmol **174a** + 0.6 mmol **164a** → **178aa**

Entry	Additive 1	Additive 2	GC-Yield [%]
1	NH_4Cl	AcOH	13
2	NH_4Cl	-	0
3	NaCl	AcOH	0
4	NaCl	5	0
6	LiCl	AcOH	0
7	LiCl	-	0
8	Et_3N	AcOH	1
9	Et_3N	-	0
10	$AgSbF_6$	AcOH	15
11	$AgSbF_6$	-	1
12	$AgBF_4$	AcOH	12
13	$AgBF_4$	-	0
14	TosOH	AcOH	8
15	TosOH	-	5
16	$Si(OEt)_3Cl$	AcOH	6
17	$Si(OEt)_3Cl$	-	0
18	$SiCl_2(Me)_2$	AcOH	3
19	$SiCl_2(Me)_2$	-	1
20	HBF_4 Et_2O	AcOH	5
21	HBF_4 Et_2O	-	5

22	HCl (6-7N) in dioxane	AcOH	25
23	HCl (6-7N) in dioxane	-	0
24	TMSI	AcOH	5
25	TMSI	-	2

Table 14: Second additive screening with and without acetic acid.

None of the mentioned additives showed an improvement. Most inorganic salts were not able to deliver the product (Table 14, entry 1-7). Catalytic amounts of cationic silver salts (Table 14, entry 10-13) and acids (Table 14, entry 14,15 and 20-23) were able to form the product, with hydrochloric acid in dioxan being the best one with 25% GC-yield. However, the solution is highly corrosive and not easy to handle, which is why it was not considered in further reactions. Interestingly other silicon sources with one or more chlorines and trimethylsilyl iodide (Table 14, entry 16-19 and 24,25), in which only the counterion was exchanged, gave only trace amounts of **178aa** leaving trimethylsilyl chloride in combination with acetic acid as the best choice.
Next the best additives (molsieves and TMSCl) were tested in different combinations (Table 15).



0.5 mmol **174a** + 0.6 mmol **164a** → **178aa**

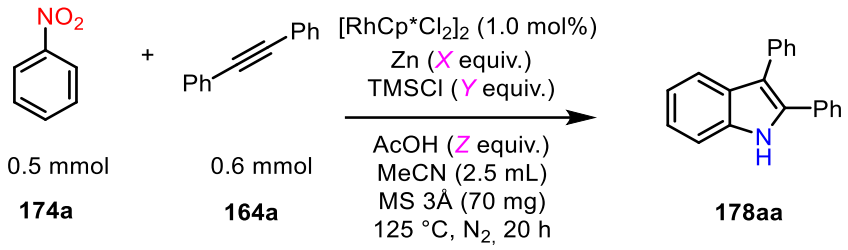
Entry	Additive 1	Additive 2	Additive 3	GC-Yield [%]
1	MS 3Å	AcOH	-	11
2	MS 4Å	AcOH	-	13
3	TMSCl	AcOH	-	14
4	TMSCl	AcOH	MS 3Å	50 (25)
5	TMSCl	AcOH	MS 4Å	40

Table 15: Different combinations of the best additives. Isolated yield in parentheses.

With the combination of these three additives a GC-yield of 50% was measured (Table 15, entry 4). However, isolation delivered only 25% of the desired product **178aa**, indicating that the isolation technique was flawed or that there was a problem with the quantitative analysis. With the strong

UV-activity (by quenching) of the product (maximum between 200-250 nm), one could follow it on column.[149] Due to tailing, the isolation process of the product can be difficult, making a direct comparison with GC-yields challenging.

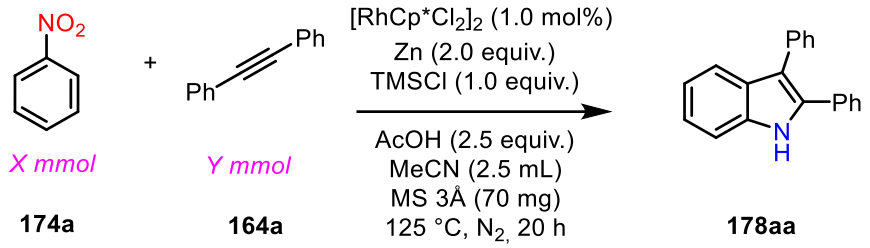
The next step was to investigate the ratio between zinc and the additives (Table 16). For the sake of clarity, only the most important combinations are shown (detailed results, see 4.3.2.3). The best ratio between additives delivered the product with a GC-yield of 45% and 40% isolated yield (Table 16, entry 5).



Entry	Zn [X equiv.]	TMSCl [Y equiv.]	AcOH [Z equiv.]	GC-Yield [%]
1	2.0	1.5	1.5	50 (25)
2	3.0	1.5	1.5	8
3	2.0	2.0	1.5	29
4	2.0	1.5	2.0	36
5	2.0	1.0	2.5	45 (40)
6	2.0	1.0	3.0	41
7	1.5	1.0	1.5	38

Table 16: Most relevant ratios of additives. Isolated yields in parentheses.

Next the ratio of substrate and the amount of solvent was varied (Table 17).



X mmol *Y mmol*

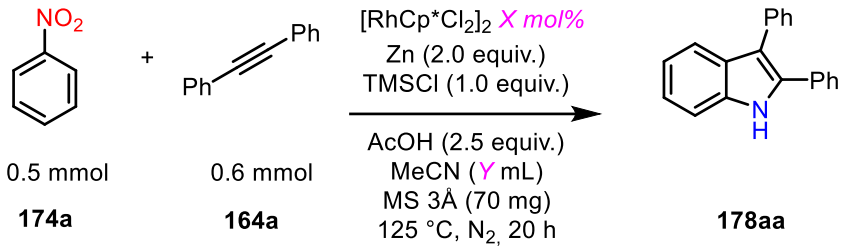
174a **164a** **178aa**

Entry	X [mmol]	Y [mmol]	GC-Yield [%]
1	0.5	0.6	45
2	0.5	0.75	40
3	0.5	1.0	42
4	0.5	1.5	32
5	0.5	0.5	43
6	0.6	0.5	41
7	0.75	0.5	42
8	1	0.5	36

Table 17: Optimization of starting material ratio.

As shown in Table 17, the substrate ratio has almost no influence on the yield.

The next step was to optimize the amount of catalyst and solvent (Table 18).



0.5 mmol **174a** | 0.6 mmol **164a** | **178aa**

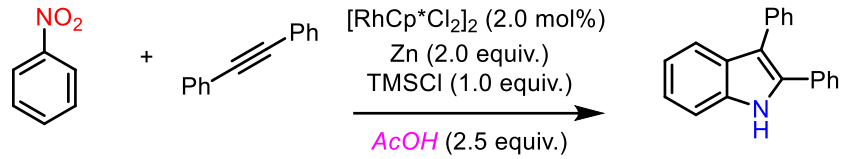
Entry	Loading [X mol%]	Solvent volume [Y mL]	GC-Yield [%]
1	1.5	2.5	44
2	2	2.5	58 (42)
3	2.5	2.5	50
4	3.0	2.5	20
5	1.0	1.5	35
6	1.0	2.0	52
7	1.0	3.0	38
8	1.0	3.5	38
9	2.0	2.0	55
10	1.0	1.75	42
11	1.0	2.25	37
12	2.0	3.0	44

Table 18: Screening of concentration and catalytic loading. Isolated yields in parentheses.

The best value of rhodium was found to be 2.0 mol% with 2.5 mL of acetonitrile resulting 58% GC-yield and 42% isolated yield (Table 18, entry 2). Reducing the amount of acetonitrile to 2.0 mL has a minimal influence on the yield, so further reactions were carried out at a higher concentration, using lesser resources (Table 18, entry 9). One rather important point is that the solvent is heated approximately 40 °C over its boiling point, therefore it is more secure by reducing the amount of solvent in the reaction vial.

It should be noted that by using 3.0 mol% rhodium, the yield drops significantly (Table 18, entry 4). This might be caused by agglomeration of the rhodium particles after a certain concentration, lowering the amount of active catalyst molecules.

Because molsieves improved the reaction significantly (Table 15, entry 4), it was suspected that the reaction is sensitive towards hydrolysis. Acetic acid is known to be hygroscopic and the amount of water in it can vary depending on the date of opening the batch and storing conditions. Therefore, two different batches of acetic acid were prepared: one stored over molsieves 4Å and one over magnesium sulfate to remove traces of water. Since acetic acid anhydride represents the condensation product of acetic acid, it was also tested (with and without AcOH). In parallel, the quantity of molsieves 3Å was screened (Table 19).



0.5 mmol **174a** | 0.6 mmol **164a** | **178aa**

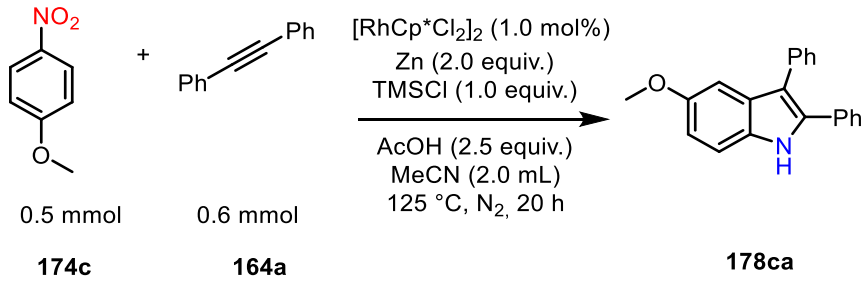
Entry	AcOH source	MS 3Å [X mg]	GC-Yield [%]
1	Dried over MS 4Å	70	60
2	Dried over $MgSO_4$	70	44
3	Dried over MS 4Å	0	26
4	Dried over MS 4Å	35	58
5	Dried over MS 4Å	105	69
6	Dried over MS 4Å	150	74 (39)
7	Dried over MS 4Å	170	70
8	Dried over MS 4Å	200	66
9	Dried over MS 4Å	230	51
10	Ac_2O (0.5 equiv.) + AcOH (1 equiv.)	-	19
11	Ac_2O (0.5 equiv.)	-	2

Table 19: Screening of acetic acid source and molsieve amount. Isolated yield in parentheses.

The method of drying the acetic acid had an impact on the yield, with molsieves 4Å being superior to magnesium sulfate (Table 19, entry 1 and 2). Acetic acid anhydride was performing relatively poorly in the reaction (Table 19, entry 10 and 11). At this point, reproducibility was inconsistent, and the best reaction was isolated with 39% (Table 19, entry 7).

For the next steps of conditions optimization, the substrate had to be changed, because there was no access to GC equipment anymore.

Even though a lot of different conditions were tested the yield was not satisfying. Rhodium is a precious metal and albeit 2.0 mol% is an acceptable amount, new efforts were attempted with only 1.0 mol%. Following reaction was carried out:

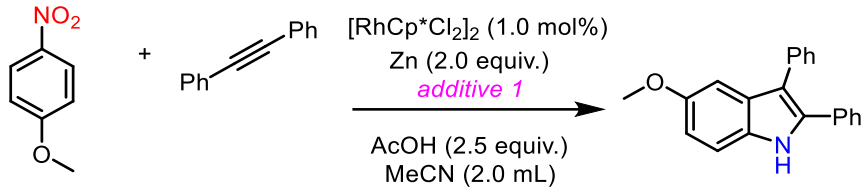


0.5 mmol **174c** | 0.6 mmol **164a** | **178ca**

Scheme 49: Starting point for reoptimization.

The product **178ca** was isolated with a yield of 28% and additional screenings were carried out. The screening was monitored with proton-NMR spectroscopy using 1,3,5-trimethoxybenzene as an internal standard.

First, potential silanes were tested (Table 20). None of the tested silanes was able to outperform TMSCl.

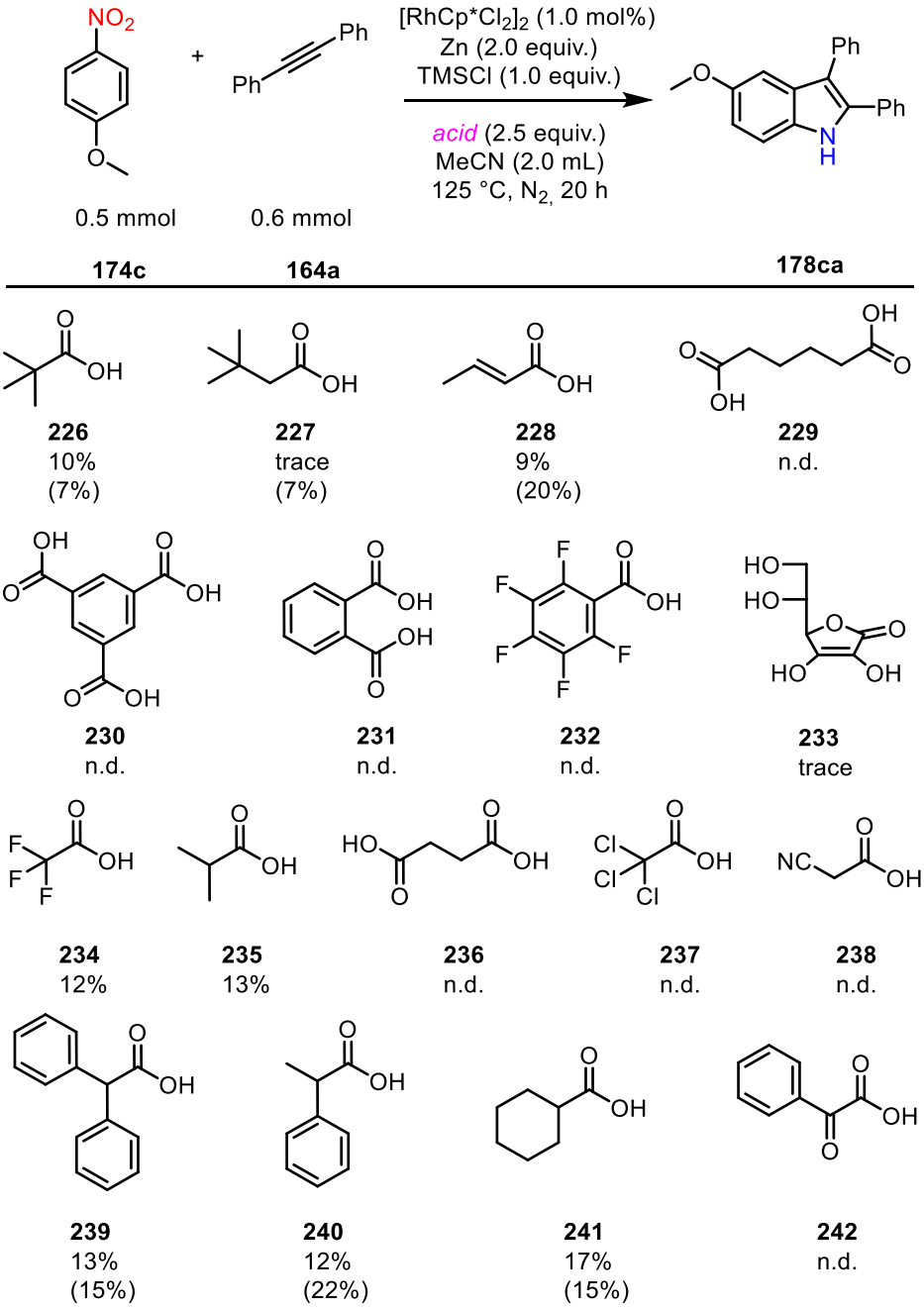


0.5 mmol **174c** | 0.6 mmol **164a** | **178ca**

Entry	Additive 1 [1 equiv.]	NMR-Yield [%]
1	TBDMSOTf	Trace
2	TMSBr	15 (15)
3	Ph_2SiH_2	n.d.
4	TESOTf	n.d.
5	TMSOTf	Trace
6	$TMS(CH_2Cl)$	8
7	$TMS(OSO_2Me)$	15 (17)
8	$(TMS)_3SiH$	10
9	$PhSiH_3$	n.d.

Table 20: potential replacements for TMSCl.

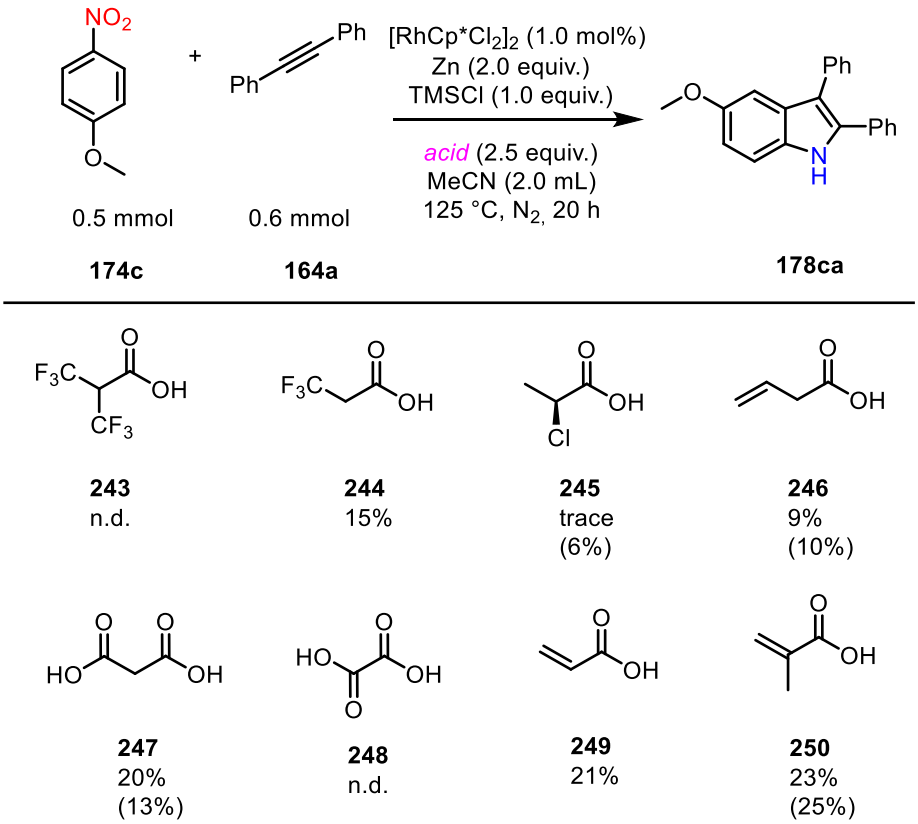
Therefore, carboxylic acids were tested (Scheme 50).



Scheme 50: Screening of potential acids. Yields determined by ^{1}H-NMR. Yields in parentheses: repetition of the same experiment.

Clearly benzoic acid derivatives are not suitable for the reaction. A relation between acidity and the ability to facilitate the reaction seems rather unlikely, even though it has been shown that the acidity has a huge impact on the kinetics of the catalytic system.[150] An explanation due to steric effects seems to be more plausible here. This has been studied for similar cases.[151] If the acid is

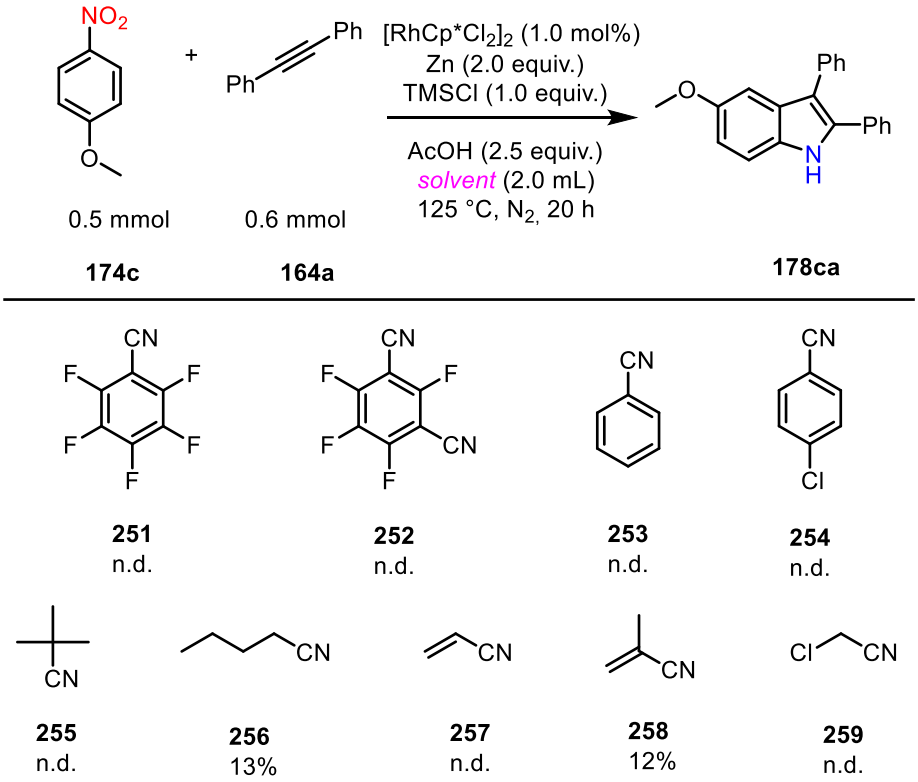
sterically to demanding, it might not have space in the coordination sphere of the catalyst to facilitate a CMD-step.



Scheme 51: Screening of potential acids part two. Yields in parentheses: repetition of the same experiment.

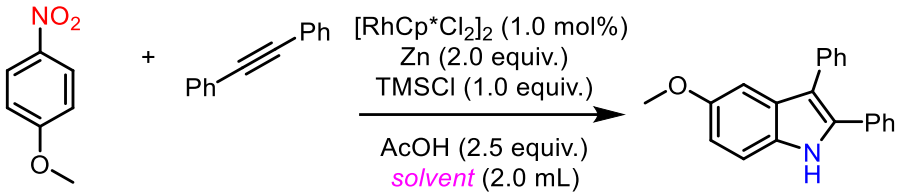
With this information, sterically smaller acids were tested (Scheme 51). The best results were observed for metacrylic acid **250** with a proton-NMR-yield of 23%, which was still no improvement to the reference conditions (Scheme 49).

The next optimization step was to test more nitrile containing solvents (Scheme 52).



Scheme 52: Screening of nitrile containing solvents.

Only two of the screened solvents (**256** & **258**) were able to give the product **178ca** in lower yields, leaving acetonitrile still as the superior solvent. A new attempt with solvent mixtures was engaged (Table 21). All experiments showed no significant improvement so far.



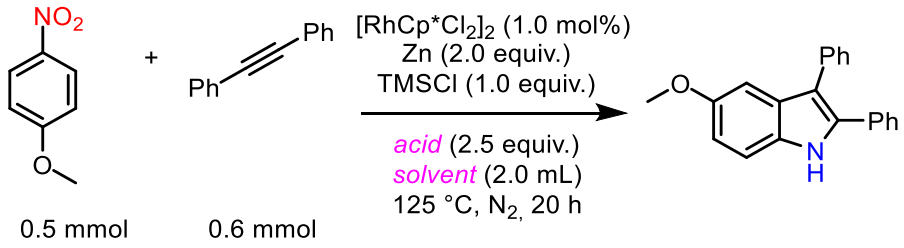
0.5 mmol 0.6 mmol

174c **164a** **178ca**

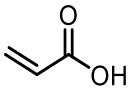
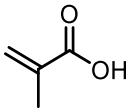
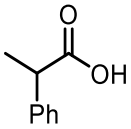
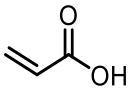
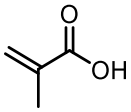
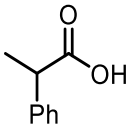
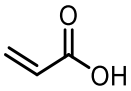
Entry	Solvent (ratio)	NMR-Yield [%]
1	MeCN + EtOH (1:1)	Trace
2	MeCN + NMP (1:1)	n.d.
3	MeCN+ H_2O (1:1)	n.d.
4	MeCN + THF (1:1)	23
5	MeCN + *t*AmOH (1:1)	Trace
6	MeCN + Dioxan (1:1)	20
7	MeCN + PhCl (1:1)	24
8	MeCN + TEC (1:1)	18
9	MeCN + Mesitylen (1:1)	17
10	MeCN + Toluene (1:1)	16
11	MeCN + Cumene (1:1)	23
12	MeCN + Valeronitrile (1:1)	19

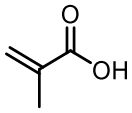
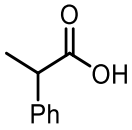
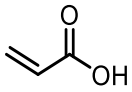
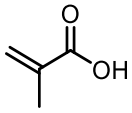
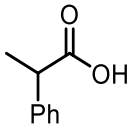
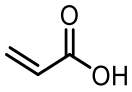
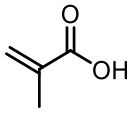
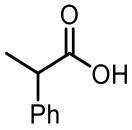
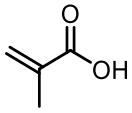
Table 21: Screening of solvent mixtures.

Therefore, the best acids were tested with the best solvent mixtures (Table 22).



0.5 mmol **174c** + 0.6 mmol **164a** → **178ca**

Entry	Acid	Solvent (ratio)	NMR-Yield [%]
1	 **249**	MeCN + THF (1:1)	n.d.
2	 **250**	MeCN + THF (1:1)	18
3	 **240**	MeCN + THF (1:1)	trace
4	 **249**	MeCN + Toluene (1:1)	n.d.
5	 **250**	MeCN + Toluene (1:1)	20
6	 **240**	MeCN + Toluene (1:1)	15
7	 **249**	MeCN + PhCl (1:1)	Trace

8	 **250**	MeCN + PhCl (1:1)	25
9	 **240**	MeCN + PhCl (1:1)	n.d.
10	 **249**	MeCN + Dioxan (1:1)	n.d.
11	 **250**	MeCN + Dioxan (1:1)	21
12	 **240**	MeCN + Dioxan (1:1)	12
13	 **249**	MeCN + Cumene (1:1)	n.d.
14	 **250**	MeCN + Cumene (1:1)	17
15	 **240**	MeCN + Cumene (1:1)	15
16	 **250**	MeCN + PhCl (1.5:0.5)	17

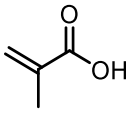
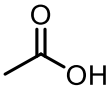
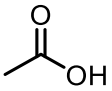
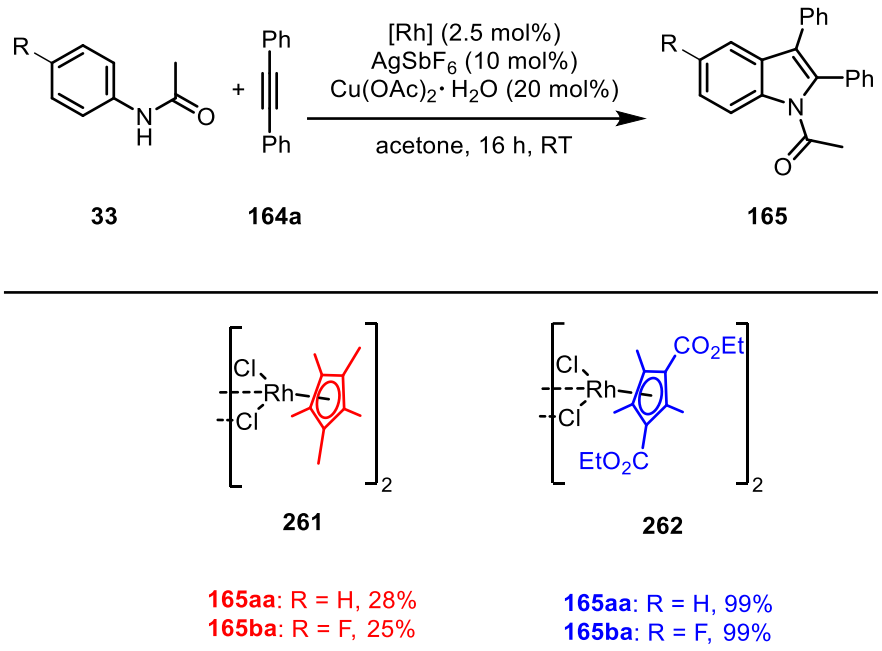
17	 **250**	MeCN + PhCl (0.5:1.5)	Trace
18	 **260**	MeCN + Cumene (1.5:0.5)	19
19	 **260**	MeCN + Cumene (0.5:1.5)	trace

Table 22: Potentially best acids with different solvent mixtures.

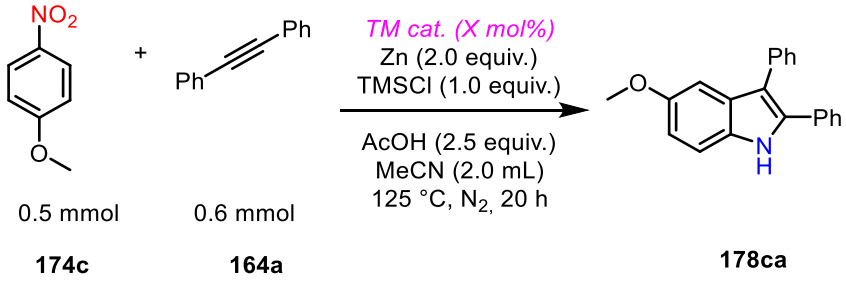
All combinations showed no improvement.

Some different potential catalysts were engaged next, particularly the Rh-catalyst **262**, developed by Tanaka and coworkers seemed very interesting (Scheme 53).[152–154]



Scheme 53: Tanakas improved Rh-catalyst for oxidative indole synthesis.[152]

Under the same conditions but with a modified catalyst (**262**), the yield of the reaction in Scheme 53 can be more than tripled. The catalyst was synthetized according to the protocol of Tanaka with an overall yield of 24%.[154]



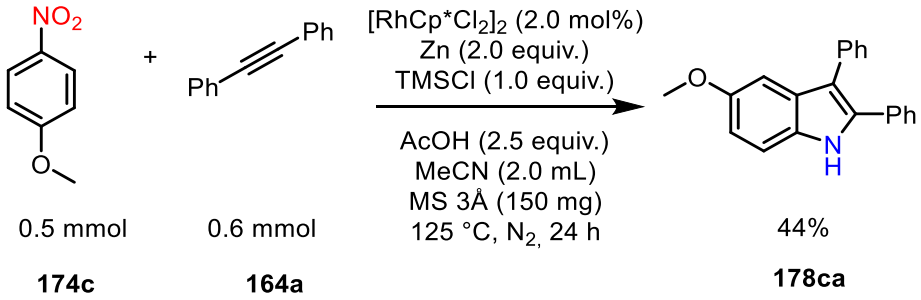
Entry	*Catalyst*	*Loading [mol%}*	*yield*
1	$[Rh[Cp(CO_2Et)_2(Me)_3]Cl_2]_2$	1.0	n.d.
2[a]	$[IrCp^*(Cl)_2]_2$	1.0	n.d.
3	Cp*Co(CO)I	1.0	n.d.

4	$[RhCp^*Cl_2]_2$	10	n.d.
5	$NiCl_2$ + 1,10-Phen	10	n.d.
6	$NiCl_2$	10	n.d.
7	$Ni(glyme)Cl_2$	10	Traces
8	$Ni(glyme)Cl_2$ + 1,10-Phen	10	n.d.
9	$Ni(Cp^*)_2$	2.0	Traces

Table 23: Test of different catalytic systems and Cp-containing catalysts. [a]*

Since $[Rh[Cp(CO_2Et)_2(Me)_3]Cl_2]_2$ **262** showed no activity at all (Table 23, entry 1), no other catalyst was synthetized and Cp^{*-} is probably necessary for the reaction to take place. Only nickel complexes gave trace amounts of product (Table 23, entry 7 & 9), but none of the tested catalysts were close to the activity of $[RhCp^*Cl_2]_2$ **261**.

Despite all efforts, the conditions in Scheme 54 remained the best.



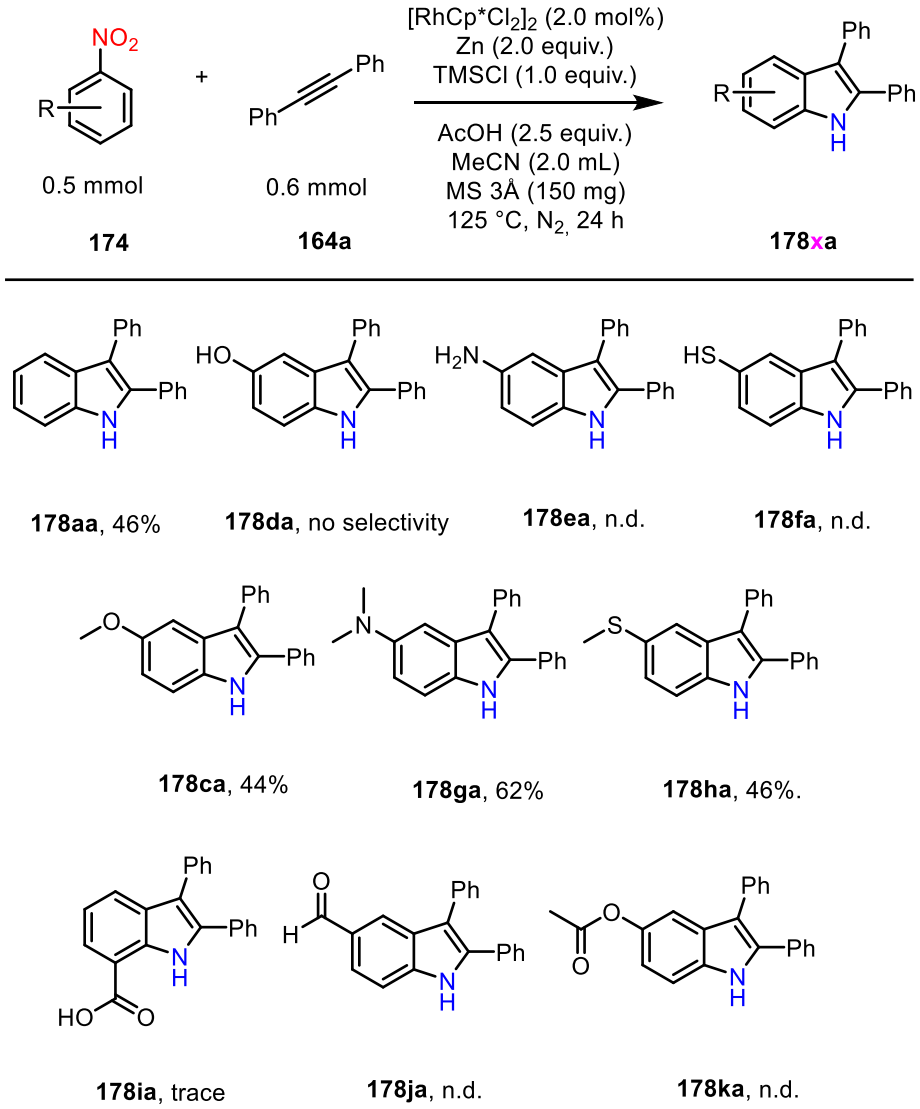
0.5 mmol **174c** | 0.6 mmol **164a** | 44% **178ca**

Scheme 54: Final optimized conditions.

The model substrate **178ca** with a methoxy group in para was isolated in 44%. Noteworthy is that full conversion was not observed, and side products were detected (see 3.3.3).

3.3.2 Examination of the substrate scope

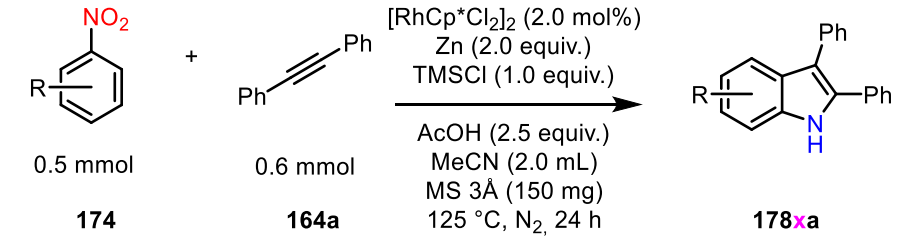
With the optimal conditions in hand, the substrate scope was examined. First nitro benzenes with different functional groups were tested (Scheme 55).



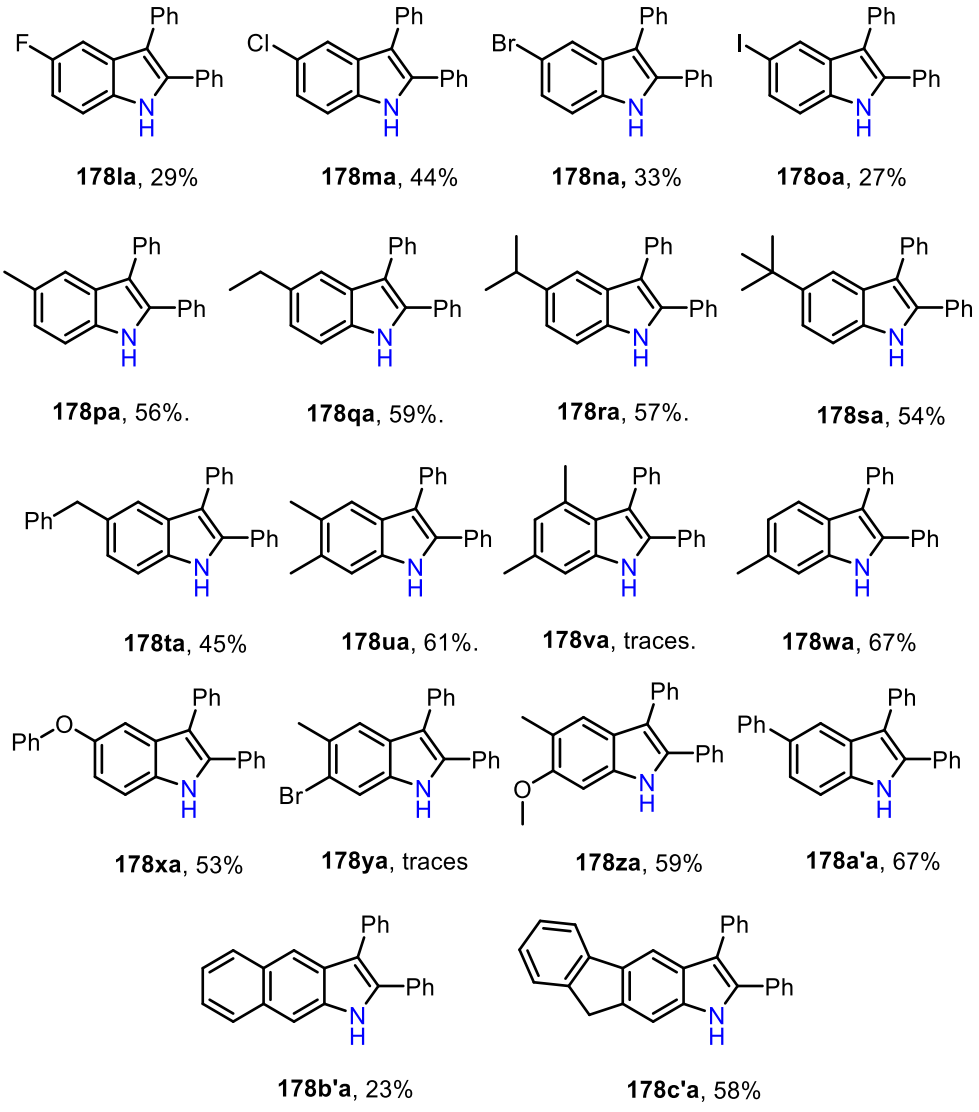
Scheme 55: Test of functional group tolerance in optimized reaction conditions.

Unsubstituted 2,3-diphenylindole **178aa** was isolated in a moderate yield of 46%. Electron-withdrawing groups, which might undergo a reduction processes, were not suited for this reaction (carboxy **178ia**, carbonyl **178ja**, ester **178ka**). Amino in *para* position of nitrobenzene did not react at all (**178ea**) and hydroxy gave a mixture of different unidentified compounds (**178da**). In fact, it is known that phenols react to benzene in the presence of zinc dust, causing a mixture of different compounds.[155] Methylation of the corresponding groups resulted in moderate to good yield (**178ca** & **178ga**).

Next some nitrobenzenes with relatively inert groups were tested (Scheme 56).



0.5 mmol **174** + 0.6 mmol **164a** → **178xa**



178la, 29%

178ma, 44%

178na, 33%

178oa, 27%

178pa, 56%.

178qa, 59%.

178ra, 57%.

178sa, 54%

178ta, 45%

178ua, 61%.

178va, traces.

178wa, 67%

178xa, 53%

178ya, traces

178za, 59%

178a'a, 67%

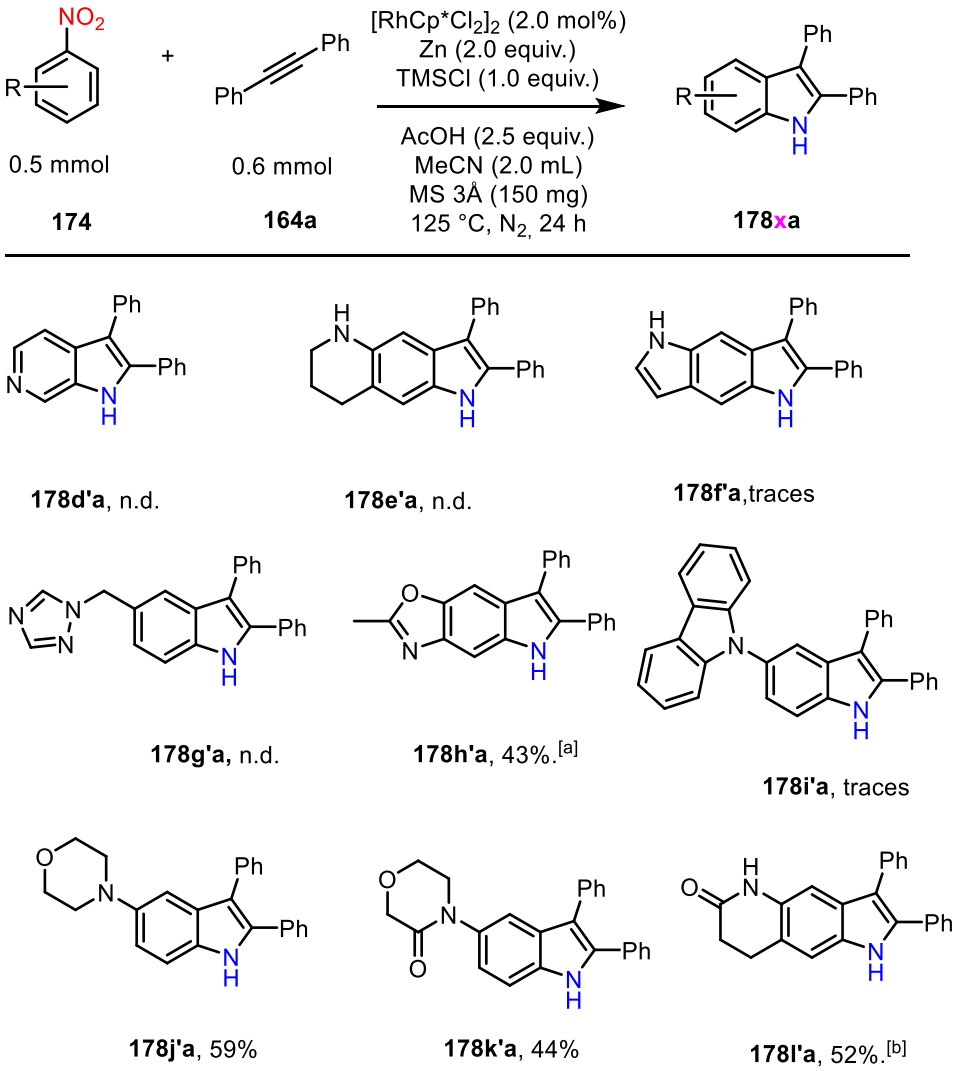
178b'a, 23%

178c'a, 58%

Scheme 56:First part of substrate scope.

Halides were tolerated in the reaction, albeit with low to moderate yield (**178la**-**178oa**). This might be explained by their nature being slightly electron withdrawing groups. In contrary, slightly electron donating in *para*-position, such as alkyl chains (+I- effect), were found to be beneficial for the reactivity of the corresponding nitrobenzene of **178pa**-**178sa**. *Para*-phenyl nitrobenzene **174a'**

and *meta*-methyl nitrobenzene **174p** were the best examples so far, giving 67% respectively. Installing a second group additionally in *meta* to the nitro group seemed beneficial. 3,4-Dimethylnitrobenzene **174u** or 3-methoxy-4-methylnitrobenzene **174z** showed good reactivity, whereas bromo instead of methoxy did not react at all (see **178ya**). It should be mentioned, that blocking both *meta*-positions with a methyl-group showed almost no reactivity (**178va**). Noteworthy is that the fluorene derivative **178c'a** was synthesized for the very first time.

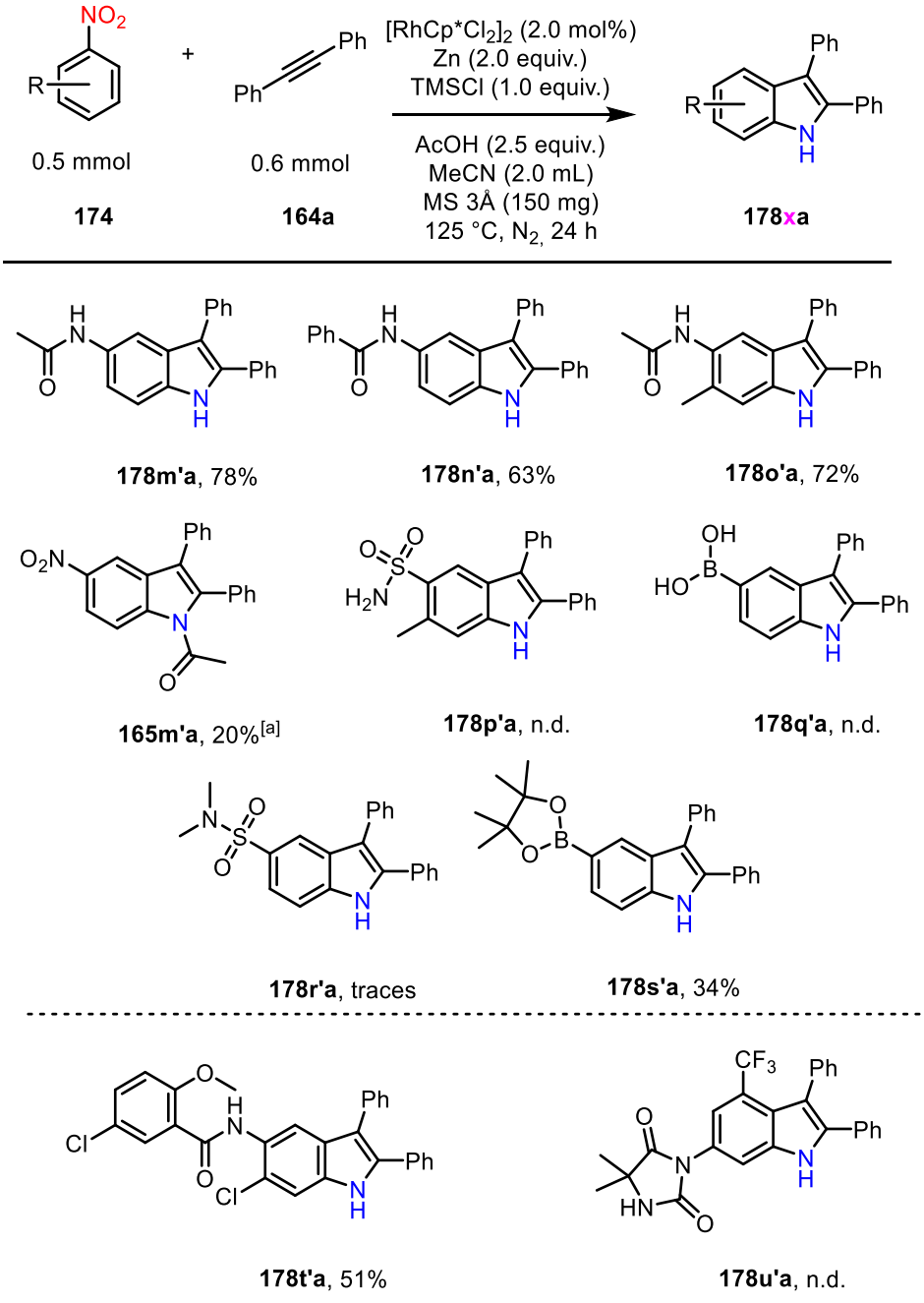


Scheme 57: Second part of substrate scope. [a] NMR shows unexpected splitting. [b] HR-MS did not give the right signal.

Afterwards, nitrogen-based heterocycles and groups were examined (Scheme 57). *Meta*-nitropyridine **174d'**, 6-nitrohydroquinoline **174e'**, 4-carbazole-nitropyridine **174i'** and 4-nitrobenzyl-1,2,4-triazole **174g'** were not successfully transformed in the reaction. In general,

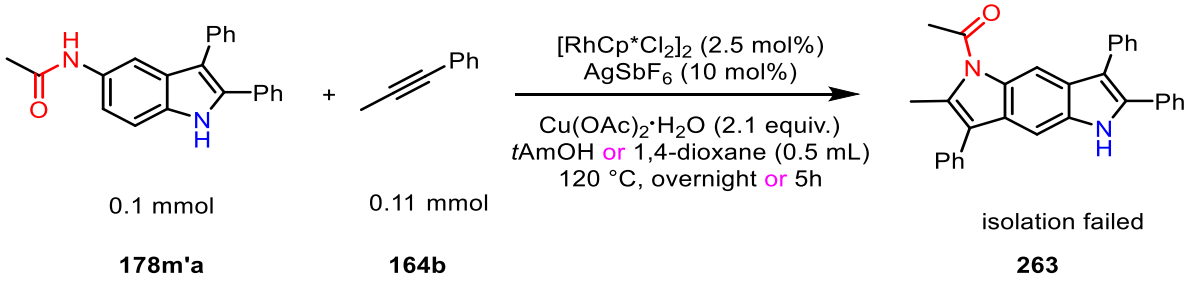
those groups and cycles tend to be electron withdrawing or cannot conjugate well with the π-electrons of the aromatic system. In case of tetrahydroquinoline, the free nitrogen might be also the reason for no reactivity (see -NH_2).

The best results were obtained for piperidine groups connected on the four position to the nitro group, especially morpholine (**174j'**) showed good reactivity (62%).



Scheme 58: Third part of substrate scope. [a] confirmed by GC-MS.

For the last part of the nitrobenzene scope, acetanilides, sulfonamides and boron containing groups were tested (Scheme 58). Especially the behavior of 4-nitro-acetanilides **174m'** was found to be remarkably interesting, since one could expect a competition of the nitro and the acetamide group, due to its excellent properties as directing group in rhodium catalyzed C-H activation.[156] Every acetanilide (**174m'**-**174o'**) was transformed with an excellent conversion and a high yield into the desired indole product (**178m'a**-**178o'a**). Exemplary, for 4-nitro-acetanilide **174m'**, the "Fagnou" product **165m'a** was isolated in 20% (identified by GC). **178m'a** was engaged with the alkyne **164b** in an oxidative cross coupling reaction (Scheme 59). Based on TLC, the desired product **263** was formed but isolation of the compound failed (few milligrams were isolated). Accordingly, the reaction was repeated twice (one with *tert*-amyl alcohol/ overnight and another with 1,4-dioxane/ 5h), but still the product **263** was not successfully isolated.



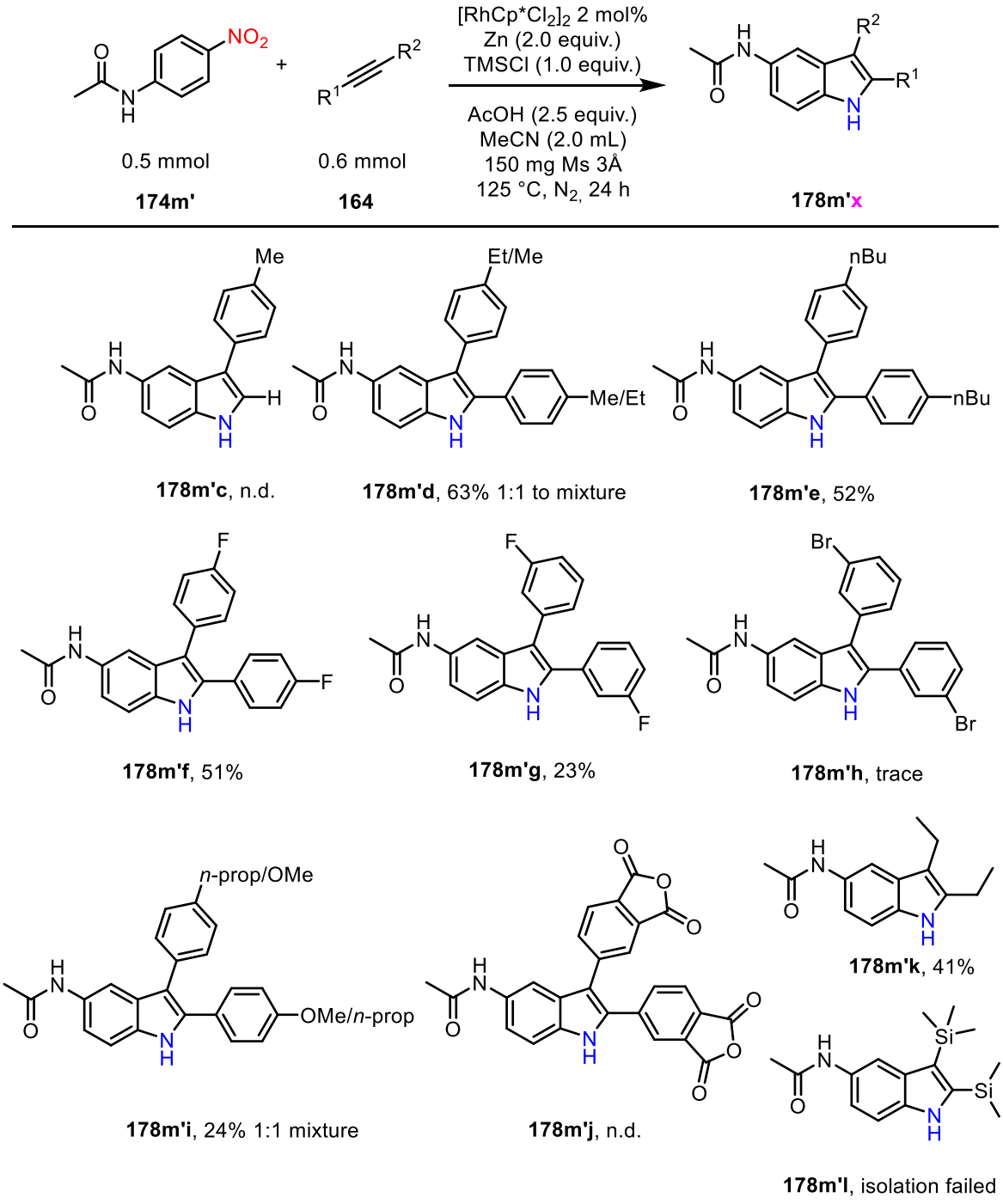
Scheme 59: Experimental application of an oxidative indole synthesis according to Fagnou.[105]

Another rather interesting group are boronic acids, due to their application in Suzuki couplings for further functionalization.[157] Even though one could not observe the product of the free boronic acid, the protected one was isolated in a promising yield of 34%. Other protecting groups could achieve more yield, making this route synthetically relevant for the synthesis of such scaffolds. In fact, 2,3-diphenyl-5-(pinacolboryl)-1*H*-indole was synthetized for the first time having huge potential. Based on the results with electron withdrawing groups (see Scheme 55 and Scheme 57), primary sulfonamides were not tolerated in the reaction and protection of the nitrogen with methyl group gave only trace amounts of product.

To show that the developed method can also be applied in late-stage functionalization, two drugs containing a nitro group were selected (Scheme 58). It should be mentioned that sensitive groups need to be protected and therefore the term late-stage functionalization is used with caution. It was possible to functionalize the methylated derivative of niclosamide **174t'**, a drug used to treat tapeworm infestations, was successfully transformed to the corresponding 2,3-diphenylindole **178t'a** with promising 51% yield.[158] However, nilutamide **174u'**, which is used to treat prostate cancer, did not react under optimized conditions.[159] This could be caused by the *ortho*-CF_3 group,

which is sterically hindering and electron withdrawing, making it unsuited for the developed method.

Finally, derivatives of acetylene were tested with 4-nitroacetanilide **174m'** as coupling partner, with most of the examples examined by Christina Bub (PhD student in the Patureau group).[160,161] The examples which were carried out in this thesis are shown here (Scheme 60).

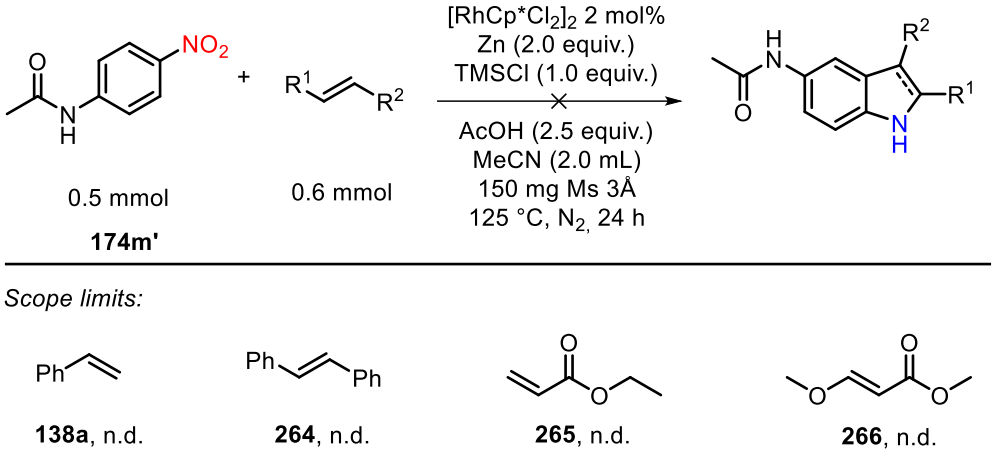


Scheme 60: Fourth part of substrate scope.

It was possible to show that terminal alkynes are not working (e.g. **164c**).[160,161] Unsymmetrical alkynes gave 1:1 mixture of the two possible regio-isomers (**178m'd** & **178m'i**), which is caused by the minimal energy difference of both isomers in the transition state at high temperatures, making it not possible for the system to distinguish between the intermediates. Electron

withdrawing groups on the acetylene seemed rather bad for the conversion, with *para*-fluorophenyl giving a moderate yield of 51% for **178m'f**. Changing it to *meta* halves the yield and replacing fluoro by bromo gives only trace amounts of the desired product (**178m'g** & **178m'h**). Surprisingly, 3-hexyne was converted with a moderate yield of 41% to the corresponding indole **178m'k**. When bis(trimethylsilyl)acetylene **164l** was engaged the product **178m'l** was speculated on TLC, however isolation of the compound failed. First it was assumed that the silyl groups are getting decomposed by the acidic conditions, but the unsubstituted indole was not isolated. The reaction was repeated: after an aqueous work up and subsequent TLC control, the same product **178m'l** was suspected but isolation failed.

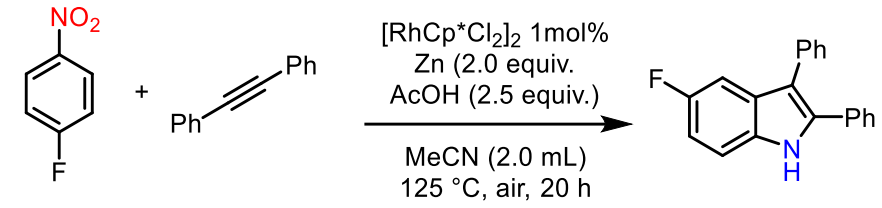
At last, other unsaturated hydrocarbons were engaged, however all of them did not react under the optimized conditions (Scheme 61).



Scheme 61: Scope limits.

3.3.3 Control reactions and mechanistic investigations

Already in the beginning of the optimization, control reactions were carried out to see which components are necessary for the reaction to take place (Table 24).



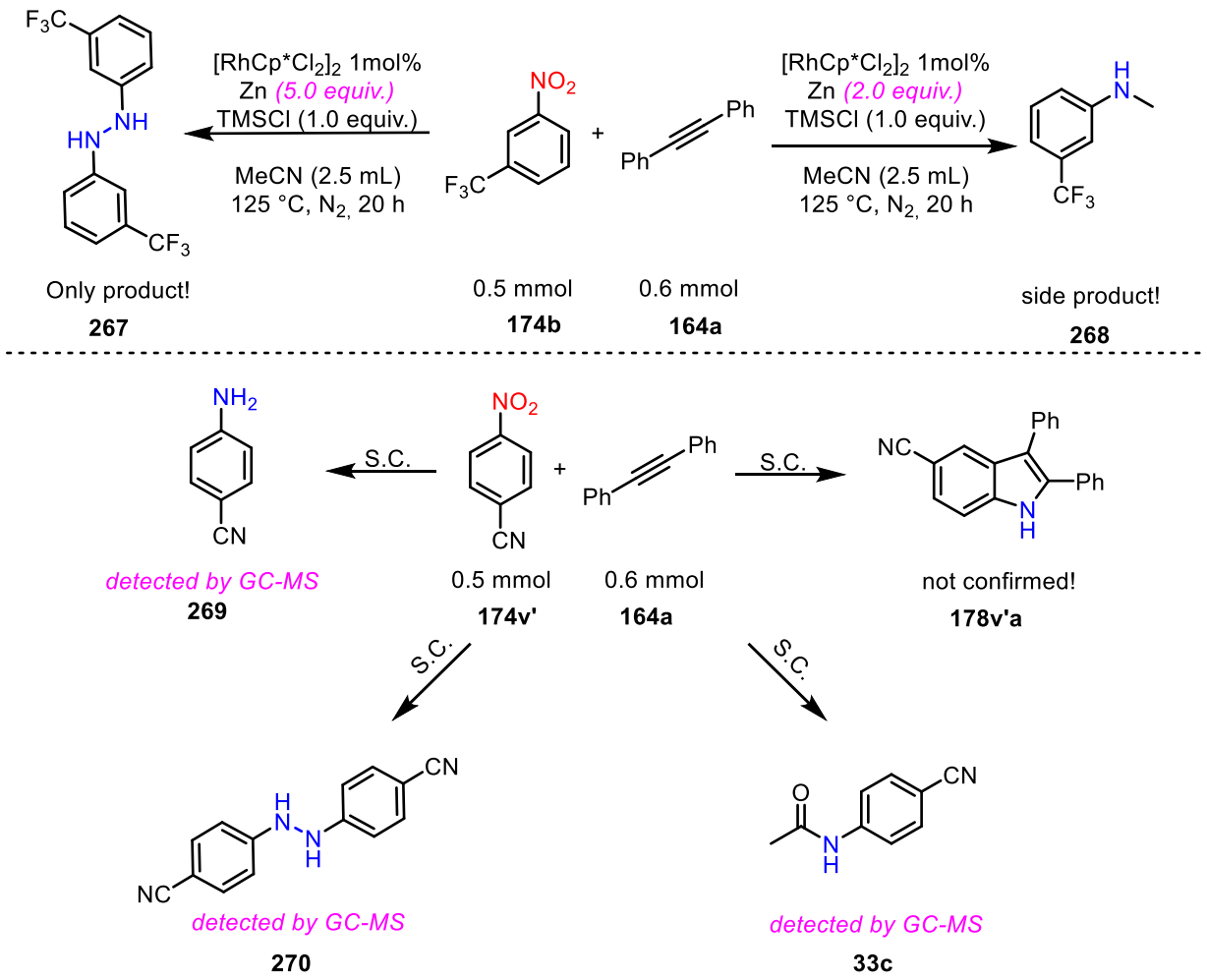
0.5 mmol 0.6 mmol

174l **164a** **178la**

Entry	Variation to s.c.	Qualitative control
1	No $[RhCp^*Cl_2]_2$	n.d.
2	No Zn	n.d.
3	No AcOH	Trace
4	N_2 instead of air	Slightly better

Table 24: Control reactions.

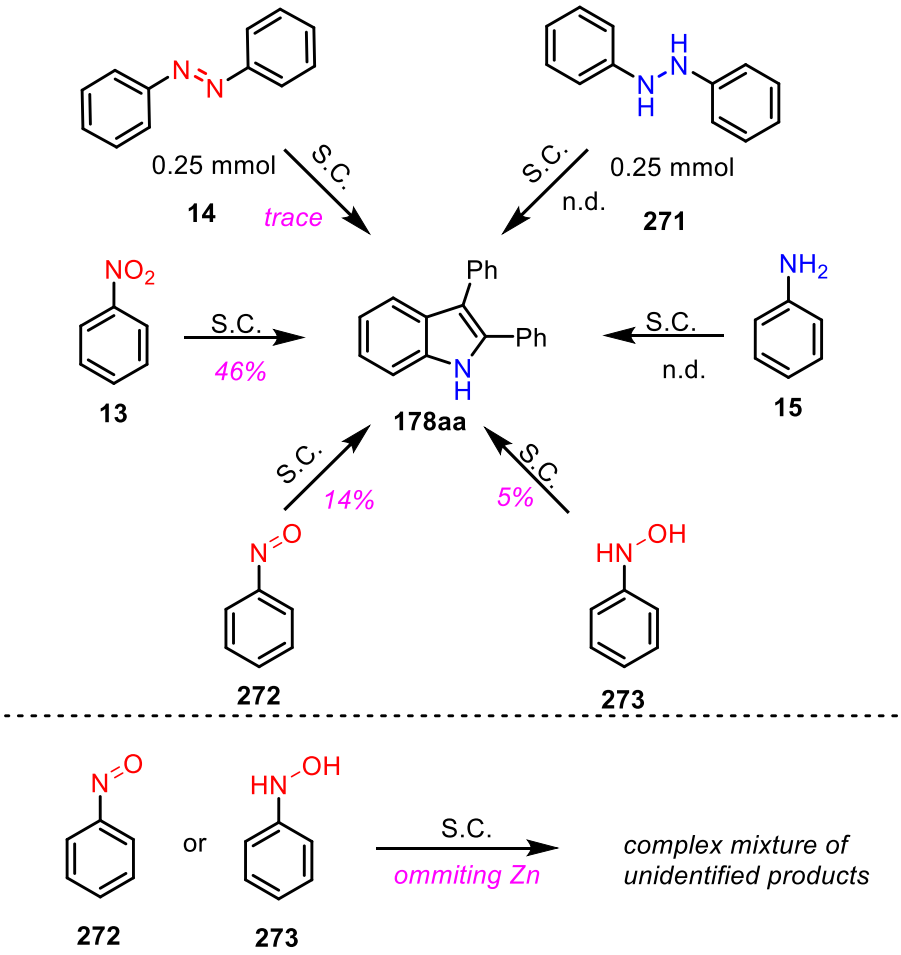
As expected, all components are necessary for the formation of the product. During the optimization, two side products were identified (Scheme 62). When five equivalents of Zn were used and acetic acid was left out, full conversion was achieved, but only the homo coupled hydrazine **267** could be identified (trace amounts). The formation of the reduced aniline cannot be excluded. For the reaction with two equivalents of Zn and no acetic acid, a lot of different compounds were detected by TLC, but only the *N*-methylaniline derivative **268** was successfully isolated (10%).



Scheme 62: Possible side products. The reaction with 4-cyanonitrobenzene was carried out by Bub. Analysis of GC-MS data was done in cooperation with Bub.

Bub carried out the reaction of 4-cyanonitrobenzene **174v'** under standard conditions while examining the substrate scope. The reaction mixture showed a lot of different compounds and the product formation could not be excluded. GC-MS analysis showed that all three possible side products (**33c**, **269** & **270**) were formed (Scheme 62). The aniline **269** was double checked by TLC. The formation of hydrazine **270** and the acetanilide **33c** is rather expected since these are known pathways for the reduction of nitro groups in the presence of acetic acid. This shows that if the coordination to the metal is kinetically to slow, overreduction can occur. Thus, resulting groups are not suited for the system and the desired indole cannot be observed.

To see which oxidation states of the nitrogen are relevant for the rhodium system, test reactions were carried out (Scheme 63).



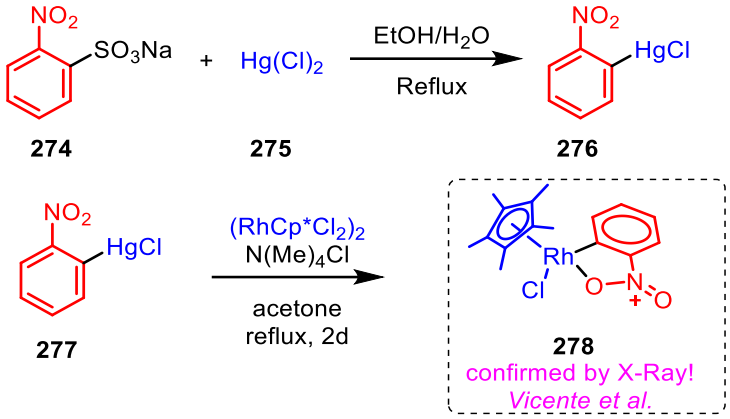
Scheme 63: Different nitrogen oxidation states and their behavior in the optimized conditions.

If one of the detected side products (**15** & **271**) were engaged, no indole **178aa** was formed in the reaction under standard conditions. This indicates that once these reduced species are formed, they cannot be transformed to the desired product **178aa** and therefore they are not formed in the catalytic cycle. 14% of indole **178aa** was isolated when nitrosobenzene **272** was engaged, being the best result. The *N*-hydroxylamine **273** and diazo compound **14** were also giving some product **178aa**, albeit the latter one in non-isolatable amounts. With these results it is not possible to conclude any certain intermediate in the reaction.

One could assume that the reaction with nitroso- **272** and *N*-Phenylhydroxylamine **273** should work, since the reaction would be redox neutral, and give the *N*-hydroxy indole when Zn was omitted. However, when the reaction was carried out without Zn, a complex mixture of different compounds was found by TLC, which could not be identified, nor by isolation or GC-MS. The fact that more compounds were detected, leads to the conclusion that Zn is not only reductant, but

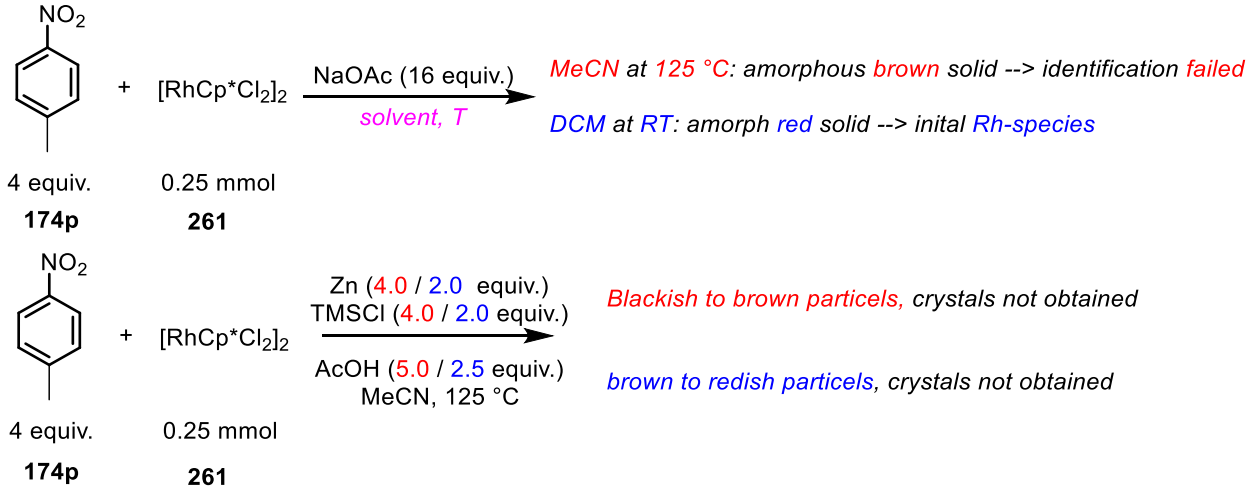
plays a decisive role in the cross-coupling process. However, this is just hypothetical and was not proven.

The best way to prove an intermediate in catalysis is the crystal structure of the organometallic compound.



Scheme 64: Conventional method for a rhodium-nitrobenzene complex using mercury.[162]

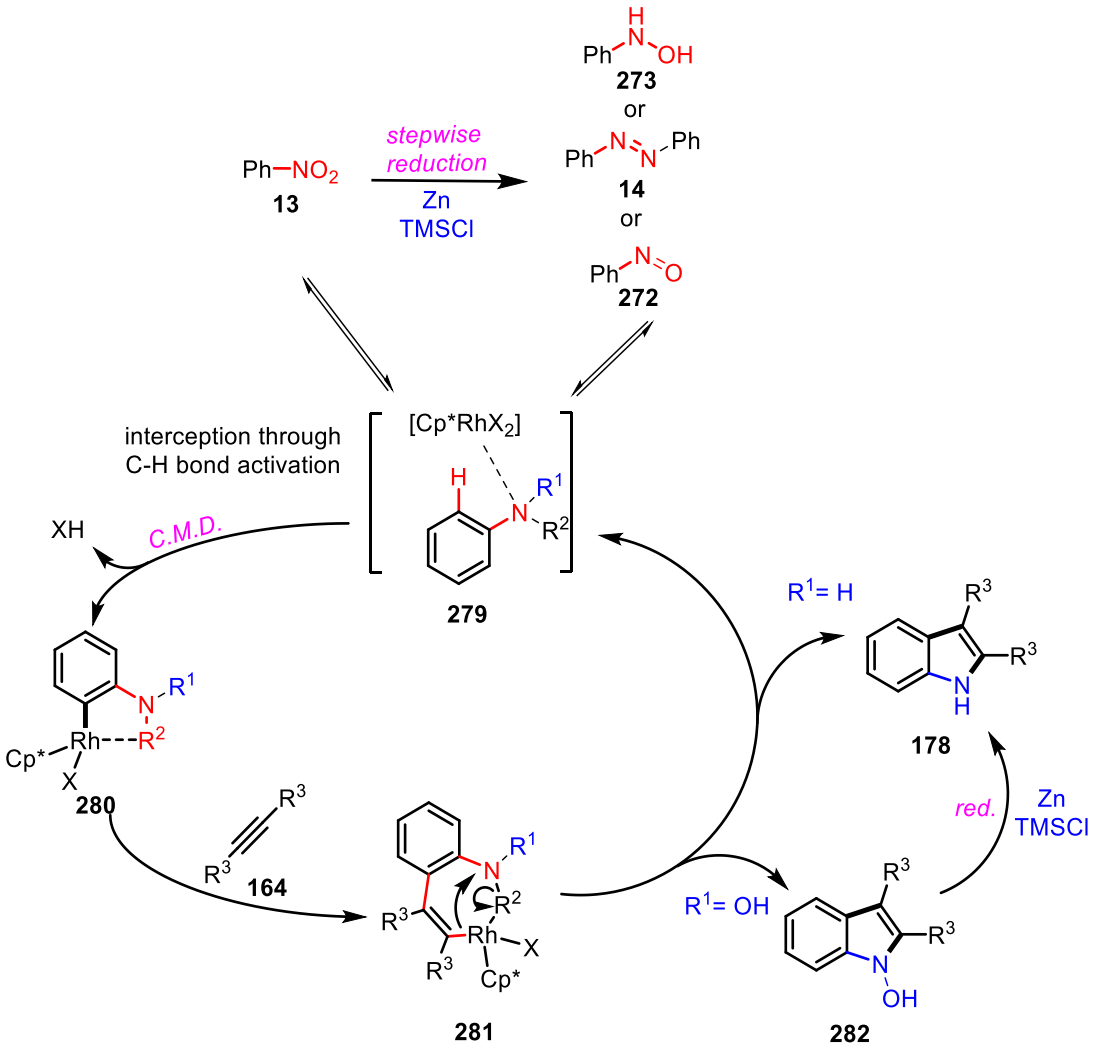
Vicente *et al.* showed that it is possible to get crystals of the showed nitroarene rhodium complex **278** (Scheme 64).[162] However, a strong trans metalating reagent is needed, which is mercury(II) chloride **275**, being very toxic. This strategy cannot be used in this work, since the complex should be formed in the reaction conditions from nitrobenzene **13**, without any prefunctionalization step.



Scheme 65: Crystalization attempts.

First, a conventional method for the synthesis of organometallic complexes was carried out, which contains a base (usually sodium acetate) in an aprotic solvent (DCM) with the starting materials

(Scheme 65). Since this method only gave the initial Rh complex, the reaction was repeated in ethanol (at RT and reflux) and in modified optimized conditions. After several purification steps and different solvents and crystallization strategies, only oils or amorph solids were obtained.
Even though, limited information could be gathered about the reaction mechanism, a plausible proposed mechanism is shown (Scheme 66). Fortunately, rhodium C-H activation has been studied and understood, which is the basis of the proposed mechanism.[163] Additionally, the reduction process by Zn and TMSCl was studied for different cross coupling reactions with nitrobenzenes by Hu and coworkers.[132,139] Even though it is very unlikely, that the reaction has the same mechanism, some information can be concluded by his work.

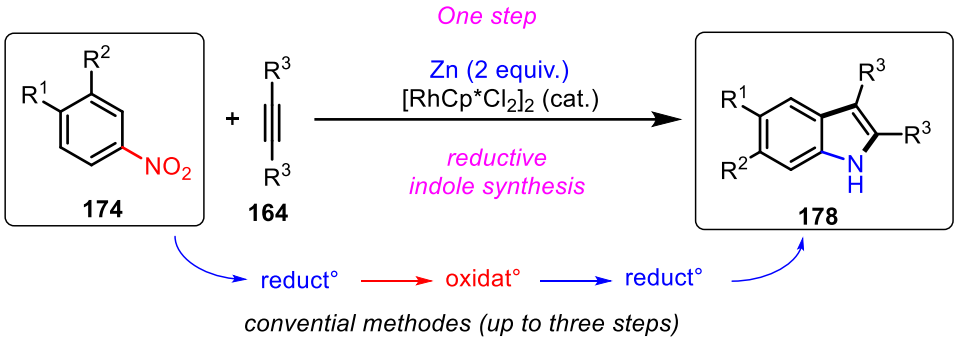


Scheme 66: plausible proposed reaction mechanism for the reductive formation of indole.

Albeit the yields for the reduced forms of nitrobenzene (**14**, **272** & **273**) are not high, they cannot be excluded in the mechanism. Therefore, it will be assumed that either the engaged nitrobenzene **13** or a reduced (**14**, **272** & **273**) form can coordinate to the rhodium. After a C.M.D step **280** is forme. An insertion of the alkyne gives **281**, which will lead to the indole **178** after a reductive elimination. If a reduced form of nitrobenzene is coordinating, one should get the *N*-hydroxyindole **282**, which will be reduced in a last step.

3.3.4 Conclusion

In conclusion, a new method for the direct synthesis of indoles **178** starting from nitroarenes **174** was developed (Scheme 67). Albeit the yields are mostly moderate, the reaction works with a non-toxic reductant and the substrate scope is not limited to a certain type of substitution pattern.



Scheme 67:Reductive nitroarene to indole synthesis.

Interesting functional groups (e.g., boron containing, amides) were tolerated and the methoxylated niclosamide derivative was transformed to the desired indole in remarkable 51%.

Control and mechanistic experiments were carried out and a plausible reaction mechanism was proposed, based on the findings and the excessive works in rhodium C-H activation.

The method is a promising addition to the known indole syntheses and is very practical due to its step and redox efficiency.

The next step would be to use hydrogen gas as a reductant to have only water as a side product making the synthesis of indoles more environmentally friendly.

4 Experimental section

4.1 General information and working methods

4.1.1 Chemicals and solvents

Unless otherwise stated, all commercially available chemicals and solvents were purchased from either *Sigma-Aldrich*, *TCI*, *abcr*, *chempur* or *Thermo Fisher Scientific* and engaged directly without further purification.

Solvents for column chromatographic purification were either purchased from *Fisher* (Analytical grade) and used without further purification or were purchased in technical grade and purified by distillation before column chromatography was engaged.

Dry solvents were either purchased from *Acros Organics* as “ExtraDry” and with an “ArcoSeal^{Tm}” or were purchased from *Th.Geyer* and purified by the Pure Solvent PS-MD-5 solvent drying system from *Innovative Technology*. Solvents from PS-MD-5 were stored in baked out (see section 4.1.2) glassware over molecular sieves 4Å and flushed with nitrogen to remove residues of oxygen in the solvents.

4.1.2 Working under inert gas

All reactions performed under argon or nitrogen were transferred to the corresponding atmosphere using standard Schlenk line technique. Air or moisture sensitive chemicals were stored under argon in a desiccator or in a glove box with nitrogen atmosphere. If reactions were moisture sensitive, vessels were backed out by heating the glassware under vacuum generated by an oil pump (10^{-3} mbar) from *vacuubrand* (“RZ-6”).

Solids were first added under air, with the air or hydrolysis-sensitive substances being the last to be rapidly added. The vessel was closed, then evacuated three times and flooded with argon or nitrogen. Liquid reagents or solvents were added last with a syringe previously rinsed with inert gas.

4.1.3 Reaction vessels

Depending on scale and conditions, the reactions were carried out either in glass vials or glass reactors with a teflon-coated stirred fish.

Vials had a volume of 20 or 50 mL and were sealed with aluminous headspace caps. The vials were heated by a magnetic stirrer by *Heidolph* (“Hei-Tec with Pt 1000 temperature sensor”) on which an aluminum block, with ten positions for vials, was placed.

Reactors had a volume of 70 or 170 mL, which were equipped with a PTFE-valve and closed with a plastic screw cap and a PTFE sealing. The vials were heated by a magnetic stirrer by *Heidolph* (“Hei-Tec with Pt 1000 temperature sensor”) on which a silicon oil bath was placed.

4.1.4 Chromatography

The course of the reaction was followed by thin layer chromatography (TLC). TLC plates were used by *Merck* and consisted of finished aluminium foils coated with silica gel and a fluorescent indicator (silica 60, 60 Å, F254, 200 mm x 200 mm x 200 µm). Detection was usually carried out by UV-light (254 or 356 nm) or a suitable staining reagent (basic potassium permanganate solution or silica saturated with elemental iodine), depending weather the structure was UV-active or not.

Column chromatography was performed on silica by *Macherey-Nagel* (60M, grain size: 0.04-0.063 mm) as the stationary phase. Depending on scale of the reaction and/or separation of the compounds on TLC, column chromatography was either performed with an overpressure (~ 0.4 bar) or gravity as driving force.

Gas chromatography was performed Trace 1300 GC by *ThermoFisher SCIENTIFIC* or GC 2030 by *Shimadzu* with SH-Rxi-5ms Cap- 30x0.25x0.25 as column.

4.2 Instrumental chemistry

4.2.1 Nuclear magnetic spectroscopy

Nuclear magnetic resonance spectroscopy (NMR) was performed on either “Avance 400”, “Avance 600”, Avance Neo 400”, “Avance Neo 600” by *Bruker* or “Varian V-NMRS 400” or “Varian V-NMRS 600” by *Agilent*. Frequencies of measurements are given in Table 25.

Table 25: Frequencies of NMR-measurements

	$\nu(^{1}H)$/ MHz	**ν (^{13}C)/ MHz**	**ν (^{19}F)/ MHz**
Avance (Neo) 400	400	101	376
Avance (Neo) 600	600	151	564
Varian V-NMRS 400	400	101	376
Varian V-NMRS 600	600	151	564

If not otherwise stated, the spectra were usually measured in deuterated chloroform-*d* or dimethyl sulfoxide-d_6 as the solvent and at room temperature (20 °C). Chemical shifts δ were given in ppm (parts per million). In case of proton and carbon nmr, chemical shifts δ were reported relatively to the not deuterated solvent molecules (chloroform: δ (^{1}H) = 7.26 ppm, δ (^{13}C) = 77.16 ppm; dimethyl sulfoxide: δ (^{1}H) = 2.50 ppm, δ (^{13}C) = 39.52 ppm). Carbon spectra were measured proton decoupled and fluorine spectra were measured carbon and proton decoupled. Signal multiplicities were abbreviated by br for broad, s for singlet, d for doublet, t for triplet, q for quatet, quin for quintet, m for multiplet and br for broad. Coupling constants *J* were given in Hertz.

Spectra were analyzed with the software MestReNova 12.0.1 © *Mestrelab Research S.L.*

4.2.2 Infrared spectroscopy

Infrared spectroscopy was performed either on a “FT-IR Spectrum 100” or “100 FT/IR” both by *PerkinElmer*. Both spectrometers were equipment with an ATR-measurement unit (“Diamond KRS-5”) and all samples were measured capillary. Wave lengths *v* were given in cm^{-1}.

4.2.3 Mass spectrometry

High resolution mass spectra (HRMS) were measured on “GCT-PremierTM” mass spectrometer by *WATERS*, “LTQ Orbitrap XL” spectrometer by *ThermoFisher Scientific* or “APCI-TOF” by *Bruker*.

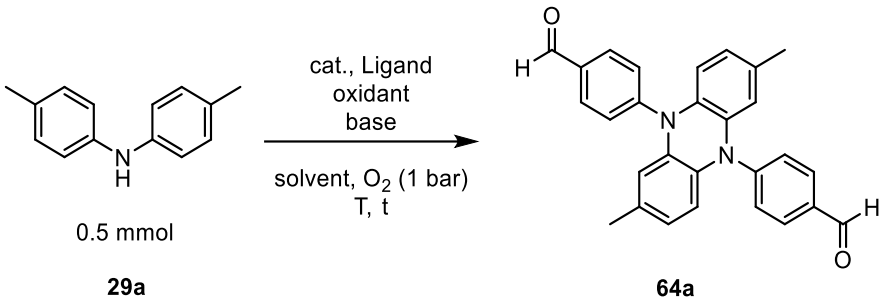
4.2.4 X-ray crystallography

Crystals suitable for X-ray structure analysis were measured on an X-ray diffractometer "Oxford Diffraction Gemini S Ultra" of the company Rigaku (Tokyo / Japan) by Dr. Harald Kelm. The subsequent analysis of the data and structure elucidation and refinement was carried out with the programs SHELXS-2018 and SHELXL-2018.

4.3 Synthesis and characterization of products

4.3.1 General procedures (GP)

4.3.1.1 GP1: Optimization of 4,4'-(2,7-dimethylphenazine-5,10-diyl)dibenzaldehyde

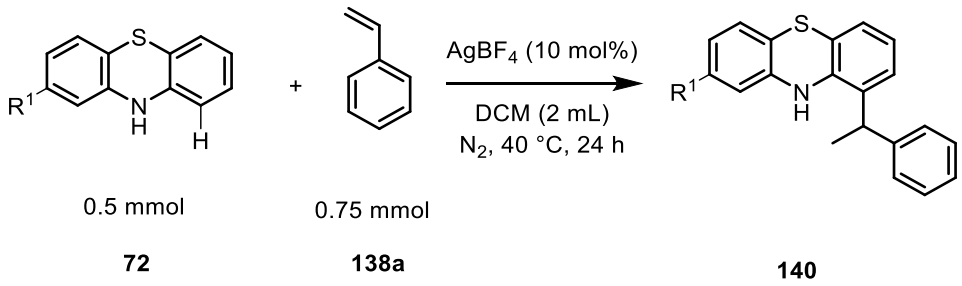


Scheme 68: General reaction for optimization of p,p'-ditolylamine homo coupling.

Unless otherwise stated, *p,p'*-ditolylamine **29a** (0.5 mmol, 98.6 mg) and all solids were added to a 20 mL crimp neck vial and closed by an aluminous headspace cap. The vial was brought into oxygen atmosphere by flushing it for approximately two min. Then the liquids were added, starting with the solvent and then the additives and heated for the corresponding time at the stated temperature. After this, the reaction was allowed to cool down and a qualitative analysis was done by TLC.

Yields were determined by proton NMR spectroscopy with 1,2 dichloroethane (0.30 mmol, ~30 mg, ~24 µL) as internal standard. A sample of the mixture was filtered over silica with deuterated chloroform in a Pasteur pipette. A proton NMR of the solution was immediately measured.

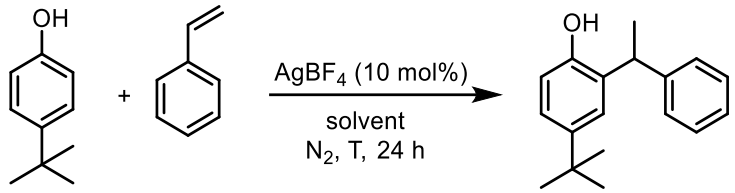
4.3.1.2 GP2: Synthesis of alkylated phenothiazine derivatives



Scheme 69: General procedure for alkylation of phenothiazines.

The reaction was caried out based on optimized conditions by Rank.[86,88] Unless otherwise specified, the phenothiazine compound **72** (0.50 mmol) was added under air in a 20 mL crimp neck vial equipped with an aluminous headspace cap. The vial was transferred into a glovebox (N_2-atmosphere), $AgBF_4$ (10 mol%, 9.73 mg) was added and the reactor was sealed. DCM (2.0 mL) and the styrene **138a** (0.75 mmol, ~ 85 µL) were added and the reaction was stirred at 40 °C for 24 h. The reactor was allowed to cool to room temperature and the crude directly engaged on SiO_2 gel column chromatography for purification, which gave the desired product after concentration *in vacuo*.

4.3.1.3 GP3: Optimization of 4-(*tert*-butyl)-2-(1-phenylethyl)phenol



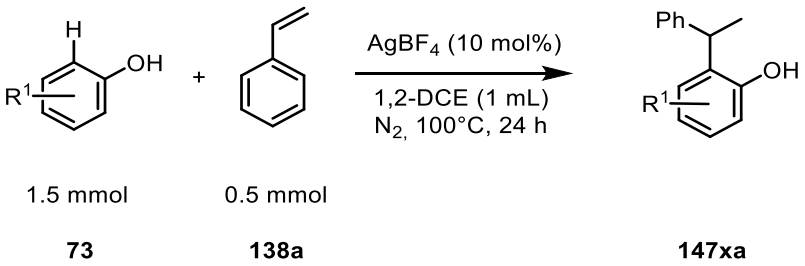
73b **138a** **147ba**

Scheme 70: General procedure for optimization of 4-(tert-butyl)-2-(1-phenylethyl)phenol.

4-*tert*-butyl-phenol **73b** was added to a 50 mL crimp neck vial equipped with an aluminous headspace cap. The vial was transferred into a glovebox (N_2- Atmosphere), $AgBF_4$ (10 mol%, 9.73 mg) was added and the reactor was sealed. The vial was closed in the glovebox and transferred outside of the glovebox, solvent and styrene **138a** were added. The reaction was stirred at the corresponding temperature and for the corresponding amount of time.

Yields were determined by GC with *n*-dodecan (100 µl, 0.44 mmol) as internal standard. A response factor was determined by utilizing different concentrations (0.1; 0.2; 0.3; 0.4; 0.5 mmol/ml) of 4-*tert*-butyl-phenol with the same amount of *n*-dodecane for all samples. To determine the yield of a reaction, *n*-dodecane was added after reaction completion and the sample was filtered over silica with ethyl acetate. A diluted sample of this filtrate was injected directly into the GC.

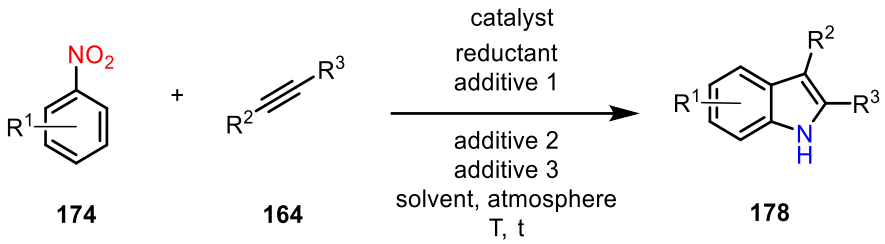
4.3.1.4 GP4: Synthesis of 1-(phenylethyl)phenols



Scheme 71: General procedure for synthesis of 1-(phenylethyl)phenols.

Unless otherwise specified, the phenol compound **73** (1.50 mmol) was added under air in a 50 mL crimp neck vial equipped with an aluminous headspace cap. The vial was transferred into a glovebox (N_2- Atmosphere), $AgBF_4$ (10 mol%, 9.73 mg) was added and the reactor was sealed. 1,2 DCE (1.0 mL) and styrene **138a** (0.5 mmol, ~ 57.2 µL) were added and the reaction was stirred at 100 °C for 24 h. The reactor was allowed to cool to room temperature and the crude directly engaged on SiO_2 gel column chromatography for purification, which gave the desired product after concentration *in vacuo*.

4.3.1.5 GP5: Optimization of reductive indole synthesis

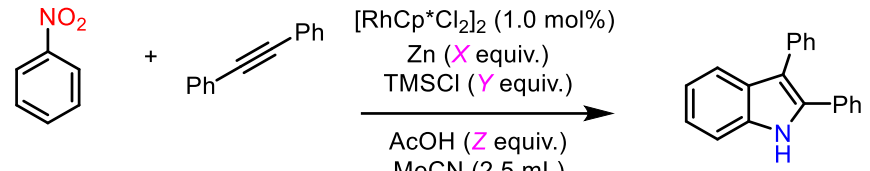


Scheme 72: General reaction for optimization.

Unless otherwise stated, the nitro-compound **174** (0.5 mmol), alkyne **164** (0.6 mmol), were added to a reaction vial (50 mL) and the liquids were added, starting with the solvent and then additives. At last, the vial was quickly sealed by an aluminous headspace cap and heated at the corresponding temperature for the specified time. Then the reaction was allowed to cool down and checked qualitatively by TLC.

For fluor containing, ^{19}F-NMR was used to quantify the yield of the corresponding product, if the product could be identified by TLC. After the reaction was cooled down, a standard was added, and the sample was measured directly. When *meta*-trifluoro nitrobenzene was engaged, *para*-fluoro nitrobenzene (~ 0.5 mmol) was added as standard. If *para*-fluoro nitrobenzene was used as a substrate trifluoroethanol was the standard.

For GC-yields, *n*-dodecan (100 µL) was added to the reaction and the crude was worked up by adding ethyl acetate and filtering over silica. A diluted sample of this filtrate was injected directly into the GC. For GC-yields, a response factor was determined by utilizing different concentrations (0.1; 0.2; 0.3; 0.4; 0.5 mmol/mL) of the pure corresponding sample with the same amount of *n*-dodecane (100 µL) for all samples.



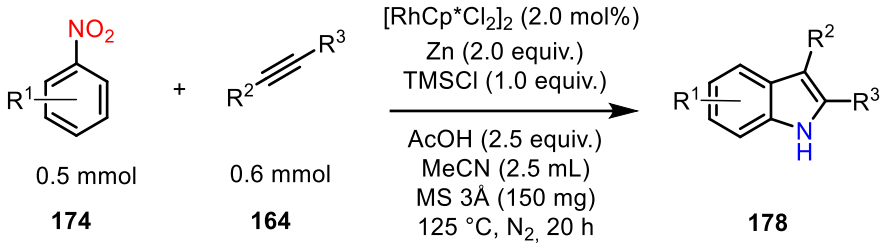
0.5 mmol **174a** | 0.6 mmol **164a** | **178aa**

Entry	Zn [X equiv.]	TMSCl [Y equiv.]	AcOH [Z equiv.]	GC-Yield [%]
1	4.0	3.0	4.0	1
2	3.0	3.0	3.0	3
3	3.0	2.0	2.0	8
4	3.0	2.0	1.5	7
5	3.0	1.5	3.0	26
6	3.0	1.5	2.5	14
7	3.0	1.5	2.0	8
8	3.0	1.5	1.5	8
9	3.0	1.0	2.5	19
10	2.5	1.0	2.5	34
11	2.2	1.0	2.5	28
12	2.0	2.0	2.0	28
13	2.0	2.0	1.5	29
14	2.0	1.5	3.0	6
15	2.0	1.5	2.5	40
16	2.0	1.5	2.0	38

17	2.0	1.5	1.5	50 (25)
18	2.0	1.25	2.5	44
19	2.0	1.0	4.0	5
20	2.0	1.0	3.5	1
21	2.0	1.0	2.5	44 (45)
22	2.0	0.75	2.5	33
23	2.0	0.5	3.0	41
24	2.0	0.5	2.5	36
25	1.8	1.0	2.5	27
26	1.5	1.5	2.5	0
27	1.5	1.0	2.5	7
28	1.5	1.0	1.5	38

Table 26: Tested ratios between Zn, TMSCl and AcOH with corresponding GC-Yields.Isolated yields in brackets.

4.3.1.6 GP6: Synthesis of 2,3- substituted indoles.



Scheme 73: General procedure for the synthesis of 2,3- substituted indoles.

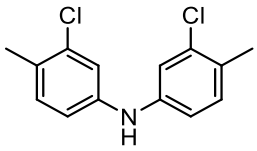
Unless otherwise stated, the nitro-compound **174** (0.5 mmol), $[Rh(Cp^*)Cl_2]_2$ (2 mol%, 6.18 mg), zinc (1 mmol, 65.4 mg), molsieves 3Å (~150 mg) and alkyne **164** (0.6 mmol) were added to the reaction vial and closed by a rubber septum. The vial was brought into nitrogen atmosphere by standard Schlenk-technique. The liquid compounds were added one after the other in the following order: first acetonitrile (2.0 mL), then TMSCl (0.5 mmol, ~ 54 mg), and finally acetic acid (1.25 mmol, ~ 75 mg). If one of the starting materials was liquid, they were added last. In the end, the vial was quickly sealed by an aluminous headspace cap and heated to 125 °C for 24 h. The

reaction was allowed to cool to room temperature. The crude was directly engaged on SiO_2 gel column chromatography for purification (including the molsieves of the reaction mixture), which gave the desired product **178** after concentration *in vacuo*.

4.3.2 Analytical data

4.3.2.1 N-N bond formation

Bis(3-chloro-4-methylphenyl)amine (29f)



A 70 mL Schlenk reactor was charged with 2-chloro-4-iodotouene (5 mmol, 1.26 g, ~ 0.70 mL), *N*-(3-chloro-4-methylphenyl)acetamide (5 mmol, 0.92 g), copper(I) iodide (10 mmol, 1.90 g), potassium phosphate (10 mmol, 2.13 g), 2,2,6,6-tetramethyl-3,5-heptadione (20.1 mmol, 3.71 g) and chlorobenzene (7 mL). The mixture was stirred at 170 °C for 24 h and fileted with dichloromethane over SiO_2. The solvent was removed under reduced pressure and the crude was purified by SiO_2 gel column chromatograph with ethyl acetate: cyclohexane (3:7).

The *N*-acetyl amine (2.27 mmol, 700 mg), potassium hydroxide (22.7 mmol, 1.27 g) and *n*-butanol (5 mL) was charged in a 150 mL Schlenk reactor and stirred at 150 °C for 24 h. The mixture was washed with water (3 x 20 mL), ethyl acetate (3 x 20 mL) and dried over magnesium sulfate. The solvent was removed under reduced pressure and the crude was purified by SiO_2 gel column chromatograph with ethyl acetate: cyclohexane (3:7).

Isolated overall-yield (2 steps): 617 mg, 2.32 mmol, 46% (brown solid).

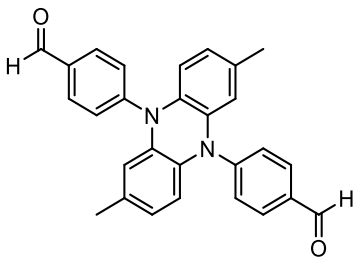
^{1}H-NMR (400 MHz, DMSO-d_6): δ (ppm) = 8.29 (s, NH), 7.18 (d, ^3J= 8.0 Hz, 2H), 7.03 (d, ^4J= 4.0 Hz, 2H), 6.93 (dd, ^3J= 8.0 Hz, ^4J= 4.0 Hz, 2H), 2.23 (s, 6H).

^{13}C{^{1}H}-NMR (101 MHz, DMSO-d_6): δ (ppm) = 142.40 (s, C_{quat}), 133.60 (s, C_{quat}), 131.69 (s, CH), 126.33 (s, C_{quat}), 116.84 (s, CH), 115.69 (s, CH), 18.69 (s, CH_3).

TOF-HRMS: $[M+H]^+$ m/z: calculated for $[C_{14}H_{14}NCl_2]^+$: 266.04978, measured: 266.05096.

IR (neat, cm^{-1}): $\tilde{\upsilon}$ = 3412, 3029, 2913, 2856, 2740, 1596, 1497, 1358, 1307, 1230, 1205,

4,4'-(2,7-dimethylphenazine-5,10-diyl)dibenzaldehyde (64a)



The diarylamine compound (0.5 mmol), carbazole or second diarylamine (0.5 mmol), copper chloride (15 mol%, 10.1 mg), 2,2'-bipyridine (15 mol%, 11.8 mg), manganese(II) oxide (0.25 mmol, 21.7 mg) and cesium carbonate (0.25 mmol, 81.5 mg) were added to the 70 mL schlenk reactor, which was baked and brought into nitrogen atmosphere by standard schlenk technique. Tetrachloroethylene (1.5 mL) and 1,2-dichlorobenzene (1.5 mL) were added and the reactor was closed loosely with a rubber septum and a screw cap. The reactor was brought into oxygen

atmosphere by flushing for approximately two minutes and the reactor was closed tightly. The mixture was stirred at 150 °C for 20 h. The reaction was allowed to cool to room temperature. Course of reaction was followed by TLC. If product was detected, the crude was directly engaged on SiO_2 gel column chromatography for purification ethyl acetate: cyclohexane (1:4).
Isolated yield: 103 mg, 0.24 mmol, 49% (red solid).
^{1}H-NMR (400 MHz, CD_2Cl_2): δ (ppm) = 9.33 (s, 2H), 7.52-7.48 (*broad*, AA' part of a AA'BB'' spin system, 4H), 7.27-7.24 (BB'' part of a AA'BB'' spin system, 4H), 6.79 (dd, ^3J= 8.2 Hz, ^4J= 1.8 Hz, 2H), 6.00 (d, ^4J= 1.8 Hz, 2H), 5.66 (d, ^3J= 8.2 Hz, 2H), 2.49 (s, 6H).
^{13}C{^{1}H}-NMR (101 MHz, DMSO-d_6): = 189.91 (s, CH), 142.97 (s, C_{quat}), 140.16 (s, C_{quat}), 136.44 (s, C_{quat}), 135.85 (s, C_{quat}), 133.10 (s, CH), 130.69 (s, C_{quat}), 130.26 (s, CH), 129.21 (s, CH), 112.38 (s, CH), 111.05 (s, CH), 21.65 (s, CH_3).

Crystallization attempts:

Crystallization method	solvents	
Ether diffusion	Dichloromethane	✓
	Pentane	
	Ether Pentan	×
	Ether Dichlormethane	×
Recrystallization	Hexane	×
	Heptane	×
	Dichloromethane	×
	ethanol	×
Slow evaporation	Dichloromethane	✓
	Ethanol	×
	Ether	×

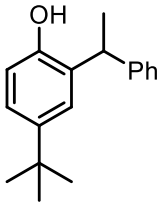
Crystal structure data:

Identification code	shelx
Empirical formula	$C_{28}H_{22}N_2O_2$
Formula weight	418.47 g/mol
Temperature	293(2) K
Wavelength	1.54184 Å

Crystal system	Triclinic	
Space group	P-1	
Unit cell dimensions	a = 7.5386(9) Å	a= 88.899(9)°.
	b = 7.7072(9) Å	b= 68.040(11)°.
	c = 10.0091(11) Å	g = 83.268(10)°.
Volume	535.44(11) $Å^3$	
Z	1	
Density (calculated)	1.298 Mg/m^3	
Absorption coefficient	0.651 mm^{-1}	
F(000)	220	
Crystal size	0.340 x 0.150 x 0.060 mm^3	
Theta range for data collection	4.765 to 62.646°.	
Index ranges	-8<=h<=8, -8<=k<=8, -11<=l<=11	
Reflections collected	2995	
Independent reflections	1695 [R(int) = 0.0180]	
Completeness to theta = 62.646°	98.5 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	1.00000 and 0.75415	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	1695 / 0 / 156	
Goodness-of-fit on F^2	1.066	
Final R indices [I>2sigma(I)]	R1 = 0.0452, wR2 = 0.1346	
R indices (all data)	R1 = 0.0497, wR2 = 0.1408	
Extinction coefficient	n/a	
Largest diff. peak and hole	0.144 and -0.125 $e.Å^{-3}$	

4.3.2.2 *Ortho*-alkylation of phenols and dirarylamines

4-*tert*-butyl-2-(1-phenylethyl)phenol (147ba)



Following **GP4**, using 4-*tert*-butylphenol (1.50 mmol, 225 mg) and styrene (0.50 mmol, 57.2 µl). The crude mixture was purified by SiO_2 gel column chromatography hexane: ethyl acetate (9:1). Isolated yield: 112 mg, 0.44 mmol, 88% (yellowish sticky solid).

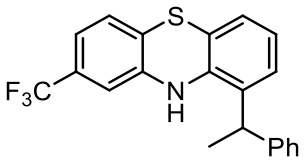
^{1}H-NMR (400 MHz, DMSO-d_6): δ (ppm) = 9.08 (s, 1H), 7.26-7.22 (m, 4H), 7.14-7.11 (m, 2H), 6.99 (dd, ^{3}J= 8.3 Hz, ^{4}J= 2.6 Hz, 1H), 6.67 (^{3}J= 8.3 Hz, 1H), 4.42 (^{3}J= 7.3 Hz, 1H), 1.51 (d, ^{3}J= 7.1 Hz, 3H), 1.19 (s, 9H).

^{13}C{^{1}H}-NMR (101 MHz, DMSO-d_6): δ (ppm) = 152.04 (s, $C_{quat.}$), 146.48 (s, $C_{quat.}$), 140.77 (s, $C_{quat.}$), 131.28 (s, $C_{quat.}$), 128.00 (s, CH), 127.42 (s, CH), 125.52 (s, CH), 124.01 (s, CH), 123.21 (s, CH), 114.40 (s, CH), 37.26 (s, CH), 33.74 (s, $C_{quat.}$), 31.49 (s, CH_3), 20.78 (s, CH_3).

TOF-HRMS: $[M+Na]^+$ m/z: calculated for $[C_{18}H_{23}O]$+: 255.17434, found: 255.17367.

IR (neat, cm^{-1}): $\tilde{\upsilon}$: 3532, 3060, 3028, 2961, 2906, 2872, 1875, 1604, 1500, 1454, 1418, 1364, 1329, 1264, 1207, 1124, 1029, 986, 895, 818, 793, 755, 698, 667.

1-(1-phenylethyl)-8-(trifluoromethyl)-10*H*-phenothiazine (140aa)



Following **GP2**, using 2-trifluoromethylphenothiazine (0.50 mmol, 133.6 mg) and styrene (0.75 mmol, 0.09 mL). The crude mixture was purified by SiO_2 gel column chromatography pentane: toluene (4:1). Isolated yield: 77.4 mg, 0.21 mmol, 42% (red solid).

^{1}H-NMR (400 MHz, DMSO-d_6): δ (ppm) = 8.07 (s, 1H), 7.30-7.29 (m, 4H), 7.23 (s, 1H), 7.20-7.14 (m, 2H), 7.09 (d, ^{3}J= 8.0 Hz, 1H), 6.93 (dd, ^{4}J= 1.6 Hz, ^{3}J= 7.5 Hz, 1H), 6.88-6.80 (m, 2H), 4.57 (q, ^{3}J= 7.0 Hz, 1H), 1.53 (d, ^{3}J= 7.0 Hz, 3H).

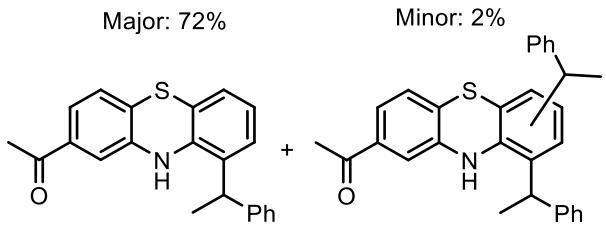
^{13}C{^{1}H}-NMR (101 MHz, DMSO-d_6): δ (ppm) = 144.86 (s, $C_{quat.}$), 142.85 (s, $C_{quat.}$), 138.30 (s, $C_{quat.}$), 131.66 (s, $C_{quat.}$), 128.36 (s, CH),127.92 (q, ^{2}J= 32.3 Hz, $C_{quat.}$), 127.47 (s, CH), 126.70 (s, CH), 126.68 (s, CH), 126.19 (s, $C_{quat.}$), 124.73 (s, CH), 124.10 (q, ^{1}J= 273.7 Hz, $C_{quat.}$), 123.54 (s, $C_{quat.}$), 122.62 (s, CH), 118.52 (q, ^{3}J= 3.0 Hz, CH), 116.76 (s, CH), 111.58 (q, ^{3}J= 3.0 Hz, CH), 36.55 (s, CH), 21.04 (s, CH_3).

^{19}F{^{1}H}-NMR (101 MHz, DMSO-d_6): δ (ppm) = - 62.97 ppm.

ESI-HRMS: $[M+Na]^+$ m/z: calculated for $[C_{21}H_{16}F_3NSNa]$+ 394.08478, found 394.08438.

IR (neat, cm^{-1}): $\tilde{\upsilon}$: 3397, 3081, 3023, 2984, 2972, 2931, 2874, 1734, 1605, 1588, 1568, 1514, 1490, 1476, 1432, 1392, 1371, 1327, 1282, 1270, 1234, 1165, 1152, 1135, 1081, 1063, 1025, 983, 963, 927, 907, 868, 824, 793, 756, 741, 725, 695, 953.

1-(1-phenylethyl)-8-(acetyl)-10*H*-phenothiazine (140ca + 140ca')



Following **GP2**, using 2-acetylphenothiazine (0.50 mmol, 120.7 mg) and styrene (0.75 mmol, 0.09 mL). The crude mixture was purified by SiO_2 gel column chromatography pentane/ ethyl acetate (9:1).

Isolated yield of a mixture: 130.8 mg. Shares were calculated by proton NMR.

Share of monosubstituted product in mixture: 124.5 mg, 0.36 mmol, 72%.

Share of disubstituted product in mixture: 6.3 mg, 0.01 mmol, 2%.

^{1}H-NMR (400 MHz, DMSO-d_6): δ (ppm) = 7.97 (s, 1H), 7.48 (d, ^4J= 1.8 Hz, 1H), 7.37 (dd, ^4J= 1.8 Hz, ^3J= 8.0 Hz, 1H), 7.32-7.27 (m, 5H), 7.06 (d, ^3J= 8.0 Hz, 1H), 7.20-7.14 (m, 2H), 7.09 (d, ^3J= 8.0 Hz, 1H), 6.90 (dd, ^4J= 1.7 Hz, ^3J= 7.6 Hz, 1H), 6.84 (dd, ^4J= 1.7 Hz, ^3J= 7.6 Hz, 1H), 6.79 (d, ^3J= 7.6 Hz, 1H), 4.61 (q, ^3J= 7.0 , 1H), 2.47 (s, 3H), 1.52 (d, ^3J= 7.0 Hz, 3H).

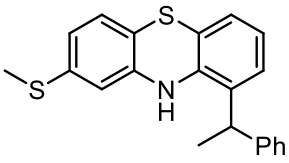
^{13}C{^{1}H}-NMR (101 MHz, DMSO-d_6): δ (ppm) = 196.92 (s, CH_3), 144.94 (s, $C_{quat.}$),142.25 (s, $C_{quat.}$), 138.54 (s, $C_{quat.}$), 136.00 (s, $C_{quat.}$), 131.47 (s, $C_{quat.}$), 128.35 (s, CH), 127.46 (s, CH), 126.65 (s, CH), 126.16 (s, CH), 125.89 (s, CH), 124.69 (s, $C_{quat.}$), 124.60 (s, CH), 122.56 (s, CH), 122.21 (s, CH), 116.62 (s, $C_{quat.}$), 114.23 (s, CH), 36.46 (s, CH), 26.52 (s, CH_3), 21.02 (s, CH_3).

ESI-HRMS: $[M+Na]^+$ m/z: calculated for $[C_{22}H_{19}NSONa]+$, 368.10796 found 368.10773.

$[M+Na]^+$ m/z: calculated for $[C_{30}H_{27}NSONa]+$ 472.17056, found 472.17011.

IR (neat, cm^{-1}): $\tilde{\nu}$: 3401, 3026, 2963, 2929, 1738, 1669, 1582, 1563, 1514, 1477, 1440, 1392, 1349, 1317, 1286, 1218, 1183, 1135, 1097, 1055, 1026, 984, 912, 891, 804, 757, 744, 729, 703, 669, 659.

1-(1-phenylethyl)-8-(thiomethyl)-10*H*-phenothiazine (140da)



Following **GP2**, using 2-thiomethylphenothiazine (0.50 mmol, 122.7 mg) and styrene (0.75 mmol, 0.09 mL). The crude mixture was purified by SiO_2 gel column chromatography pentane/ toluene (4:1).

Isolated yield: 46.1 mg, 0.13 mmol, 26% (greenish solid).

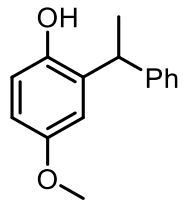
More analytical data could not be provided.

^{1}H-NMR (400 MHz, DMSO-d_6): δ (ppm) = 7.74 (s, 1H), 7.30-7.27 (*broad*, m, 4H), 7.20-7.17 (m, 1H), 6.94-6.77 (m, 5H), 6.69 (dd, ^4J= 1.9 Hz, ^3J= 8.0 Hz, 1H), 4.56 (q, ^3J= 7.0 , 1H), 2.40 (s, 3H), 1.53 (d, ^3J= 7.0 Hz, 3H).

^{13}C{^{1}H}-NMR (101 MHz, DMSO-d_6): δ (ppm) = 145.04 (s, $C_{quat.}$),142.79 (s, $C_{quat.}$), 139.06 (s, $C_{quat.}$), 137.18 (s, $C_{quat.}$), 131.33 (s, $C_{quat.}$), 128.39 (s, CH), 127.46 (s, CH), 126.28 (s, CH), 126.18 (s, CH),

124.66 (s, CH), 122.01 (s, CH), 119.82 (s, CH), 117.97 (s, $C_{quat.}$), 114.38 (s, $C_{quat.}$), 112.88 (s, CH), 36.70 (s, CH), 21.09 (s, CH_3), 14.81 (s, CH_3).

4-methoxy-2-(1-phenylethyl)phenol (147da)



Following **GP4**, using 4-hydroxyanisole (1.50 mmol, 186 mg) and styrene (0.50 mmol, 57.2 µl). The crude mixture was purified by SiO_2 gel column chromatography hexane/ethyl acetate (9:1). Isolated yield: 57.9 mg, 0.25 mmol, 51% (yellowish sticky solid).

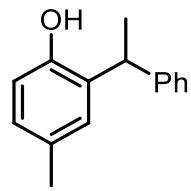
^{1}H-NMR (400 MHz, DMSO-d_6): δ (ppm) = 8.89 (s, 1H), 7.27-7.22 (m, 4H), 7.17-7.11 (m, 1H), 6.68 (d, ^3J= 8.64, 1H), 6.64 (d, ^4J= 3.0 Hz, 1H), 6.58 (dd, ^4J= 3.0 Hz ^3J= 8.6 Hz, 1H), 4.42 (q, ^3J= 7.2 Hz, 1H), 3.62 (s, 3H), 1.49 (d, ^3J= 7.3 Hz, 3H).

^{13}C{^{1}H}-NMR (101 MHz, DMSO-d_6): δ (ppm) = 152.13 (s, $C_{quat.}$),148.18 (s, $C_{quat.}$), 146.11 (s, $C_{quat.}$), 133.30 (s, $C_{quat.}$), 128.05 (s, CH), 127.43 (s, CH), 125.63 (s, CH), 115.33 (s, CH), 113.67 (s, CH), 111.08 (s, CH), 55.20 (s, CH_3), 36.99 (s, CH), 20.58 (s, CH_3).

ESI-HRMS: $[M+Na]^+$ m/z: calculated for $[C_{15}H_{16}O_2Na]+$: 251.10425, found: 251.10394.

IR (neat, cm^{-1}): $\tilde{\upsilon}$: 3399, 3026, 2966, 2934, 2873, 2834, 1599, 1491, 1448, 1429, 1373, 1336, 1282, 1202, 1177, 1152, 1118, 1081, 1026, 985, 911, 872, 858, 795, 760, 730, 655.

4-methyl-2-(1-phenylethyl)phenol (147ea)



Following **GP4**, using 4-methylphenole (1.50 mmol, 162 mg) and styrene (0.50 mmol, 57.2 µl). The crude mixture was purified by SiO_2 gel column chromatography hexane/ethyl acetate (9:1). Isolated yield: 83.2 mg, 0.44 mmol, 78% (colorless sticky solid).

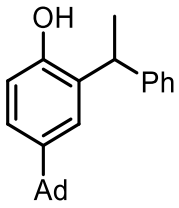
^{1}H-NMR (400 MHz, DMSO-d_6): δ (ppm) = 9.07 (s, 1H), 7.26-7.21 (m, 4H), 7.15-7.10 (m, 1H), 6.88 (d, ^4J= 1.4, 1H), 6.78 (dd, ^4J= 1.8 Hz ^3J= 8.1 Hz, 1H), 6.65 (d, ^3J= 8.1 Hz, 1H), 4.42 (q, ^3J= 7.2 Hz, 1H), 2.15 (s, 3H), 1.49 (d, ^3J= 7.3 Hz, 3H).

^{13}C{^{1}H}-NMR (101 MHz, DMSO-d_6): δ (ppm) = 152.01 (s, $C_{quat.}$),146.40 (s, $C_{quat.}$), 132.02 (s, $C_{quat.}$), 128.02 (s, $C_{quat.}$), 127.81 (s, CH), 127.41 (s, CH), 127.15 (s, $C_{quat.}$), 127.05 (s, CH), 125.53 (s, CH), 114.85 (s, CH), 36.68 (s, CH), 20.70 (s, CH_3), 20.42 (s, CH_3).

ESI-HRMS: $[M+Na]^+$ m/z: calculated for $[C_{15}H_{16}ONa]+$: 235.10934, found: 235.10930.

IR (neat, cm^{-1}): $\tilde{\upsilon}$: 3527, 2037, 2969, 2932, 2874, 1601, 1494, 1450, 1421, 1374, 1323, 1254, 1180, 1150, 1116, 1059, 1029, 1006, 937, 909, 883, 809, 794, 758.

4-adamantyl-2-(1-phenylethyl)phenol (147fa)



Following **GP4**, using 4-(1-adamantyl)phenol (1.50 mmol, 342 mg) and styrene (0.50 mmol, 57.2 µl). The crude mixture was purified by SiO_2 gel column chromatography hexane/ethyl acetate (9:1). Isolated yield: 132 mg, 0.40 mmol, 80% (yellow resin).

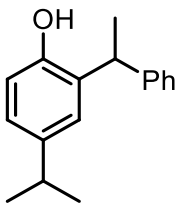
^{1}H-NMR (400 MHz, DMSO-d_6): δ (ppm) = 9.07 (s, 1H), 7.26-7.21 (m, 4H), 7.13-7.09 (m, 2H), 6.95 (dd, ^4J= 2.4 Hz, ^3J= 8.4 Hz, 1H), 6.68 (d, ^3J= 8.4 Hz, 1H), 4.42 (q, ^3J= 7.2 Hz, 1H), 2.01 (broad s, 3H), 1.77 (d, ^4J= 2.44 Hz, 6H), 1.69 (t, ^3J= 13 Hz, 6H), 1.51 (d, ^3J= 7.3 Hz, 3H).

^{13}C{^{1}H}-NMR (101 MHz, DMSO-d_6): δ (ppm) = 152.10 (s, C_{quat}), 146.55 (s, C_{quat}), 141.28 (s, C_{quat}), 131.24 (s, C_{quat}), 128.00 (s, CH), 127.41 (s, CH), 125.50 (s, CH), 123.40 (s, CH), 122.80 (s, CH), 114.49 (s, CH), 42.97 (s, CH2), 37.72 (s, CH), 36.25 (s, CH2), 35.06 (s, CH), 28.38 (s, CH), 20.83 (s, CH3) ppm.

ESI-HRMS: $[M+Na]^+$ m/z: calculated for $[C_{24}H_{28}ONa]+$: 355.20324, found: 355.20340.

IR (neat, cm^{-1}): $\tilde{\nu}$ = 3520, 3027, 2968, 2900, 2846, 1601, 1496, 1449, 1419, 1370, 1344, 1316, 1252, 1193, 1116, 1102, 1048, 1028, 1003, 975, 932, 905, 887, 854, 827, 804, 768, 755, 677, 666.

4-*iso*-propyl-2-(1-phenylethyl)phenol (147ga)



Following **GP4**, using 4-*iso*-propylphenol (1.50 mmol, 204 mg) and styrene (0.50 mmol, 57.2 µl). The crude mixture was purified by SiO_2 gel column chromatography hexane/ethyl acetate (9:1). Isolated yield: 99.5 mg, 0.41 mmol, 83% (yellow oil).

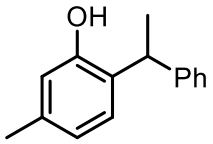
^{1}H-NMR (400 MHz, DMSO-d_6): δ (ppm) = 9.07 (s, 1H), 7.26-7.23 (m, 4H), 7.14-7.11 (m, 1H), 6.96 (d, ^4J= 1.7 Hz, 1H), 6.85 (dd, ^4J= 1.9 Hz, ^3J= 8.2 Hz, 1H), 6.67 (d, ^3J= 8.2 Hz, 1H), 4.42 (q, ^3J= 7.2 Hz, 1H), 2.73 (sept, ^3J= 6.9 Hz, 1H), 1.50 (d, ^3J= 6.1 Hz, 3H), 1.11 (d, ^3J= 6.8 Hz, 6H).

^{13}C{^{1}H}-NMR (101 MHz, DMSO-d_6): δ (ppm) = 152.34 (s, $C_{quat.}$), 146.49 (s, $C_{quat.}$), 138.55 (s, $C_{quat.}$), 131.74 (s, $C_{quat.}$), 128.00 (s, CH), 127.41 (s, CH), 125.52 (s, CH), 125.27 (s, CH), 124.04 (s, CH), 114.77 (s, CH), 37.01 (s, CH), 32.77 (s, CH_3), 24.32 (s, CH_3), 24.27 (s, CH_3), 20.77 (s, CH).

HRMS-ESI: $[M+Na]^+$ m/z: calculated for $[C_{17}H_{20}ONa]+$: 263.14064, found: 263.14075.

IR (neat, cm^{-1}): $\tilde{\nu}$ = 3529. 3027, 2961, 2929, 2870, 1601, 1494, 1451, 1428, 1362, 1305, 1256, 1194, 1166, 1116, 1055, 1029, 989, 913, 891, 863, 815, 790, 758, 740, 669.

3-methyl-2-(1-phenylethyl)phenol (147ha)



Following **GP4**, using 3-methylphenole (1.50 mmol, 162 mg) and styrene (0.50 mmol, 57.2 µl). The crude mixture was purified by SiO_2 gel column chromatography hexane/ethyl acetate (9:1). Isolated yield: 7.50 mg, 0.04 mmol, 7% (yellowish oil).

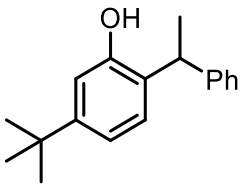
More analytical data could not be provided.

^{1}H-NMR (400 MHz, DMSO-d_6): δ (ppm) = 9.09 (s, 1H), 7.25-7.17 (m, 4H), 7.13-7.09 (m, 1H), 6.88 (*pseudo*-t, 1H), 6.62 (d, ^3J= 8.0 Hz, 1H), 6.56 (d, ^3J= 7.5 Hz, 1H), 4.58 (q, ^3J= 7.2 Hz, 1H), 2.10 (s, 3H), 1.60 (d, ^3J= 7.2 Hz, 3H).

^{13}C{^{1}H}-NMR (101 MHz, DMSO-d_6): δ (ppm) = 155.43 (s, $C_{quat.}$),145.55 (s, $C_{quat.}$), 136.86 (s, $C_{quat.}$), 130.52 (s, $C_{quat.}$), 127.74 (s, CH), 126.96 (s, CH), 126.53 (s, $C_{quat.}$), 125.05 (s, CH), 121.63 (s, CH), 113.64 (s, CH), 20.38 (s, CH_3), 17.34 (s, CH_3).

IR (neat, cm^{-1}): $\tilde{\upsilon}$: 3421, 1656, 1374, 1223, 1004, 822, 761, 681.

3-*tert*-butyl-2-(1-phenylethyl)phenol (147ia)



Following **GP4**, using 3-*tert*-butylphenol (1.50 mmol, 225 mg) and styrene (0.50 mmol, 57.2 µl). The crude mixture was purified by SiO_2 gel column chromatography hexane/ethyl acetate (9:1). Isolated yield: 107 mg, 0.42 mmol, 84% (yellow resin).

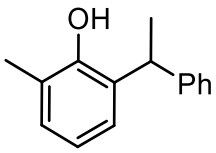
^{1}H-NMR (400 MHz, DMSO-d_6): δ (ppm) = 9.15 (s, 1H), 7.26-7.24 (m, 4H), 7.14-7.11 (m, 1H), 7.00 (d, ^3J= 8.0 Hz, 1H), 6.77 (dt, ^4J= 1.8 Hz, ^3J= 9.0 Hz, 2H), 4.40 (q, ^3J=7.2 Hz, 1H), 1.48 (d, ^3J= 7.3 Hz, 3H), 1.21 (broad s, 9H).

^{13}C{^{1}H}-NMR (101 MHz, DMSO-d_6): δ (ppm) = 153.86 (s, C_{quat}), 149.29 (s, C_{quat}), 146.49 (s, C_{quat}), 129.29 (s, C_{quat}), 128.02 (s, CH), 127.42 (s, CH), 126.88 (s, CH), 125.52 (s, CH), 115.82 (s, CH), 112.04 (s, CH), 36.59 (s, CH), 33.94 (s, C_{quat}), 31.17 (s, CH_3), 20.88 (s, CH_3).

ESI-HRMS: $[M+Na]^+$ m/z: calculated for $[C_{18}H_{22}ONa]+$: 277.15629, found: 277.15634.

IR (neat, cm^{-1}): $\tilde{\upsilon}$ = 3390, 3039, 3007, 2973, 2943, 2907, 2841, 1609, 1504, 1458, 1444, 1389, 1314, 1295, 1239, 1213, 1185, 1170, 1155, 1107,1100, 1026, 957, 941, 931, 914, 891, 876, 809, 771, 721, 706, 690, 670, 663, 654.

2-methyl-2-(1-phenylethyl)phenol (147ja)



Following **GP4**,, using 2-methylphenol (1.50 mmol, 162 mg) and styrene (0.50 mmol, 57.2 µl). The crude mixture was purified by SiO_2 gel column chromatography hexane/ethyl acetate (9:1). Isolated yield: 34.4 mg, 0.16 mmol, 32% (orange resin).

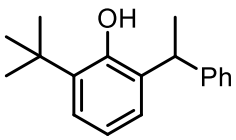
More analytical data could not be provided.

^{1}H-NMR (400 MHz, DMSO-d$_6$): δ (ppm) = 8.22 (s, 1H), 7.27-7.20 (m, 4H), 7.15-7.11 (m, 1H), 6.92 (dd, ^3J= 7.6 Hz, ^3J= 15.3 Hz, 2H), 6.70 (t, ^3J= 7.5 Hz, 1H), 4.54 (q, ^3J= 7.2 Hz, 1H), 2.15 (s, 3H), 1.49 (d, ^3J= 7.2 Hz, 3H).

^{13}C{^{1}H}-NMR (101 MHz, DMSO-d$_6$): δ (ppm) = 152.06 (s, C_{quat}), 146.50 (s, C_{quat}), 133.22 (s, C_{quat}), 128.28 (s, CH), 128.06 (s, CH), 127.44 (s, CH), 125.57 (s, CH), 124.97 (s, CH), 124.43 (s, C_{quat}), 119.40 (s, CH), 36.89 (s, CH), 21.06 (s, CH_3), 16,86 (s, CH_3) ppm.

IR (neat, cm^{-1}): $\tilde{\nu}$ = 3046, 3003, 2965, 2838, 1666, 1605, 1586, 1501, 1463, 1443, 1369, 1325, 1290, 1243, 1219, 1180, 1169, 1154, 1106, 1094, 1031, 987, 932, 830, 790, 730.

2-*tert*-butyl-2-(1-phenylethyl)phenol (147ka)



Following **GP4**, using 2-*tert*-butylphenol (1.50 mmol, 225 mg) and styrene (0.50 mmol, 57.2 µl). The crude mixture was purified by SiO_2 gel column chromatography hexane/ethyl acetate (10:1). Isolated yield: 22.7 mg, 0.09 mmol, 18% (yellow resin). NMR data shows impurities of difunctionalized product and styrene.

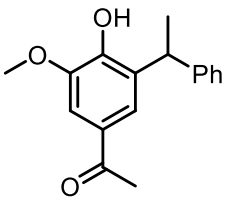
More analytical data could not be provided.

^{1}H-NMR (400 MHz, DMSO-d$_6$): δ (ppm) = 8.14 (s, 1H), 7.26-7.20 (m, 4H), 7.16-7.13 (m, 1H), 7.01 (dd, ^4J= 1.3 Hz, ^3J= 7.7 Hz, 1H), 6.88 (dd, ^4J= 1.4 Hz, ^3J= 7.6 Hz, 2H), 4.63 (q, ^3J=7.1 Hz, 1H), 1.48 (d, ^3J= 7.0 Hz, 3H), 1.35 (broad s, 9H).

^{13}C{^{1}H}-NMR (101 MHz, DMSO-d$_6$): δ (ppm) = 152.42 (s, C_{quat}), 146.09 (s, C_{quat}), 137.42 (s, C_{quat}), 134.33 (s, C_{quat}), 128.11 (s, CH), 127.47 (s, CH), 125.71 (s, CH), 125.39 (s, CH), 124.02 (s, CH), 119.63 (s, CH), 35.96 (s, CH), 34.60 (s, C_{quat}), 29.88 (s, CH_3), 21.44 (s, CH_3).

IR (neat, cm^{-1}): $\tilde{\nu}$ = 3520, 3027, 2959, 2923, 2872, 1742, 1601, 1493, 1450, 1391, 1362, 1245, 1217, 1199, 1174, 1062, 1029,1004, 928, 909, 882, 839, 830, 809, 794, 777, 751, 706, 659.

2-methoxy-4-acetyl-2-(1-phenylethyl)phenol (147la)



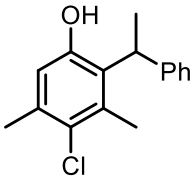
Following **GP4**, using 4'-hydroxy-3'-methoxyacetophenone (1.50 mmol, 249 mg) and styrene (0.50 mmol, 57.2 µl). The crude mixture was purified by SiO_2 gel column chromatography hexane/ethyl acetate (10:1). Isolated yield: 13.4 mg, 0.05 mmol, 10% (orange resin).

More analytical data could not be provided.

^{1}H-NMR (400 MHz, DMSO-d_6): δ (ppm) = 9.52 (*broad* s, 1H), 7.46 (d, ^4J= 2.0 Hz, 1H), 7.36 (d, ^4J= 2.0 Hz, 1H), 7.28-7.22 (m, 5H), 4.49 (q, ^3J=7.1 Hz, 1H), 3.85 (s, 3H), 2.49 (s, 3H), 1.54 (d, ^3J= 7.3 Hz, 3H).

^{13}C{^{1}H}-NMR (101 MHz, DMSO-d_6): δ (ppm) = 196.32 (s, C_{quat}), 148.50 (s, C_{quat}), 146.97 (s, C_{quat}), 145.73 (s, C_{quat}), 132.16 (s, C_{quat}), 128.16 (s, CH), 127.36 (s, CH), 125.81 (s, CH), 121.05 (s, CH), 109.06 (s, CH), 55.93 (s, CH_3), 37.05 (s, CH), 26.29 (s, CH_3), 20.60 (s, CH_3).

4-chloro-3,5-dimethyl-2-(1-phenylethyl)phenol (major product) (147ma)



Following **GP4**, using 4-chloro-3,5-dimethylphenol (1.50 mmol, 235 mg) and styrene (0.50 mmol, 57.2 µl). The crude mixture was purified by SiO_2 gel column chromatography hexane/ethyl acetate (10:1). Isolated yield: 90.3 mg, 0.35 mmol, 60% (colorless sticky solid).

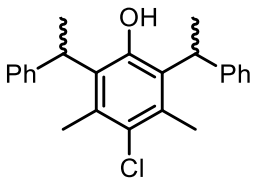
^{1}H-NMR (400 MHz, DMSO-d_6): δ (ppm) = 9.38 (s, 1H), 7.26-7.22 (m, 3H), 7.19-7.16 (m, 2H), 6.67 (s, 1H), 4.73 (q, ^3J= 6.9 Hz, 1H), 2.21 (s, 3H), 2.08 (s, 3H), 1.59 (d, ^3J= 7.3 Hz, 3H).

^{13}C{^{1}H}-NMR (101 MHz, DMSO-d_6): δ (ppm) = 152.62 (s, $C_{quat.}$), 145.17 (s, $C_{quat.}$), 134.50 (s, $C_{quat.}$), 133.77 (s, $C_{quat.}$), 130.30 (s, $C_{quat.}$), 127.91 (s, CH), 126.68 (s, CH), 125.15 (s, CH), 124.65 (s, $C_{quat.}$), 115.63 (s, CH), 35.38 (s, CH), 20.56 (s, CH_3), 17.49 (s, CH_3), 17.31 (s, CH_3).

HRMS-ESI: $[M+Na]^+$ m/z: calculated for $[C_{16}H_{17}ClONa]+$: 283.08601, found: 283.08597.

IR (neat, cm^{-1}): $\tilde{\nu}$ = 3523, 3026, 2965, 2927, 1601, 1564, 1493, 1446, 1396, 1376, 1310, 1264, 1218, 1175, 1153, 1112, 1089, 1068, 1028, 1006, 953, 908, 887, 842, 801, 778, 764, 739, 718, 698, 673.

4-chloro-3,5-dimethyl-2,6-bis(1-phenylethyl)phenol (side product) (147ma')



Isolated yield: 9.13 mg, 0.04 mmol, 7% (colorless sticky solid).

^{1}H-NMR (400 MHz, DMSO-d_6): δ (ppm) = 9.43 (*broad* s, 1H), 7.12-7.01 (m, 10H), 4.64-3.85 (2H), 2.23 (*broad* s, 3H), 1.78 (*broad* s, 3H), 1.20 (dd, ^3J= 6.2 Hz, ^3J= 23 Hz, 6H).

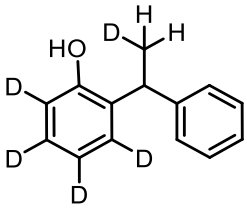
^{13}C{^{1}H}-NMR (101 MHz, DMSO-d_6): δ (ppm) = 154.22 (s, $C_{quat.}$), 147.66 (s, $C_{quat.}$), 146.71 (s, $C_{quat.}$), 144.44 (s, $C_{quat.}$), 144.14 (s, $C_{quat.}$), 135.22 (s, $C_{quat.}$), 133.96 (s, $C_{quat.}$), 128.30 (s, CH), 128.28 (s,

CH), 127.00 (s, CH), 126.80 (s, CH), 125.90 (s, CH), 125.82 (s, CH), 115.98 (s, $C_{quat.}$), 38.13 (s, CH), 37.66 (s, CH), 23.93 (s, CH_3), 21.45 (s, CH_3), 20.66 (s, CH_3), 17.17 (s, CH_3).

HRMS-ESI: $[M+Na]^+$ m/z: calculated for $[C_{24}H_{25}ClONa]+$: 387.14920, found: 387.114868.

IR (neat, cm^{-1}): $\tilde{\nu}$ = 3523, 3026, 2965, 2927, 1601, 1564, 1493, 1446, 1396, 1376, 1310, 1264, 1218, 1175, 1153, 1112, 1089, 1068, 1028, 1006, 953, 908, 887, 842, 801, 778, 764, 739, 718, 698, 673.

4-*tert*-butyl-2-(1-phenylethyl)phenol-D_5 (147aa-D_5)



Following **GP4**, using phenol-d_6 (1.50 mmol, 150 mg) and styrene (0.50 mmol, 57.2 µl). The crude mixture was purified by SiO_2 gel column chromatography hexane/ethyl acetate (9:1).

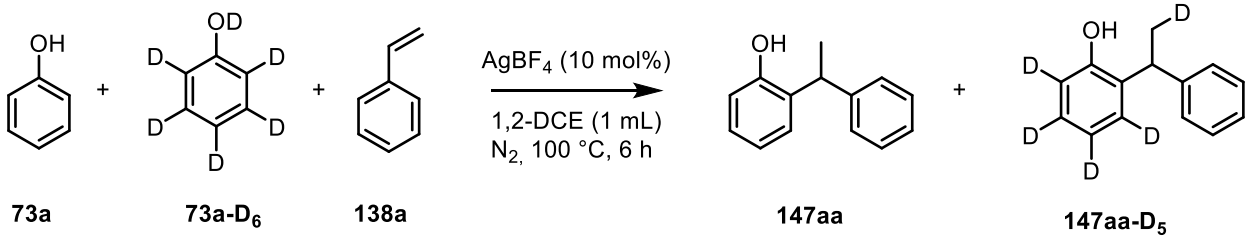
Isolated yield: 20.2 mg, 0.10 mmol, 20% (colorless sticky solid).

^{1}H-NMR (400 MHz, DMSO-d_6): δ (ppm) = 9.31 (s, 1H), 7.26-7.21 (m, 4H), 7.15-7.11 (m, 1H), 4.44 (~t, ^3J= 7.1 Hz, 1H), 1.49 (m, ***2.25H***).

HRMS-ESI: $[M+Na]^+$ m/z: calculated for $[C_{14}H_9D_5ONa]+$: 226.12507, found: 226.12476.

IR (neat, cm^{-1}): $\tilde{\nu}$ = 3529. 3027, 2961, 2929, 2870, 1601, 1494, 1451, 1428, 1362, 1305, 1256, 1194, 1166, 1116, 1055, 1029, 989, 913, 891, 863, 815, 790, 758, 740, 669.

Kinetic Isotope Effect (KIE)



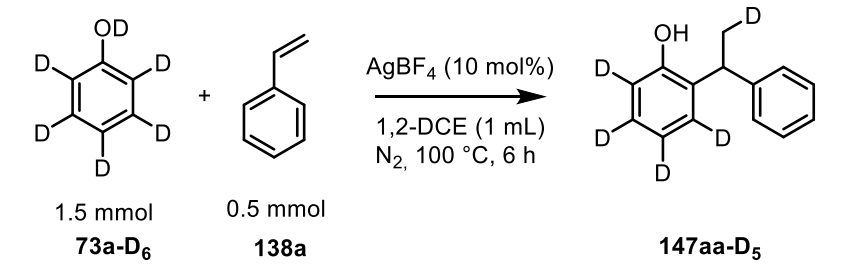
Phenol **73a** (0.75 mmol, 70.6 mg) and phenol-D_6 **73a-D_6** (0.75 mmol, 75.1 mg) was added under air in a 50 mL crimp neck vial equipped with an aluminous headspace cap. Afterwards the vial was smuggled into the glove-box, $AgBF_4$ (10 mol%, 9.73 mg) was added and the reactor was sealed, 1,2-DCE (1 mL) and styrene **138a** (0.50 mmol, 57.2 µL) were added and the reaction was stirred at 100 °C for 6h. The vial was allowed to cool down to room temperature. The crude mixture was purified by SiO_2 gel column chromatography hexane/ethyl acetate (9:1), which gave the product after concentration *in vacuo*. Isolated yield: 17.3 mg, 0.09 mmol, 17% (colorless sticky solid).

The yields of 7a and 7a-D_5 were obtained in 10.1% and 7.2%, respectively and the kH/kD is 1.4.

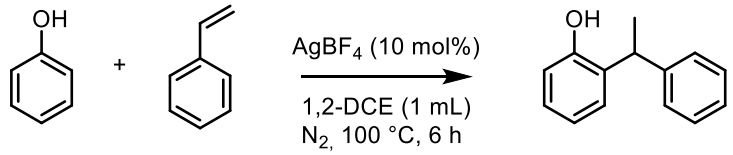
Parallel KIE measurement:

In the parallel KIE experiment with phenol **73a** or phenol-d_6 **73a-D_6** the corresponding products were isolated in 12.3% (12.2 mg, 61.5 µmol) for the not deuterated compound **147aa** and 5.0% (5.1 mg, 25.0 µmol) for the deuterated compound **147aa- D_5**.

The KIE was determined as 2.4.



1.5 mmol **73a-D_6** 0.5 mmol **138a** **147aa-D_5**

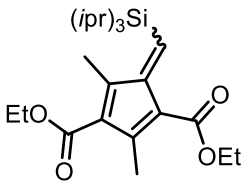


1.5 mmol **73a** 0.5 mmol **138a** **147aa**

4.3.2.3 Redox efficient indole synthesis

[Rh[Cp(CO$_2$Et)$_2$(Me)$_3$]Cl$_2$]$_2$ (262)

The catalyst was prepared according to the literature.[154]



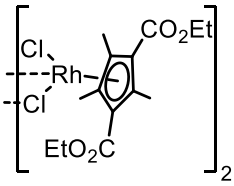
To a suspension of [Rh(cod)$_2$]BF$_4$ (0.14 mmol, 56.9 mg) in 1,4-dioxane (8.0 mL), ethyl 2-butanoate (5 mmol, 560.7 mg) and ethynyltriisopropylsilane (2.5 mmol, 456.0 mg) were added and the mixture was stirred at 80 °C vigorously for 16 h. The crude mixture was purified by SiO$_2$ gel column chromatography hexane/ethyl acetate (9.5:0.5). E and Z isomers were not separated. Isolated yield: 740 mg, 1.82 mmol, 73% (E/Z: ~4.5:1) (red oil).

E-Isomer: **^{1}H-NMR** (600 MHz, $CDCl_3$): δ (ppm) = 7.84 (s, 1H), 4.31 (m, 4H), 2.45 (s, 3H), 2.35 (s, 3H), 1.37-1.31 (m, 9H), 1.11 (d, ^3J= 7.5 Hz, 18H).

^{13}C{^{1}H}-NMR (151 MHz, $CDCl_3$): δ (ppm) = 165.74 (s, C_{quat}), 165.39 (s, C_{quat}), 157.11 (s, C_{quat}), 152.07 (s, C_{quat}), 147.52 (s, C_{quat}), 145.00 (s, C_{quat}), 134.13 (s, C_{quat}), 121.18 (s, CH), 60.49 (s, CH_2), 60.05 (s, CH_2), 19.29 (s, CH_3), 15.40 (s, CH), 14.63 (s, CH_3), 14.47 (s, CH_3), 13.86 (s, CH_3), 13.44 (s, CH_3).

Z-Isomer: **^{1}H-NMR** (600 MHz, $CDCl_3$): δ (ppm) = 7.01 (s, 1H), 4.21 (q, ^3J= 7.1 Hz, 4H), 2.38 (s, 3H), 2.32 (s, 3H), 1.31-1.28 (m, 9H), 1.07 (d, ^3J= 7.5 Hz, 18H).

^{13}C{^{1}H}-NMR (151 MHz, $CDCl_3$): δ (ppm): 165.66 (s, C_{quat}), 165.36 (s, C_{quat}), 156.43 (s, C_{quat}), 152.30 (s, C_{quat}), 146.11 (s, C_{quat}), 144.62 (s, C_{quat}), 126.16 (s, C_{quat}), 119.28 (s, CH), 60.40 (s, CH_2), 60.17 (s, CH_2), 19.47 (s, CH_3), 15.42 (s, CH), 14.59 (s, CH_3), 14.17 (s, CH_3), 13.86 (s, CH_3), 13.61 (s, CH_3), 13.26 (s, CH_3).



To a solution of $RhCl_3 \cdot H_2O$ (1.85 mmol, 390 mg) in ethanol (10 mL), a solution of the before synthesized silylfulvene (1.82 mmol, 740 mg) in ethanol (10 mL) was added and stirred for 16 h at 80 °C. The solvent was removed under reduced pressure, diluted in dichloromethane (20 mL) and filtrated. The filtrate was slowly poured into cold hexane (100 mL). The resulting solid was collected and washed with ethanol (3x 10 mL) and pentane (3x 10mL).

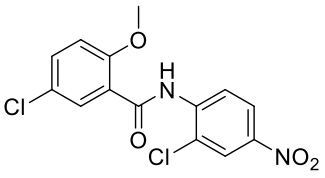
Isolated yield: 500 mg, 0.588 mmol, 33% (red powder).

^{1}H-NMR (600 MHz, $CDCl_3$): δ (ppm) = 4.43-4.37 (m, 4H), 2.24 (s, 3H), 1.97 (s, 6H), 1.11 (d, ^3J= 7.5 Hz, 18H).

$^{13}C\{^{1}H\}$-NMR (151 MHz, $CDCl_3$): δ (ppm) = 164.04 (s, C_{quat}), 109.54 (*broad* s, C_{quat}), 102.57 (d, ^{3}J= 7.6 Hz, C_{quat}), 79.80 (*broad* s, C_{quat}), 62.76 (s, C_{quat}), 14.30 (s, CH_2), 12.71 (s CH_3), 11.39 (s, CH_3).

ESI-HRMS: $[M+H]^+$ m/z: calculated for: $[C_{28}H_{39}O_8CL_3]^+$ 813.98151, found: 813.98120.

5-Chloro-*N*-(2-chloro-4-nitrophenyl)-2-methoxybenzamide (174t')



Preparation of the methoxylated derivative was prepared based on a known procedure.[164]

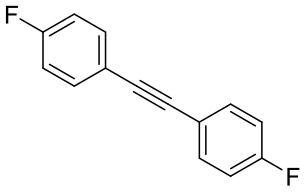
A solution of niclosamide (5 mmol, 1.64 g) in acetone (50 mL) was prepared and potassium carbonate (6.5 mmol, 0.9 g) and methyl iodide (6.5 mmol, ~0.4 mL) were added. The mixture was heated to reflux and stirred overnight (15 h). The reaction was quenched with saturated ammonium chloride solution (50 mL) and the residue was filtered. The solid was washed with water (50 mL), ethanol (50 mL) and pentante (50 mL), leaving a pure yellow powder to collect as the product. Isolated yield: 1.60 g, 4.69 mmol, 94%.

Due to high insolubility of the compound, only a proton NMR at 100 °C is provided.

^{1}H-NMR (400 MHz at 100 °C, DMSO-d_6): δ (ppm) = 10.73 (s, NH), 8.72 (d, ^{3}J= 9.2 Hz, 1H), 8.39 (d, ^{4}J= 2.6 Hz, 1H), 8.26 (dd, ^{3}J= 9.2 Hz, ^{4}J= 2.6 Hz, 1H), 8.01 (d, ^{4}J= 2.8 Hz, 1H), 7.66 (dd, ^{3}J= 8.9 Hz, ^{4}J= 2.8 Hz, 1H), 7.37 (d, ^{3}J= 8.9 Hz, 1H), 4.12 (s, 3H).

APCI-TOF-HRMS: $[M+H]^+$ m/z: calculated for $[C_{14}H_{11}Cl_2N_2O_4]^+$ 341.00904, found 341.00883.

1,2-bis(4-fluorophenyl)ethyne (164f)



The diarylakyne was prepared according to the literature.[165]

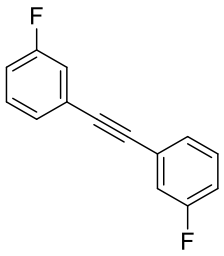
$Pd(PPh_3)_2Cl_2$ (105 mg, 0.15 mmol), 1,4-bis(diphenylphosphino)butane (128 mg, 0.30 mmol), 1-bromo-4-fluorobenzene (6.00 mmol), and 2-butynedioic acid (342 mg, 3.0 mmol) were combined with DBU (913 mg, 6.0 mmol) in a 50 mL reaction vial. DMSO (15.0 mL) was added, and the flask was sealed with an aluminous headspace cap. The resulting mixture was heated 110 °C for 3 h. The reaction was set twice according to this protocol and combined for further work-up. Both reaction mixtures were poured into 50 mL of saturated aqueous ammonium chloride and extracted with diethyl ether (4 x 50 mL). The combined ether extracts were washed with brine (200 mL), dried over $MgSO_4$, and filtered. The solvent was removed under vacuum, and the resulting crude product was purified by SiO_2 gel column chromatography with hexane. Isolated yield: 743 mg, 3.47 mmol, 58% (colorless oil).

^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.52-7.47 (m, 4H), 7.07-7.02 (m, 4H).

$^{13}C\{^1H\}$-NMR (101 MHz, $CDCl_3$): δ (ppm) = 162.67 (d, ^1J= 251 Hz, C_{quat}), 133.58 (d, ^3J= 8.5 Hz, CH), 119.32 (d, ^4J= 3.0 Hz, C_{quat}), 115.83 (d, ^2J= 22.1 Hz, CH), 88.09 (s, C_{quat}).

^{19}F-NMR (101 MHz, $CDCl_3$): δ (ppm) = - 110.86 (m).

1,2-bis(3-fluorophenyl)ethyne (164g)



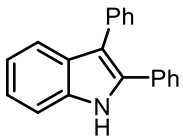
The diarylakyne was prepared according to the literature.[165] $Pd(PPh_3)_2Cl_2$ (105 mg, 0.15 mmol), 1,4-bis(diphenylphosphino)butane (128 mg, 0.30 mmol), 1-bromo-4-fluorobenzene (6.00 mmol), and 2-butynedioic acid (342 mg, 3.0 mmol) were combined with DBU (913 mg, 6.0 mmol) in a 50 mL reaction vial. DMSO (15.0 mL) was added, and the flask was sealed with an aluminous headspace cap. The resulting mixture was heated 110 °C for 3 h. The reaction was set twice according to this protocol and combined for further work-up. Both reaction mixtures were poured into 50 mL of saturated aqueous ammonium chloride and extracted with diethyl ether (4 x 50 mL). The combined ether extracts were washed with brine (200 mL), dried over $MgSO_4$, and filtered. The solvent was removed under vacuum, and the resulting crude product was purified by SiO_2 gel column chromatography with hexane. Isolated yield: 899 mg, 4.20 mmol, 70% (colorless oil)

^1H-NMR (600 MHz, $CDCl_3$): δ (ppm) = 7.33-7.31 (m, 4H), 7.24 (dd, ^3J= 9.6 Hz, ^4J= 2.7 Hz, 2H), 7.10-7.05 (m, 2H).

$^{13}C\{^1H\}$-NMR (151 MHz, $CDCl_3$): δ (ppm) = 162.54 (d, ^1J= 247 Hz, C_{quat}), 130.12 (d, ^3J= 8.6 Hz, CH), 127.70 (d, ^4J= 3.0 Hz, CH), 124.78 (d, ^3J= 9.3 Hz, C_{quat}), 118.58 (d, ^2J= 22.1 Hz, CH), 116.08 (d, ^2J= 21.1 Hz, CH), 89.06 (d, ^4J= 3.5 Hz, C_{quat}).

^{19}F-NMR (151 MHz, $CDCl_3$): δ (ppm) = - 112.74 (m).

2,3-Diphenyl-1*H*-indole (178aa)



Following general procedure **5**, using nitrobenzene **174a** (0.50 mmol, 61.5 mg) and diphenylacetylene **164a** (0.6 mmol, 107 mg). The crude mixture was purified by SiO_2 gel column chromatography hexane/ethyl acetate (9.5:0.5). Isolated yield: 61.4 mg, 0.23 mmol, 46% (brown crystals).

^1H-NMR (600 MHz, $CDCl_3$): δ (ppm) = 8.20 (s, NH), 7.85 (d, ^3J= 8.0 Hz, 1H), 7.59-7.58 (m, 2H), 7.52-7.46 (m, 5H), 7.43-7.35 (m, 5H), 7.31-7.29 (m, 1H).

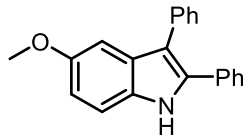
$^{13}C\{^1H\}$-NMR (151 MHz, $CDCl_3$): δ (ppm) = 135.96 (s, C_{quat}), 135.17 (s, C_{quat}), 134.18 (s, C_{quat}), 132.70 (s, C_{quat}), 130.24 (s, CH), 128.81 (s, C_{quat}), 128.71 (s, CH), 128.63 (s, CH), 128.28 (s, CH),

127.74 (s, CH), 126.31 (s, CH), 122.74 (s, CH), 120.50 (s, CH), 119.75 (s, CH), 115.04 (s, C_{quat}), 111.08 (s, CH).

ESI-HRMS: $[M+H]^+$ m/z: calculated for $[C_{20}H_{16}N]^+$ 270.12773, found 270.12701.

IR (neat, cm^{-1}): $\tilde{\nu}$: 3391, 3053, 1600, 1502, 1448, 1371, 1325, 1246, 1150, 1068, 1027, 965, 919, 828, 747, 694.

5-Methoxy-2,3-diphenyl-1*H*-indole (178ca)



Following general procedure **5**, using 4-methoxynitrobenzene **174c** (0.50 mmol, 76.5 mg) and diphenylacetylene **164a** (0.6 mmol, 107 mg). The crude mixture was purified by SiO_2 gel column chromatography hexane/ethyl acetate (9:1). Isolated yield: 67.0 mg, 0.23 mmol, 45% (yellow solid).

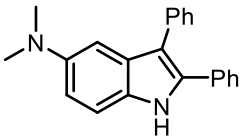
^{1}H-NMR (600 MHz, $CDCl_3$): δ (ppm) = 8.19 (s, NH), 7.47-7.45 (m, 2H), 7.43-7.40 (m, 4H), 7.34-7.28 (m, 5H), 7.16 (d, ^4J= 2.2 Hz, 1H), 6.92 (dd, ^4J= 2.4 Hz, ^3J= 8.7 Hz, 1H), 3.84 (s, 3H).

^{13}C{^{1}H}-NMR (151 MHz, $CDCl_3$): δ (ppm) = 154.88 (s, C_{quat}), 135.35 (s, C_{quat}), 135.09 (s, C_{quat}), 132.84 (s, C_{quat}), 131.19 (s, C_{quat}), 130.21 (s, CH), 129.28 (s, C_{quat}), 128.76 (s, CH), 128.73 (s, CH), 128.20 (s, CH), 127.72 (s, CH), 126.31 (s, CH), 115.03 (s, C_{quat}), 113.12 (s, CH), 111.85 (s, CH), 101.33 (s, CH), 56.05 (s, CH_3).

ESI-HRMS: $[M+H]^+$ m/z: calculated for $[C_{21}H_{18}ON]^+$ 300.13829, found 300.13752.

IR (neat, cm^{-1}): $\tilde{\nu}$: 3406, 3060, 2935, 2834, 1893, 1732, 1592, 1456, 1299, 1222, 1155, 1118, 1069, 1027, 929, 835, 793, 759, 695.

***N,N*-Dimethyl-2,3-diphenyl-1*H*-indol-5-amine (178ga)**



Following general procedure **5**, using *N,N*-dimethyl-4-nitroaniline **174g** (0.50 mmol, 83.1 mg) and diphenylacetylene **164a** (0.6 mmol, 107 mg). The crude mixture was purified by SiO_2 gel column chromatography hexane/ethyl acetate (9:1). Isolated yield: 97.5 mg, 0.31 mmol, 62% (yellow solid).

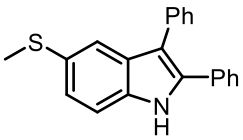
^{1}H-NMR (600 MHz, $CDCl_3$): δ (ppm) = 8.07 (s, NH), 7.46-7.38 (m, 6H), 7.34-7.26 (m, 5H), 7.06 (d, ^3J= 1.6 Hz, 1H), 6.96 (dd, ^4J= 2.2 Hz, ^3J= 8.8 Hz, 1H), 2.91 (s, 6H).

^{13}C{^{1}H}-NMR (151 MHz, $CDCl_3$): δ (ppm) = 146.83 (s, C_{quat}), 135.61 (s, C_{quat}), 134.79 (s, C_{quat}), 133.09 (s, C_{quat}), 130.46 (s, C_{quat}), 130.28 (s, CH), 129.50 (s, C_{quat}), 128.74 (s, CH), 128.67 (s, CH), 128.20 (s, CH), 127.59 (s, CH), 126.15 (s, CH), 114.77 (s, C_{quat}), 113.78 (s, CH), 111.45 (s, CH), 103.67 (s, CH), 43.02 (s, CH_3).

ESI-HRMS: $[M+H]^+$ m/z: calculated for $[C_{22}H_{21}N_2]^+$ 313.16993, found 313.17075.

IR (neat, cm^{-1}): $\tilde{\upsilon}$: 3126, 3029, 2938, 2826, 2740, 1733, 1597, 1453, 1427, 1379, 1296, 1171, 1122, 1030, 954, 921, 861, 762, 691.

5-(Methylthio)-2,3-diphenyl-1*H*-indole (178ha)



Following general procedure **5**, using methyl(4-nitrophenyl)sulfane **174h** (0.50 mmol, 84.6 mg) and diphenylacetylene **164a** (0.6 mmol, 107 mg). The crude mixture was purified by SiO_2 gel column chromatography hexane/ethyl acetate (9:1). Isolated yield: 73.2 mg, 0.23 mmol, 46 % (yellow resin).

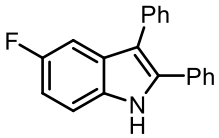
^{1}H-NMR (600 MHz, $CDCl_3$): δ (ppm) = 8.24 (s, NH), 7.68 (d, ^4J= 1.6 Hz, 1H), 7.43-7.34 (m, 8H), 7.34-7.27 (m, 5H), 2.49 (s, 3H).

^{13}C{^{1}H}-NMR (151 MHz, $CDCl_3$): δ (ppm) = 134.95 (s, C_{quat}), 134.81 (s, C_{quat}), 134.75 (s, C_{quat}), 132.56 (s, C_{quat}), 130.25 (s, CH), 129.64 (s, C_{quat}), 128.88 (s, CH), 128.77 (s, CH), 128.25 (s, CH), 128.00 (s, CH), 126.53 (s, CH), 124.88 (s, CH), 120.60 (s, CH), 114.82 (s, C_{quat}), 111.58 (s, CH), 19.04 (s, CH_3).

ESI-HRMS: $[M+H]^+$ m/z: calculated for $[C_{21}H_{18}NS]^+$ 316.11545, found 316.11508.

IR (neat, cm^{-1}): $\tilde{\upsilon}$: 3399, 3064, 3021, 2924, 1879, 1756, 1601, 1550, 1501, 1450, 1308, 1282, 1097, 1064, 1025, 966, 919, 863, 836, 791, 762, 694.

5-Fluro-2,3-diphenyl-1*H*-indole (178la)



Following general procedure **5**, using 1-fluoro-4-nitrobenzene **174l** (0.50 mmol, 70.1 mg) and diphenylacetylene **164a** (0.6 mmol, 107 mg). The crude mixture was purified by SiO_2 gel column chromatography hexane/ethyl acetate (9:1). Isolated yield: 42.0 mg, 0.15 mmol, 29% (yellow solid).

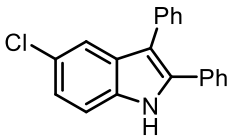
^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) = 8.10 (s, NH), 7.32-7.28 (m, 6H), 7.24-7.11 (m, 6H), 6.88 (td, ^4J= 2.5 Hz, ^3J= 9.0 Hz, 1H).

^{13}C{^{1}H}-NMR (101 MHz, $CDCl_3$): δ (ppm) = 158.64 (d, $^1J_{CF}$= 235.8 Hz, $C_{quat.}$), 136.02 (s, C_{quat}), 134.75 (s, C_{quat}), 132.51 (d, $^4J_{CF}$= 1.8 Hz, $C_{quat.}$), 130.08 (s, CH), 129.39 (d, $^3J_{CF}$= 10.0 Hz, $C_{quat.}$), 128.88 (s, CH), 128.78 (s, CH), 128.27 (s, CH), 128.10 (s, CH), 126.57 (s, C_{quat}), 115.36 (d, $^4J_{CF}$= 4.7 Hz, $C_{quat.}$), 111.69 (d, $^3J_{CF}$= 9.7 Hz, CH), 111.15 (d, $^2J_{CF}$= 26.6 Hz, CH), 104.73 (d, $^2J_{CF}$= 24.1 Hz, CH).

ESI-HRMS: $[M+H]^+$ m/z: calculated for $[C_{20}H_{15}NF]^+$ 288.11830, found 288.11832.

IR (neat, cm^{-1}): $\tilde{\upsilon}$: 3422, 3054, 2926, 1720, 1599, 1479, 1450, 1371, 1285, 1243, 1149, 1115, 1072, 1029, 952, 915, 857, 797, 756, 690.

5-Chloro-2,3-diphenyl-1*H*-indole (178ma)



Following general procedure **5**, using 1-chloro-4-nitrobenzene **174m** (0.50 mmol, 78.8 mg) and diphenylacetylene **164a** (0.6 mmol, 107 mg). The crude mixture was purified by SiO_2 gel column chromatography hexane/ethyl acetate (9:1). Isolated yield: 66.5 mg, 0.22 mmol, 44% (yellow solid).

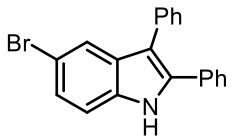
^{1}H-NMR (600 MHz, $CDCl_3$): δ (ppm) = 8.24 (s, NH), 7.65 (d, ^4J= 2.0 Hz, 1H), 7.42-7.39 (m, 6H), 7.35-7.30 (m, 5H), 7.20 (dd, ^4J= 2.0 Hz, ^3J= 8.6 Hz, 1H).

^{13}C{^{1}H}-NMR (151 MHz, $CDCl_3$): δ (ppm) = 135.53 (s, C_{quat}), 134.49 (s, C_{quat}), 134.32 (s, C_{quat}), 132.29 (s, C_{quat}), 130.16 (s, CH), 130.03 (s, C_{quat}), 128.90 (s, CH), 128.81 (s, CH), 128.25 (s, CH), 128.17 (s, CH), 126.68 (s, CH), 126.29 (s, C_{quat}), 123.06 (s, CH), 119.25 (s, CH), 114.89 (s, C_{quat}), 112.04 (s, CH).

TOF-HRMS: $[M+H]^+$ m/z: calculated for $[C_{20}H_{15}ClN]^+$ 304.08875, found 304.08907.

IR (neat, cm^{-1}): $\tilde{\upsilon}$: 3458, 3062, 2921, 2852, 1879, 1739, 1602, 1504, 1452, 1367, 1305, 1283, 1238, 1175, 1127, 1062, 1028, 968, 922, 872, 787, 761, 731, 691.

5-Bromo-2,3-diphenyl-1*H*-indole (178na)



Following general procedure **5**, using 1-bromo-4-nitrobenzene **174n** (0.50 mmol, 101 mg) and diphenylacetylene **164a** (0.6 mmol, 107 mg). The crude mixture was purified by SiO_2 gel column chromatography hexane/ethyl acetate (9.5:0.5). Isolated yield: 57.1 mg, 0.16 mmol, 33% (yellow solid).

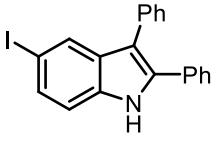
^{1}H-NMR (600 MHz, $CDCl_3$): δ (ppm) = 8.27 (s, NH), 7.80 (s, 1H), 7.42-7.38 (m, 6H), 7.35-7.28 (m, 6H).

^{13}C{^{1}H}-NMR (151 MHz, $CDCl_3$): δ (ppm) = 135.35 (s, C_{quat}), 134.59 (s, C_{quat}), 134.45 (s, C_{quat}), 132.23 (s, C_{quat}), 130.66 (s, CH), 130.17 (s, CH), 128.89 (s, CH), 128.81 (s, CH), 128.25 (s, CH), 128.17 (s, CH), 126.70 (s, CH), 125.60 (s, CH), 122.30 (s, CH), 114.78 (s, C_{quat}), 113.83 (s, C_{quat}), 112.47 (s, CH).

TOF-HRMS: $[M+H]^+$ m/z: calculated for $[C_{20}H_{15}NBr]^+$ 348.03824, found 348.03935.

IR (neat, cm^{-1}): $\tilde{\upsilon}$: 3414, 3058, 2924, 1883, 1714, 1601, 1503, 1457, 1365, 1308, 1284, 1243, 1216, 1179, 1096, 1070, 1052, 1028, 965, 921, 868, 796, 758, 696.

5-Iodo-2,3-diphenyl-1*H*-indole (178oa)



Following general procedure **5**, using 1-iodo-4-nitrobenzene **174o** (0.50 mmol, 125 mg) and styrene **164a** (0.75 mmol, 0.09 mL).

The crude mixture was purified by SiO_2 gel column chromatography hexane/ethyl acetate (9:1). Isolated yield: 52.6 mg, 0.13 mmol, 27% (yellow solid).

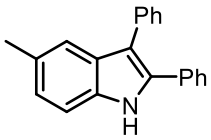
^{1}H-NMR (600 MHz, $CDCl_3$): δ (ppm) = 8.21 (s, NH), 7.94 (d, ^4J= 1.6 Hz, 1H), 7.45 (dd, ^4J= 1.7 Hz, ^3J= 8.5 Hz, 1H), 7.38-7.33 (m, 6H), 7.31-7.21 (m, 4H), 7.17 (d, ^3J= 8.4 Hz, 1H).

^{13}C{^{1}H}-NMR (151 MHz, $CDCl_3$): δ (ppm) = 135.06 (s, C_{quat}), 134.94 (s, C_{quat}), 134.46 (s, C_{quat}), 132.23 (s, C_{quat}), 131.50 (s, C_{quat}), 131.15 (s, CH), 130.25 (s, CH), 128.92 (s, CH), 128.84 (s, CH), 128.62 (s, CH), 128.28 (s, CH), 126.75 (s, CH), 114.56 (s, C_{quat}), 112.96 (s, CH).

TOF-HRMS: $[M+H]^+$ m/z: calculated for $[C_{20}H_{15}NI]^+$ 369.02437, found 369.02517.

IR (neat, cm^{-1}): $\tilde{\upsilon}$: 3410, 3055, 2924, 2685, 1888, 1737, 1601, 1552, 1503, 1453, 1362, 1307, 1179, 1130, 1094, 1070, 1027, 964, 919, 871, 793, 763.

5-Methyl-2,3-diphenyl-1*H*-indole (178pa)



Following general procedure **5**, using 1-methyl-4-nitrobenzene **174p** (0.50 mmol, 68.6 mg) and diphenylacetylene **164a** (0.6 mmol, 107 mg). The crude mixture was purified by SiO_2 gel column chromatography hexane/ethyl acetate (9.5:0.5). Isolated yield: 78.7 mg, 0.28 mmol, 56% (white solid).

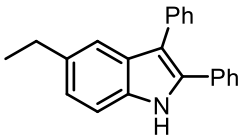
^{1}H-NMR (600 MHz, $CDCl_3$): δ (ppm) = 8.12 (s, NH), 7.51-7.40 (m, 6H), 7.40-7.29 (m, 5H), 7.11 (m, 1H), 2.48 (m, 3H).

^{13}C{^{1}H}-NMR (151 MHz, $CDCl_3$): δ (ppm) = 135.38 (s, C_{quat}), 134.33 (s, C_{quat}), 132.93 (s, C_{quat}), 130.32 (s, CH), 129.85 (s, C_{quat}), 129.14 (s, C_{quat}), 128.76 (s, CH), 128.63 (s, CH), 128.22 (s, CH), 127.68 (s, CH), 126.28 (s, CH), 124.42 (s, CH), 119.35 (s, CH), 114.77 (s, C_{quat}), 110.70 (s, C_{quat}), 21.68 (s, CH_3).

ESI-HRMS: $[M+H]^+$ m/z: calculated for $[C_{21}H_{18}N]^+$ 284.14338, found 284.14285.

IR (neat, cm^{-1}): $\tilde{\upsilon}$: 3368, 3021, 1741, 1600, 1447, 1367, 1305, 1082, 780, 695.

5-Ethyl-2,3-diphenyl-1*H*-indole (178qa)



Following general procedure **5**, using 1-ethyl-4-nitrobenzene **174q** (0.50 mmol, 75.6 mg) and diphenylacetylene **164a** (0.6 mmol, 107 mg). The crude mixture was purified by SiO_2 gel column chromatography hexane/ethyl acetate (9.5:0.5). Isolated yield: 88.7 mg, 0.30 mmol, 59% (yellow resin).

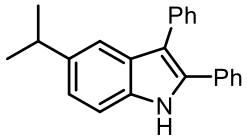
^{1}H-NMR (600 MHz, $CDCl_3$): δ (ppm) = 8.15 (s, NH), 7.48 (s, 1H), 7.45-7.37 (m, 6H), 7.35-7.26 (m, 5H), 7.11 (dd, ^4J= 1.3 Hz, ^3J= 8.2 Hz, 1H), 2.74 (q, ^3J= 7.6 Hz, 2H), 1.27 (t, ^3J= 7.6 Hz, 3H).

^{13}C{^{1}H}-NMR (150 MHz, $CDCl_3$): δ (ppm) = 136.75 (s, C_{quat}), 135.41 (s, C_{quat}), 134.54 (s, C_{quat}), 134.42 (s, C_{quat}), 133.01 (s, C_{quat}), 130.36(s, CH), 129.10 (s, C_{quat}), 128.80 (s, CH), 128.65 (s, CH), 128.25 (s, CH), 127.72 (s, CH), 126.30 (s, CH), 123.44 (s, CH), 118.23 (s, CH), 114.97 (s, C_{quat}), 110.83 (s, CH), 29.32 (s, CH_2), 16.78 (s, CH_3).

ESI-HRMS: $[M+H]^+$ m/z: calculated for $[C_{22}H_{20}N]^+$ 298.15903, found 298.15878.

IR (neat, cm^{-1}): $\tilde{\upsilon}$: 3389, 3053, 2961, 2927, 2861, 1814, 1745, 1600, 1549, 1502, 1472, 1450, 1371, 1311, 1251, 1153, 1092, 1069, 1027, 963, 911, 883, 842, 807, 757, 694.

5-Isopropyl-2,3-diphenyl-1*H*-indole (178ra)



Following general procedure **5**, using 1-isopropyl-4-nitrobenzene **174r** (0.50 mmol, 82.6 mg) and diphenylacetylene **164a** (0.6 mmol, 107 mg). The crude mixture was purified by SiO_2 gel column chromatography hexane/ethyl acetate (9.5:0.5). Isolated yield: 89.2 mg, 0.29 mmol, 57% (white solid).

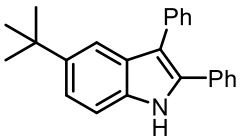
^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) = 8.05 (s, NH), 7.44 (s, 1H), 7.39-7.28 (m, 7H), 7.26-7.16 (m, 4H), 7.08 (d, ^3J= 8.2 Hz, 1H), 2.95 (sept, , ^3J= 6.9 Hz, 1H), 1.23 (d, ^3J= 6.9 Hz, 6H).

^{13}C{^{1}H}-NMR (101 MHz, $CDCl_3$): δ (ppm) = 141.47 (s, C_{quat}), 135.43 (s, C_{quat}), 134.65 (s, C_{quat}), 134.50 (s, C_{quat}), 133.04 (s, C_{quat}), 130.37 (s, CH), 128.94 (s, C_{quat}), 128.79 (s, CH), 128.66 (s, CH), 128.28 (s, CH), 127.71 (s, CH), 126.28 (s, CH), 121.96 (s, CH), 116.74 (s, CH), 115.10 (s, C_{quat}), 110.86 (s, CH), 34.55 (s, CH), 19.04 (s, CH_3).

ESI-HRMS: $[M+H]^+$ m/z: calculated for $[C_{23}H_{22}N]^+$ 312.17468, found 312.17468.

IR (neat, cm^{-1}): $\tilde{\upsilon}$: 3389, 3050, 2956, 2925, 2866, 1734, 1602, 1551, 1504, 1472, 1452, 1427, 1363, 1309, 1261, 1096, 1067, 1028, 970, 940, 912, 885, 842, 805, 755, 694.

5-*tert*-butyl-2,3-diphenyl-1*H*-indole (178sa)



Following general procedure **5**, using 1-(*tert*-butyl)-4-nitrobenzene **174s** (0.50 mmol, 89.6 mg) and diphenylacetylene **164a** (0.6 mmol, 107 mg). The crude mixture was purified by SiO_2 gel column chromatography hexane/ethyl acetate (9.5:0.5). Isolated yield: 88.2 mg, 0.27 mmol, 54% (yellow resin).

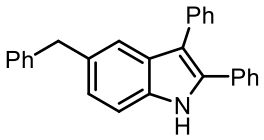
^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) = 8.08 (s, NH), 7.59 (s, 1H), 7.38 (d, ^3J= 7.1 Hz, 2H), 7.34-7.28 (m, 6H), 7.26-7.20 (m, 4H), 7.19 (s, 1H), 1.31 (s, 9H).

^{13}C{^{1}H}-NMR (101 MHz, $CDCl_3$): δ (ppm) = 143.66 (s, C_{quat}), 135.42 (s, C_{quat}), 134.54 (s, C_{quat}), 134.23 (s, C_{quat}), 133.09 (s, C_{quat}), 130.37 (s, CH), 128.80 (s, CH), 128.68 (s, CH), 128.60 (s, C_{quat}), 128.30 (s, CH), 127.70 (s, CH), 126.27 (s, CH), 121.21 (s, CH), 115.45 (s, C_{quat}), 115.34 (s, C_{quat}), 110.55 (s, CH), 34.87 (s, C_{quat}), 32.06 (s, CH_3).

ESI-HRMS: $[M+H]^+$ m/z: calculated for $[C_{24}H_{24}N]^+$ 326.19033, found 326.18961.

IR (neat, cm^{-1}): $\tilde{\upsilon}$: 3383, 3051, 2956, 2864, 1863, 1735, 1602, 1502, 1467, 1424, 1361, 1303, 1255, 1202, 1154, 1097, 1070, 1026, 971, 913, 889, 841, 805, 758, 695.

5-Benzyl-2,3-diphenyl-1*H*-indole (178ta)



Following general procedure **5**, using 1-benzyl-4-nitrobenzene **174t** (0.50 mmol, 107 mg) and diphenylacetylene **164a** (0.6 mmol, 107 mg). The crude mixture was purified by SiO_2 gel column chromatography hexane/ethyl acetate (9.5:0.5). Isolated yield: 80.9 mg, 0.23 mmol, 45% (yellowish resin).

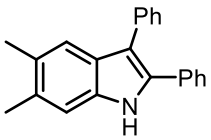
^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) = 8.08 (s, NH), 7.47 (s, 1H), 7.37-7.26 (m, 6H), 7.24-7.06 (m, 9H), 6.98 (dd, ^4J= 1.4 Hz, ^3J= 8.3 Hz, 1H), 4.00 (s, 2H).

^{13}C{^{1}H}-NMR (101 MHz, $CDCl_3$): δ (ppm) = 142.46 (s, C_{quat}), 135.26 (s, C_{quat}), 134.76 (s, C_{quat}), 134.58 (s, C_{quat}), 133.33 (s, C_{quat}), 132.94 (s, C_{quat}), 130.32 (s, CH), 129.10 (s, C_{quat}), 128.92 (s, CH), 128.83 (s, C_{quat}), 128.68 (s, CH), 128.47 (s, CH), 128.29 (s, CH), 127.80 (s, CH), 126.35 (s, CH), 125.93 (s, CH), 124.43 (s, CH), 119.78 (s, CH), 115.08 (s, C_{quat}), 111.09 (s, CH), 42.32 (s, CH_2).

ESI-HRMS: $[M+H]^+$ m/z: calculated for $[C_{27}H_{22}N]^+$ 360.17468, found 360.17456.

IR (neat, cm^{-1}): $\tilde{\upsilon}$: 3404, 3021, 2891, 1813, 1600, 1474, 1448, 1368, 1317, 1249, 1183, 1153, 1069, 1027, 975, 944, 925, 877, 811, 759, 738, 694.

5,6-Dimethyl-2,3-diphenyl-1*H*-indole (178ua)



Following general procedure **5**, using 1,2-dimethyl-4-nitrobenzene **174u** (0.50 mmol, 75.6 mg) and diphenylacetylene **164a** (0.6 mmol, 107 mg). The crude mixture was purified by SiO_2 gel column chromatography hexane/ethyl acetate (9.5:0.5). Isolated yield: 90.8 mg, 0.31 mmol, 61% (yellow solid).

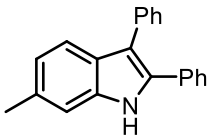
^{1}H-NMR (600 MHz, $CDCl_3$): δ (ppm) = 8.05 (s, NH), 7.45-7.37 (m, 7H), 7.32-7.25 (m, 5H), 7.21 (s, 1H), 2.40 (s, 3H), 2.35 (s, 3H).

^{13}C{^{1}H}-NMR (151 MHz, $CDCl_3$): δ (ppm) = 135.60 (s, C_{quat}), 135.04 (s, C_{quat}), 133.39 (s, C_{quat}), 133.15 (s, C_{quat}), 132.04 (s, C_{quat}), 130.30 (s, CH), 129.30 (s, C_{quat}), 128.76 (s, CH), 128.61 (s, CH), 128.14 (s, CH), 127.51 (s, CH), 127.35 (s, C_{quat}), 126.21 (s, CH), 119.79 (s, CH), 114.71 (s, C_{quat}), 111.38 (s, C_{quat}), 20.64 (s, CH_3), 20.29 (s,CH_3).

ESI-HRMS: $[M+H]^+$ m/z: calculated for $[C_{22}H_{20}N]^+$ 298.15903, found 298.15823.

IR (neat, cm^{-1}): $\tilde{\upsilon}$: 3411, 3054, 2923, 1884, 1601, 1544, 1499, 1446, 1382, 1330, 1285, 1248, 1216, 1177, 1096, 1072, 1025, 1001, 961, 915, 849, 801, 758, 695.

6-Methyl-2,3-diphenyl-1*H*-indole (178wa)



Following general procedure **5**, using 1-methyl-3-nitrobenzene **174w** (0.50 mmol, 68.6 mg) and diphenylacetylene **164a** (0.6 mmol, 107 mg). The crude mixture was purified by SiO_2 gel column chromatography hexane/ethyl acetate (9.5:0.5). Isolated yield: 94.8 mg, 0.33 mmol, 67% (yellowish resin).

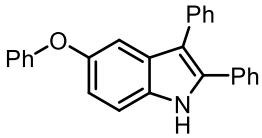
^{1}H-NMR (600 MHz, $CDCl_3$): δ (ppm) = 8.09 (s, NH), 7.60 (d, ^3J= 8.1 Hz, 1H), 7.47 (m, 2H), 7.44-7.39 (m, 4H), 7.35-7.29 (m, 4H), 7.23 (s, 1H), 7.02 (d, ^3J= 8.2 Hz, 1H), 2.52 (s, 3H).

^{13}C{^{1}H}-NMR (151 MHz, $CDCl_3$): δ (ppm) = 136.46 (s, C_{quat}), 135.37 (s, C_{quat}), 133.51 (s, C_{quat}), 132.99 (s, C_{quat}), 132.75 (s, C_{quat}), 130.23 (s, CH), 128.77 (s, CH), 128.62 (s, CH), 128.19 (s, CH), 127.62 (s, CH), 126.78 (s, C_{quat}), 126.27 (s, CH), 122.32 (s, CH), 119.49 (s, CH), 115.02 (s, C_{quat}), 110.96 (s, CH), 21.89 (s, CH_3).

ESI-HRMS: $[M+H]^+$ m/z: calculated for $[C_{21}H_{18}N]^+$ 284.14338, found 284.14407.

IR (neat, cm^{-1}): $\tilde{\nu}$: 3404, 3257, 3053, 2916, 2863, 1720, 1602, 1550, 1500, 1449, 1324, 1248, 1131, 1025, 953, 915, 855, 805, 760, 694.

5-Phenoxy-2,3-diphenyl-1*H*-indole (178xa)



Following general procedure **5**, using 1-phenoxy-4-nitrobenzene **174x** (0.50 mmol, 108 mg) and diphenylacetylene **164a** (0.6 mmol, 107 mg). The crude mixture was purified by SiO_2 gel column chromatography hexane/ethyl acetate (9:1). Isolated yield: 95.0 mg, 0.26 mmol, 53 % (yellowish solid).

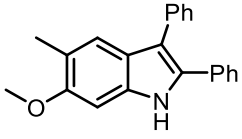
^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) = 8.16 (s, NH), 7.37-7.31 (m, 6H), 7.28 (s, 1H), 7.26-7.22 (m, 3H), 7.22-7.16 (m, 4H), 6.93-6.86 (m, 4H).

^{13}C{^{1}H}-NMR (101 MHz, $CDCl_3$): δ (ppm) = 159.64 (s, C_{quat}), 150.50 (s, C_{quat}), 135.62 (s, C_{quat}), 134.82 (s, C_{quat}), 133.13 (s, C_{quat}), 132.68 (s, C_{quat}), 130.13 (s, CH), 129.74 (s, C_{quat}), 129.63 (s, CH), 128.90 (s, CH), 128.73 (s, CH), 128.32 (s, CH), 128.04 (s, CH), 126.48 (s, CH), 121.95 (s, CH), 117.10 (s, CH), 116.80 (s, CH), 115.38 (s, C_{quat}), 111.97 (s, CH), 110.98 (s, CH).

ESI-HRMS: $[M+Na]^+$ m/z: calculated for $[C_{26}H_{19}NONa]^+$ 384.13589, found 384.13498.

IR (neat, cm^{-1}): $\tilde{\nu}$: 3405, 3051, 1586, 1474, 1373, 1311, 1215, 1150, 1070, 1024, 975, 951, 912, 854, 800, 759, 692.

6-Methoxy-5-methyl-2,3-diphenyl-1*H*-indole (178za)



Following general procedure **5**, using 2-methoxy-1-methyl-4-nitrobenzene **174z** (0.50 mmol, 82.6 mg) and diphenylacetylene **164a** (0.6 mmol, 107 mg). The crude mixture was purified by SiO_2 gel column chromatography

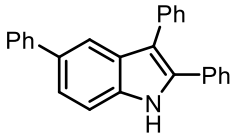
hexane/ethyl acetate (9.5:0.5). Isolated yield: 91.2 mg, 0.29 mmol, 59% (white solid). Due to very broad signals, a ^{13}C-NMR could not be provided.

^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.97 (s, NH), 7.43-7.11 (m, 11H), 6.79 (s, 1H), 3.82 (s, 3H), 2.22 (s, 3H).

ESI-HRMS: $[M+Na]^+$ m/z: calculated for $[C_{22}H_{19}NONa]^+$ 336.13589, found 336.13654.

IR (neat, cm^{-1}): $\tilde{\upsilon}$: 3331, 3062, 2925, 1745, 1602, 1558, 1454, 1337, 1291, 1245, 1192, 1134, 1081, 1014, 957, 882, 826, 761, 693.

6-Methyl-2,3-diphenyl-1*H*-indole (178a'a)



Following general procedure **5**, using 4-nitro-1,1'-biphenyl **174a'** (0.50 mmol, 99.6 mg) and diphenylacetylene **164a** (0.6 mmol, 107 mg). The crude mixture was purified by SiO_2 gel column chromatography hexane/ethyl acetate (9.5:0.5). Isolated yield: 94.8 mg, 0.27 mmol, 55 % (yellow resin).

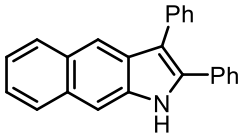
^{1}H-NMR (600 MHz, $CDCl_3$): *δ* (ppm) = 8.27 (s, NH), 7.89 (s, 1H), 7.64 (d, ^{3}J= 7.2 Hz, 2H), 7.53-7.40 (m, 10H), 7.36-7.31 (m, 5H).

^{13}C{^{1}H}-NMR (151 MHz, $CDCl_3$): *δ* (ppm) = 142.63 (s, C_{quat}), 135.55 (s, C_{quat}), 135.07 (s, C_{quat}), 134.91 (s, C_{quat}), 134.27 (s, C_{quat}), 132.74 (s, C_{quat}), 130.35 (s, CH), 129.43 (s, C_{quat}), 128.86 (s, CH), 128.75 (s, CH), 128.28 (s, CH), 127.92 (s, CH), 127.57, 126.54 (s, CH), 126.48 (s, CH), 122.74 (s, CH), 118.33 (s, CH), 115.57 (s, C_{quat}), 111.26 (s, CH).

ESI-HRMS: $[M+H]^+$ m/z: calculated for $[C_{26}H_{20}N]^+$ 346.15903, found 346.15897.

IR (neat, cm^{-1}): $\tilde{\upsilon}$: 3410, 3050, 1738, 1597, 1459, 1369, 1312, 1253, 1173, 1072, 1028, 963, 911, 885, 808, 755, 691.

2,3-Diphenyl-1*H*-benzo[*f*]indole (178b'a)



Following general procedure **5**, using 2- nitronaphthalene **174b'** (0.50 mmol, 86.6 mg) and diphenylacetylene **164a** (0.6 mmol, 107 mg). The crude mixture was purified by SiO_2 gel column chromatography hexane/ethyl acetate (9.5:0.5). Isolated yield: 37.5 mg, 0.12 mmol, 23% (yellow resin).

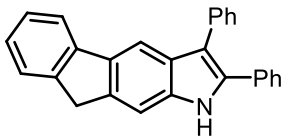
More analytical data could not be provided.

^{1}H-NMR (400 MHz, $CDCl_3$): *δ* (ppm) = 8.16 (s, 1H), 8.13 (s, NH), 7.91 (dd, ^{3}J= 8.3 Hz, ^{4}J= 3.0 Hz 2H), 7.81 (s, 1H), 7.55-7.49 (m, 4H), 7.47- 7.43 (m, 2H), 7.41-7.31 (m, 6H).

^{13}C{^{1}H}-NMR (151 MHz, $CDCl_3$): *δ* (ppm) = 137.82 (s, C_{quat}), 136.76 (s, C_{quat}), 135.09 (s, C_{quat}), 132.58 (s, C_{quat}), 130.95 (s, C_{quat}), 130.40 (s, CH), 129.38 (s, C_{quat}), 128.89 (s, CH), 128.83 (s,

CH), 128.49 (s, CH), 128.43 (s, CH), 128.33 (s, CH), 127.37 (s, CH), 126.60 (s, CH), 124.12 (s, CH), 122.91 (s, CH), 117.30 (s, C_{quat}), 114.31 (s, C_{quat}), 106.17(s, CH).

2,3-Diphenyl-1,9-dihyroindeno[1,2-*f*]indole (178c'a)



Following general procedure **5**, using 3-nitro-*9H*-fluorene **174c'** (0.50 mmol, 106 mg) and diphenylacetylene **164a** (0.6 mmol, 107 mg). The crude mixture was purified by SiO_2 gel column chromatography hexane/ethyl acetate (9.5:0.5). Isolated yield: 104.2 mg, 0.29 mmol, 58% (slightly pink solid).

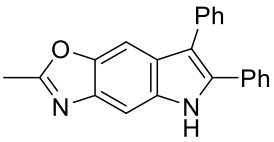
^{1}H-NMR (600 MHz, $CDCl_3$): δ (ppm) = 8.22 (s, NH), 8.03 (s, 1H), 7.79 (d, ^3J= 7.6 Hz, 1H), 7.56 (s, 1H), 7.52-7.51 (m, 3H), 7.45-7.43 (m, 4H), 7.36-7.32 (m, 4H), 7.31-7.28 (m, 1H), 7.25-7.23 (m, 1H), 4.02 (s, 2H).

^{13}C{^{1}H}-NMR (151 MHz, $CDCl_3$): δ (ppm) = 143.09 (s, C_{quat}), 142.57 (s, C_{quat}), 139.19 (s, C_{quat}), 136.25 (s, C_{quat}), 135.61 (s, C_{quat}), 135.39 (s, C_{quat}), 134.24 (s, C_{quat}), 132.90 (s, C_{quat}), 130.42 (s, CH), 128.84 (s, CH), 128.79 (s, CH), 128.55 (s, C_{quat}), 128.17 (s, CH), 127.74 (s, CH), 126.83 (s, CH), 126.83 (s, CH), 126.47 (s, CH), 125.85 (s, CH), 125.03 (s, CH), 119.53 (s, CH), 115.47 (s, C_{quat}), 110.43 (s, CH), 107.40 (s, CH), 36.74 (s, CH_2).

ESI-HRMS: $[M+H]^+$ m/z: calculated for $[C_{27}H_{20}N]^+$ 358.15903, found 358.15900.

IR (neat, cm^{-1}): $\tilde{\upsilon}$: 3389, 3053, 1600, 1503, 1480, 1449, 1411, 1364, 1278, 1242, 1150, 1115, 1069, 1026, 950, 910, 871, 843, 758, 729, 695.

2-Methyl-6,7-diphenyl-5*H*-oxazolo[5,4-*f*]indole (178h'a)



Following general procedure **5**, using 2-methyl-6-nitrobenzo[d]oxazole **174h'** (0.50 mmol, 89.1 mg) and diphenylacetylene **164a** (0.6 mmol, 107 mg). The crude mixture was purified by SiO_2 gel column chromatography hexane/ethyl acetate (9:1). Isolated yield: 70.2 mg, 0.22 mmol, 43% (white solid).

There is an irregularity in the NMR and the component cannot be 100% assigned to the suggested structure, although the HR-MS can be assigned to the corresponding mass

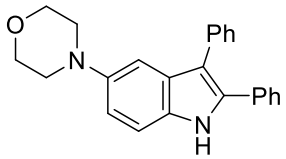
^{1}H-NMR (600 MHz, $CDCl_3$): δ (ppm) = 11.3.7 (s, 1H), 9.86 (s, NH), 7.44-7.38 (m, 4H), 7.35-7.23 (m, 6H), 7.00 (s, 1H), 2.97 (t, ^3J= 7.3 Hz, 1.5H), 2.43 (t, ^3J= 7.3 Hz, 1.5H).

^{13}C{^{1}H}-NMR (151 MHz, $CDCl_3$): δ (ppm) = 170.08 (s, C_{quat}), 135.51 (s, C_{quat}), 134.12 (s, C_{quat}), 132.48 (s, C_{quat}), 132.36 (s, C_{quat}), 132.07 (s, C_{quat}), 129.68 (s, CH), 129.60 (s, CH), 128.64 (s, CH), 128.46 (s, CH), 128.02 (s, C_{quat}), 127.92 (s, CH), 127.35 (s, CH), 126.97 (s, CH), 126.06 (s, CH), 120.13 (s, CH), 115.62 (s, C_{quat}), 113.02 (s, CH), 111.89 (s, C_{quat}), 110.19 (s, CH), 103.71 (s, CH), 31.57 (s, unidentified), 25.68 (s, unidentified).

ESI-HRMS: $[M+H]^+$ m/z: calculated for $[C_{22}H_{16}N_2ONa]^+$ 347.11548, found 358.11536.

IR (neat, cm^{-1}): $\tilde{\upsilon}$: 3432, 3209, 3056, 2924, 2325, 2082, 1737, 1608, 1516, 1443, 1400, 1341, 1225, 1160, 1041, 914, 831, 762, 693.

4-(2,3-Diphenyl-1*H*-indol6-yl)-morpholine (178j'a)



Following general procedure **5**, using 4-(4-nitrophenyl)morpholine **174j'** (0.50 mmol, 104 mg) and diphenylacetylene **164a** (0.6 mmol, 107 mg). The crude mixture was purified by SiO_2 gel column chromatography ethyl acetate/ hexane → ethyl acetate/ dichloromethane (1:4). Isolated yield: 104.5 mg, 0.29 mmol, 59% (yellow resin).

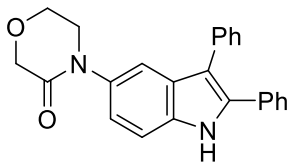
^{1}H-NMR (600 MHz, DMSO-d_6): δ (ppm) = 11.33 (s, NH), 7.42-7.38 (m, 4H), 7.35-7.32 (m, 5H), 7.28-7.26 (m, 2H), 6.96 (dd, ^4J= 2.1 Hz, ^3J= 6.0 Hz), 6.92 (d, ^4J= 1.9 Hz, 1H), 3.73 (t, ^3J= 4.6 Hz, 4H), 2.99 (t, ^3J= 4.6 Hz, 4H).

^{13}C{^{1}H}-NMR (151 MHz, DMSO-d_6): δ (ppm) = 145.90 (s, C_{quat}), 135.57 (s, C_{quat}), 134.36 (s, C_{quat}), 132.64 (s, C_{quat}), 131.50 (s, C_{quat}), 129.73 (s, CH), 128.67 (s, C_{quat}), 128.44 (s, CH), 128.25 (s, C_{quat}), 127.99 (s, CH), 127.30 (s, CH), 125.93 (s, CH), 114.88 (s, C_{quat}), 113.15 (s, C_{quat}), 111.93 (s, CH), 104.11 (s, CH), 66.37 (s, CH_2) 51.02 (s, CH_2).

ESI-HRMS: $[M+H]^+$ m/z: calculated for $[C_{24}H_{23}N_2O]^+$ 355.18049, found 355.18137.

IR (neat, cm^{-1}): $\tilde{\upsilon}$: 3325, 3047, 2867, 1735, 1598, 1455, 1375, 1306, 1229, 1170, 1108, 1063, 950, 899, 843, 806, 758, 692.

4-(2,3-Diphenyl-1*H*-indol-5-yl)morpholin-3-one (178k'a)



Following general procedure **5**, using 4-(4-nitrophenyl)morpholin-3-one **174k'** (0.50 mmol, 111 mg) and diphenylacetylene **164a** (0.6 mmol, 107 mg). The crude mixture was purified by SiO_2 gel column chromatography hexane/ethyl acetate (1:1). Isolated yield: 80.8 mg, 0.22 mmol, 44% (white solid).

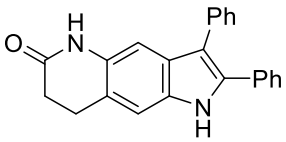
^{1}H-NMR (600 MHz, DMSO-d_6): δ (ppm) = 11.67 (s, NH), 7.47-7.45 (m, 3H), 7.42-7.36 (m, 5H), 7.33-7.29 (m, 4H), 7.12 (d, ^3J= 8.6 Hz, 1H), 4.18 (s, 2H), 3.96 (t, ^3J= 5.1 Hz, 1H), 3.71 (t, ^3J= 5.2 Hz, 2H).

^{13}C{^{1}H}-NMR (151 MHz, DMSO-d_6): δ (ppm) = 166.02 (s, C_{quat}), 135.19 (s, C_{quat}), 134.95 (s, C_{quat}), 134.62 (s, C_{quat}), 134.48 (s, C_{quat}), 132.20 (s, C_{quat}), 129.72 (s, CH), 128.69 (s, CH), 128.52 (s, CH), 128.13 (s, CH), 128.04 (s, C_{quat}), 127.67 (s, CH), 126.19 (s, CH), 120.59 (s, CH), 116.21 (s, CH), 113.54 (s, C_{quat}), 111.74 (s, CH), 67.78 (s, CH_2), 63.59 (s, CH_2), 50.16 (s, CH_2).

ESI-HRMS: $[M+H]^+$ m/z: calculated for $[C_{24}H_{20}N_2O_2Na]$+ 391.14170, found 391.14166.

IR (neat, cm^{-1}): $\tilde{\upsilon}$: 3184, 3044, 2925, 2868, 1740, 1632, 1480, 1432, 1319, 1246, 1186, 1158, 1120, 1027, 995, 941, 907, 856, 809, 766, 694.

2,3-Diphenyl-1,5,7,8-tetrahydro-6*H*-pyrrolo[2,3-*g*]quinolin-6-one (178l'a)



Following general procedure **5**, using 6-nitro-3,4-dihydroquinolin-2(1H)-one **174l'** (0.50 mmol, 81.1 mg) and diphenylacetylene **164a** (0.6 mmol, 107 mg). The crude mixture was purified by SiO_2 gel column chromatography hexane/ethyl acetate (1:1). Isolated yield: 87.7 mg, 0.26 mmol, 52% (yellow resin).

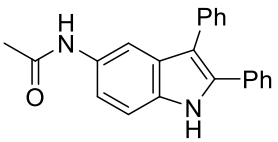
^{1}H-NMR (600 MHz, DMSO-d_6): δ (ppm) = 11.36 (s, NH), 9.84 (s, NH), 7.41-7.23 (m, 12H), 7.00 (*broad* s, 1H), 2.97 (*broad* s, 2H), 2.43 (*broad* s, 2H).

^{13}C{^{1}H}-NMR (151 MHz, DMSO-d_6): = 170.06 (s, C_{quat}), 135.50 (s, C_{quat}), 134.10 (s, C_{quat}), 132.47 (s, C_{quat}), 132.35 (s, C_{quat}), 132.06 (s, C_{quat}), 129.66 (s, CH), 129.58 (s, C_{quat}), 128.62 (s, CH), 128.43 (s, CH), 128.00 (s, C_{quat}), 127.90 (s, CH), 127.33 (s, CH), 126.96 (s, CH), 126.04 (s, CH), 120.12 (s, CH), 113.01 (s, C_{quat}), 110.17 (s, CH), 103.70 (s, CH), 31.05 (s, CH_2), 25.67 (s, CH_2).

ESI-HRMS: $[M+Na]^+$ m/z: calculated for $[C_{23}H_{18}N_2ONa]^+$ 349.13168, measured: 369.19577, 391.17764, 409.14966, 668.32398. Mass could not be found.

IR (neat, cm^{-1}): $\tilde{\upsilon}$: 3397, 3280 3023, 2963, 2925, 2866, 2325, 1721, 1658, 1592, 1546, 1522, 1475, 1371, 1309, 1262, 1180, 1111, 1015, 957, 874, 802, 720, 674.

***N*-(2,3-diphenyl-1H-indol-5-yl)acetamide (178m'a)**



Following general procedure **5**, using *N*-(4-nitrophenyl)acetamide **174m'** (0.50 mmol, 90.1 mg) and diphenylacetylene **164a** (0.6 mmol, 107 mg). The crude mixture was purified by SiO_2 gel column chromatography hexane/ethyl acetate (1:1). Isolated yield: 126.7 mg, 0.39 mmol, 78 % (white solid).

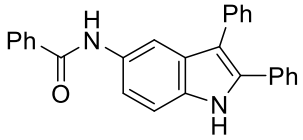
^{1}H-NMR (600 MHz, DMSO-d_6): δ (ppm) = 11.48 (s, NH), 9.78 (s, NH), 7.81 (s, 1H), 7.44-7.39 (m, 4H), 7.37-7.28 (m, 8H), 2.01 (s, 3H).

^{13}C{^{1}H}-NMR (151 MHz, DMSO-d_6): δ (ppm) = 167.62 (s, C_{quat}), 135.44 (s, C_{quat}), 134.66 (s, C_{quat}), 132.77 (s, C_{quat}), 132.48 (s, C_{quat}), 132.37 (s, C_{quat}), 129.77 (s, CH), 128.69 (s, CH), 128.54 (s, CH), 128.09 (s, CH), 127.90 (s, CH), 127.52 (s, C_{quat}), 126.11 (s, CH), 115.69 (s, CH), 113.34 (s, C_{quat}), 111.31 (s, CH), 108.82 (s, CH), 23.96 (s, CH_3).

ESI-HRMS: $[M+Na]^+$ m/z: calculated for $[C_{23}H_{22}N_2ONa]^+$ 349.13113, found 349.13159.

IR (neat, cm^{-1}): $\tilde{\upsilon}$: 3410, 3177, 3058, 2927, 1882, 1658, 1592, 1527, 1476, 1432, 1371, 1323, 1261, 1216, 1158, 1098, 1068, 1030, 1097, 952, 914, 866, 790, 757, 687.

***N*-(2,3-diphenyl-1*H*-indol-5-yl)benzamide (178n'a)**



Following general procedure **5**, using *N*-(4-nitrophenyl)benzamide **174m'** (0.50 mmol, 121 mg) and diphenylacetylene **164a** (0.6 mmol, 107 mg). The crude mixture was purified by SiO_2 gel column chromatography hexane/ethyl acetate (4:1). Isolated yield: 123.5 mg, 0.32 mmol, 64 % (yellowish solid).

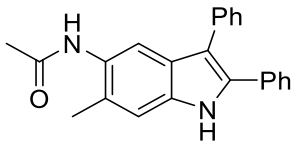
^{1}H-NMR (600 MHz, DMSO-d_6): δ (ppm) = 11.55 (s, NH), 10.15 (s, NH), 8.01 (s, 1H), 7.98 (d, ^3J= 7.6 Hz, 2H), 7.60-7.41 (m, 9H), 7.37-7.29 (m, 6H).

^{13}C{^{1}H}-NMR (151 MHz, DMSO-d_6): δ (ppm) = 165.00 (s, C_{quat}), 135.40 (s, C_{quat}), 135.29 (s, C_{quat}), 134.71 (s, C_{quat}), 133.14 (s, C_{quat}), 132.44 (s, C_{quat}), 132.00 (s, C_{quat}), 131.25 (s, CH), 129.80 (s, CH), 128.70 (s, CH), 128.54 (s, CH), 128.31 (s, CH), 128.08 (s, CH), 127.88 (s, C_{quat}), 127.54 (s, CH), 126.13 (s, CH), 116.92 (s, CH_t), 113.47 (s, C_{quat}), 111.20 (s, CH), 110.42 (s, CH).

ESI-HRMS: $[M+H]^+$ m/z: calculated for $[C_{27}H_{20}N_2ONa]^+$ 411.14678, found 411.14786.

IR (neat, cm^{-1}): $\tilde{\upsilon}$: 3421, 3288, 3055, 2921, 1741, 1653, 1536, 1437, 1378, 1315, 1258, 1182, 1073, 1027, 973, 914, 847, 809, 760, 695.

***N*-(4-Methyl-2,3-diphenyl-1*H*-indol-5-yl)acetamide (178o'a)**



Following general procedure **5**, using *N*-(2-methyl-4-nitrophenyl)acetamide **174o'** (0.50 mmol, 83.6 mg) and diphenylacetylene **164a** (0.6 mmol, 107 mg). Due to high insolubility of the compound, the reaction mixture was filtered and washed with cold hexane (3x 50 mL). The residue was dissolved in ethanol and recrystallized. The solid was filtered, washed with pentane (3x 20 mL) and dried. NMR-Analysis showed an unidentified impurity (s at 1.80 ppm in DMSO-d_6), which was removed by three portions SiO_2 gel column chromatograph with ethyl acetate:dichloromethane (1:4). Isolated yield: 123.2 mg, 0.36 mmol, 72% (beige solid).

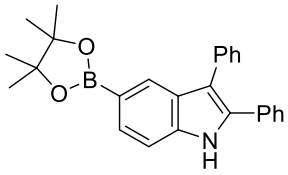
^{1}H-NMR (600 MHz, DMSO-d_6): δ (ppm) = 11.40 (s, NH), 9.22 (s, NH), 7.44 (d, ^3J= 7.5 Hz, 2H), 7.40-7.26 (m, 10H), 2.29 (s, 3H), 2.02 (s, 3H).

^{13}C{^{1}H}-NMR (151 MHz, DMSO-d_6): δ (ppm) = 168.29 (s, C_{quat}), 135.40 (s, C_{quat}), 134.44 (s, C_{quat}), 133.97 (s, C_{quat}), 132.51 (s, C_{quat}), 129.61 (s, CH), 128.67 (s, CH), 128.51 (s, CH), 128.13 (s, CH), 128.04 (s, CH), 127.73 (s, C_{quat}), 127.43 (s, CH), 126.30 (s, C_{quat}), 126.05 (s, CH), 115.66 and 115.63 (splitted- possibly rotamers, CH), 113.09 (s, C_{quat}), 111.93 and 111.91 (splitted- possibly rotamers, CH), 23.16 (s, CH_3), 18.56 (s, CH_3).

ESI-HRMS: $[M+H]^+$ m/z: calculated for $[C_{23}H_{20}N_2ONa]^+$ 363.14678, found 363.14670.

IR (neat, cm^{-1}): $\tilde{\upsilon}$: 3360, 3190, 3050, 2921, 2853, 1745, 1656, 1509, 1438, 1363, 1271, 1176, 1138, 1068, 1001, 915, 859, 761, 690.

2,3-Diphenyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indole (178s'a)



Following general procedure **5**, 4,4,5,5-tetramethyl-2-(4-nitrophenyl)-1,3,2-dioxaborolane **174s'** (0.50 mmol, 124 mg) and diphenylacetylene **164a** (0.6 mmol, 107 mg). The crude mixture was purified by SiO_2 gel column chromatography hexane/ethyl acetate (3:1). Isolated yield: 66.9 mg, 0.17 mmol, 34 % (yellowish solid).

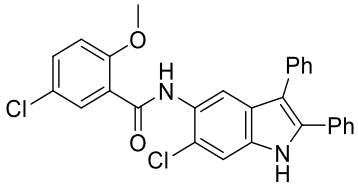
^{1}H-NMR (400 MHz, DMSO-d_6): δ (ppm) = 11.70 (s, NH), 7.84 (s, 1H), 7.52-7.28 (m, 13H), 1.28 (s, 12H).

^{13}C{^{1}H}-NMR (101 MHz, DMSO-d_6): = 138.06 (s, C_{quat}), 135.15 (s, C_{quat}), 134.14 (s, C_{quat}), 132.16 (s, C_{quat}), 129.93 (s, CH), 128.73 (s, CH), 128.48 (s, CH), 127.99 (s, CH), 127.92 (s, C_{quat}), 127.56 (s, CH), 126.33 (s, CH), 126.08 (s, CH), 113.85 (s, C_{quat}), 110.92 (s, CH), 83.15 (s, C_{quat}), 24.68 (s, CH_3).

ESI-HRMS: $[M+Na]^+$ m/z: calculated for $[C_{26}H_{26}NO_2BNa]$+ 418.19488, found 418.19592.

IR (neat, cm^{-1}): $\tilde{\upsilon}$: 3312, 3052, 2978, 2923, 1741, 1599, 1488, 1430, 1353, 1309, 1139, 1070, 963, 908, 855, 815, 755, 690.

5-Chloro-*N*-(6-chloro-2,3-diphenyl-1*H*-indol-5-yl)-2-methoxybenzamide (178t'a)



Following general procedure **5**, 5-chloro-*N*-(2-chloro-4-nitrophenyl)-2-methoxybenzamide **174s'** (0.50 mmol, 170 mg) and diphenylacetylene **164a** (0.6 mmol, 107 mg). The crude mixture was purified by SiO_2 gel column chromatography hexane/ethyl acetate (4:1). Isolated yield: 113.2 mg, 0.24 mmol, 47 % (white solid).

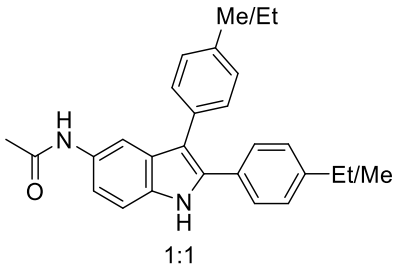
^{1}H-NMR (600 MHz, DMSO-d_6): δ (ppm) = 11.75 (s, NH), 10.45 (s, NH), 8.51 (s, 1H), 8.01-7.96 (m, 1H), 7.63 (dd, ^3J= 8.7 Hz, ^4J= 2.8 Hz, 2H), 7.59 (s, 1H), 7.46-7.31 (m, 11H), 4.07 (s, 3H).

^{13}C{^{1}H}-NMR (151 MHz, DMSO-d_6): δ (ppm) = 161.18 (s, C_{quat}), 155.91 (s, C_{quat}), 135.84 (s, C_{quat}), 134.65 (s, C_{quat}), 133.03 (s, C_{quat}), 132.79 (s, CH), 131.38 (s, C_{quat}), 130.35 (s, CH), 129.73 (s, CH), 128.82 (s, CH), 128.59 (s, CH), 128.10 (s, CH), 127.90 (s, CH), 127.54 (s, C_{quat}), 127.10 (s, C_{quat}), 126.48 (s, CH), 125.05 (s, C_{quat}), 123.11 (s, C_{quat}), 119.08 (s, C_{quat}), 114.76 (s, CH), 113.65 (s, C_{quat}), 112.55 (s, CH), 111.64 (s, CH) 57.06 (CH_3).

ESI-HRMS: $[M+H]^+$ m/z: calculated for $[C_{28}H_{21}N_2O_2Cl_2]^+$ 487.09746, found 487.09709.

IR (neat, cm^{-1}): $\tilde{\upsilon}$: 3269, 3076, 2938, 1681, 1645, 1587, 1538, 1473, 1402, 1345, 1321, 1269, 1235, 1177, 1143, 1115, 1073, 1017, 915, 879, 845, 810, 755, 697, 674.

***N*-(2-(4-ethylphenyl)-3-(*p*-tolyl)-1*H*-indol-5-yl)acetamide + *N*-(3-(4-ethylphenyl)-2-(*p*-tolyl)-1*H*-indol-5-yl)acetamide (1:1) (178m'd)**



1:1

Following general procedure **5**, using *N*-(4-nitrophenyl)acetamide **174m'** (0.50 mmol, 90.1 mg) and 1-ethyl-4-(p-tolylethynyl)-benzene **164d** (0.60 mmol, 132 mg). The crude mixture was purified by SiO_2 gel column chromatography hexane/ethyl acetate (4:1). Isolated yield: 115.6 mg, 0.32 mmol, 63 % (white solid). Regio-isomers were isolated together.

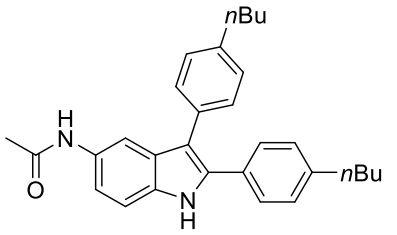
^{1}H-NMR (600 MHz, DMSO-d_6): δ (ppm) = 11.34 (broad s, 2 NH), 10.56 + 9.74 (s, 2 NH), 7.77 (broad d, ^4J= 3.8 Hz, 2H) 7.36-7.31 (m, 8H), 7.24-7.15 (m, 12H), 2.65 (quat., ^3J= 7.5 Hz, 2H), 2.60 (quat., ^3J= 7.5 Hz, 2H), 2.35 (s, 3H), 2.30 (s, 3H), 2.12 + 2.00 (s, 6H), 1.23 (t, ^3J= 7.4 Hz, 3H), 1.18 (t, ^3J= 7.5 Hz, 3H).

^{13}C{^{1}H}-NMR (151 MHz, DMSO-d_6): = 167.52 (s, C_{quat}), 142.99 (s, C_{quat}), 141.28 (s, C_{quat}), 136.75 (s, C_{quat}), 135.03 (s, C_{quat}), 134.49 (s, C_{quat}), 132.73 (s, C_{quat}), 132.65 (s, C_{quat}), 132.50 (s, C_{quat}), 132.17 (s, C_{quat}), 129.95 (s, C_{quat}), 129.70 (s, C_{quat}), 129.60 (s, CH), 129.26 (s, CH), 129.06 (s, CH), 128.11 (s, C_{quat}), 128.00 (s, CH), 127.86 (s, CH), 115.40 (s, CH), 112.87 (s, C_{quat}), 112.82 (s, C_{quat}), 111.08 (s, CH), 108.93 (s, CH), 27.89 (s, CH_2), 27.84 (s, CH_2) 23.91 (s, CH_3), 20.80 (s, CH_3), 20.77 (s, CH_3), 15.51 (s, CH_3), 15.34 (s, CH_3).

ESI-HRMS: $[M+H]^+$ m/z: calculated for $[C_{24}H_{24}N_2ONa]$+ 391.17808, found 391.17804.

IR (neat, cm^{-1}): $\tilde{\upsilon}$: 3395, 3282, 3025, 2964, 2927, 1727, 1657, 1548, 1471, 1372, 1397, 1259, 1181, 1110, 1036, 950, 809, 714.

***N*-(2,3-bis(4-*n*-butylphenyl)-1*H*-indol-5-yl)acetamide (178m'e)**



Following general procedure **5**, using *N*-(4-nitrophenyl)acetamide **174m'** (0.50 mmol, 90.1 mg) and 1,2-bis(4-butylphenyl)ethyne **164e** (0.60 mmol, 174 mg). The crude mixture was purified by SiO_2 gel column chromatography hexane/ethyl acetate (1:1). Isolated yield: 113.0 mg, 0.26 mmol, 51% (yellow resin).

^{1}H-NMR (400 MHz, DMSO-d_6): δ (ppm) = 11.31 (s, NH), 9.71 (s, NH), 7.73 (s, 1H), 7.33-7.29 (m, 4H), 7.19-7.16 (m, 4H), 7.14-7.11 (m, 2H), 2.59 (t, ^3J= 5.2 Hz, 2H), 2.55 (t, ^3J= 5.1 Hz, 2H), 1.98

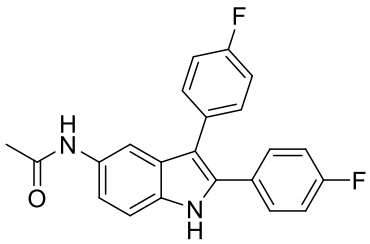
(s, 3H), 1.59 (quint, ^{3}J= 5.1 Hz, 2H), 1.54 (quint, ^{3}J= 5.3 Hz, 2H), 1.35 (quint, ^{3}J= 4.9 Hz, 2H), 1.29 (quint, ^{3}J= 4.9 Hz, 2H), 0.91 (t, ^{3}J= 4.9 Hz, 3H), 0.88 (t, ^{3}J= 4.9 Hz, 3H).

^{13}C{^{1}H}-NMR (101 MHz, DMSO-d_6): δ (ppm) = 167.50 (s, C_{quat}), 141.60 (s, C_{quat}), 139.90 (s, C_{quat}), 134.54 (s, C_{quat}), 132.74 (s, C_{quat}), 132.69 (s, C_{quat}), 132.17 (s, C_{quat}), 129.97 (s, C_{quat}), 129.95 (s, CH), 128.47 (s, CH), 128.31 (s, CH), 128.08 (s, C_{quat}), 127.82 (s, CH), 115.41 (s, CH), 112.88 (s, C_{quat}), 111.05 (s, CH), 108.89 (s, CH), 34.62 (s, CH_2), 34.53 (s, CH_2), 33.14 (s, CH_2), 32.94 (s, CH_2), 23.88 (s, CH_3), 21.91 (s, CH_2), 21.83 (s, CH_2), 13.81 (s, CH_3), 13.75 (s, CH_3).

TOF-HRMS: $[M+H]^+$ m/z: calculated for $[C_{30}H_{35}N_2O]^+$ 439.27439, found 439.27401.

IR (neat, cm^{-1}): $\tilde{\upsilon}$: 3400, 3280, 3031, 2929, 2861, 1658, 1542, 1466, 1372, 1269, 1176, 1108, 1014, 957, 804, 729.

N-(2,3-bis(4-fluorophenyl)-1*H*-indol-5-yl)acetamide (178m'f)



Following general procedure **5**, using *N*-(4-nitrophenyl)acetamide **174m'** (0.50 mmol, 90.1 mg) and 1,2-bis(4-butylphenyl)ethyne **164f** (0.60 mmol, 174 mg). The crude mixture was purified by SiO_2 gel column chromatography dichloromethane/ethyl acetate (4:1). Isolated yield: 92.3 mg, 0.26 mmol, 51% (yellowish solid).

More analytical data could not be provided.

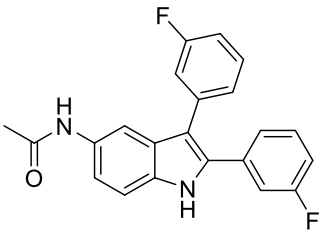
^{1}H-NMR (600 MHz, DMSO-d_6): δ (ppm) = 11.50 (s, NH), 9.77 (s, NH), 7.77 (s, 1H), 7.52-7.42 (m, 2H), 7.36-7.21 (m, 8H), 2.65 (quat., ^{3}J= 7.5 Hz, 2H), 2.00 (s, 3H).

^{13}C{^{1}H}-NMR (151 MHz, DMSO-d_6): = 167.59 (s, C_{quat}), 161.53 (d, ^{1}J= 245 Hz, C_{quat}), 160.81 (d, ^{1}J= 243 Hz, C_{quat}), 133.79 (s, C_{quat}), 132.59 (s, C_{quat}), 132.44 (s, C_{quat}), 131.51 (d, ^{3}J= 7.6 Hz, CH), 130.09 (d, ^{3}J= 8.4 Hz, CH), 128.78 (d, ^{4}J= 3.1 Hz, C_{quat}), 127.76 (s, C_{quat}), 126.04 (d, ^{4}J= 2.7 Hz, C_{quat}), 115.76 (s, CH), 115.62 (d, ^{2}J= 21.2 Hz, CH), 115.57 (d, ^{2}J= 21.6 Hz, CH), 112.20 (s, C_{quat}), 111.29 (s, CH), 108.60 (s, CH), 23.90 (s, CH_3).

^{19}F-NMR (151 MHz, DMSO-d_6): δ (ppm) = -114.17 (tt, ^{3}J= 9.1 Hz, ^{4}J= 5.4 Hz), -116.42 (tt, ^{3}J= 9.2 Hz, ^{4}J= 5.6 Hz).

IR (neat, cm^{-1}): $\tilde{\upsilon}$: 3418, 3170, 3058, 1660, 1602, 1524, 1476, 1373, 1328, 1296, 1259, 1225, 1156,1090, 1011, 950, 834, 722, 680.

N-(2,3-bis(3-fluorophenyl)-1*H*-indol-5-yl)acetamide (178m'g)



Following general procedure **5**, using *N*-(4-nitrophenyl)acetamide **174m'** (0.50 mmol, 90.1 mg) and 1,2-bis(3-fluorophenyl)ethyne **164g** (0.60 mmol, 174 mg). The crude mixture was purified by SiO_2 gel column chromatography dichloromethane/ethyl acetate (4:1). Isolated yield: 41.4 mg, 0.12 mmol, 23% (yellowish solid).

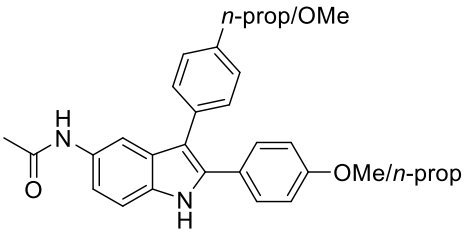
More analytical data could not be provided.

^{1}H-NMR (600 MHz, DMSO-d_6): δ (ppm) = 11.65 (s, NH), 9.82 (s, NH), 7.84 (s, 1H), 7.48-7.38 (m, 4H), 7.24 (d, ^3J= 8.2 Hz, 2H), 7.16-7.11 (m, 4H), 2.02 (s, 3H).

^{13}C{^{1}H}-NMR (151 MHz, DMSO-d_6): = 167.70 (s, C_{quat}), 162.41 (d, ^1J= 244 Hz, C_{quat}), 162.09 (d, ^1J= 244 Hz, C_{quat}), 137.58 (d, ^3J= 8.2 Hz, C_{quat}), 134.41 (d, ^3J= 8.2 Hz, CH), 133.60 (s, C_{quat}), 134.41 (d, ^4J= 6.4 Hz, CH), 130.68 (d, ^3J= 9.1 Hz, CH), 130.62 (d, ^3J= 8.9 Hz, CH), 127.50 (s, C_{quat}), 125.95 (s, C_{quat}), 125.00 (s, CH), 124.27 (s, C_{quat}), 118.55 (s, CH), 116.15 (d, ^2J= 19.6 Hz, CH), 114.62 (d, ^2J= 22.9 Hz, CH), 114.62 (d, ^2J= 20.8 Hz, CH), 113.13 (d, ^2J= 20.7 Hz, CH), 112.81 (s, C_{quat}), 111.55 (s, CH), 108.53 (s, CH), 23.95 (s, CH_3).

^{19}F-NMR (151 MHz, DMSO-d_6): δ (ppm) = -112.73 (tt, ^3J= 9.1 Hz, ^4J= 5.4 Hz), -113.01 (tt, ^3J= 9.6 Hz, ^4J= 6.2 Hz).

_N_-(2-(4-methoxyphenyl)-3-(4-propylphenyl)-1_H_-indol-5-yl)acetamide + _N_-(3-(4-methoxyphenyl)-2-(4-propylphenyl)-1_H_-indol-5-yl)acetamide (1:1) (178m'i)



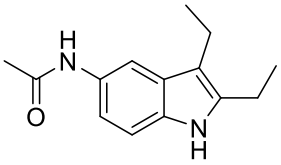
Following general procedure **5**, using *N*-(4-nitrophenyl)acetamide **174m'** (0.50 mmol, 90.1 mg) and 1-methoxy-4-((4-propylphenyl)ethynyl)benzene **164i** (0.60 mmol, 174 mg). The crude mixture was purified by SiO_2 gel column chromatography dichloromethane/ethyl acetate (4:1). Isolated yield: 48.5 mg, 0.12 mmol, 24 % (yellow resin). More analytical data could not be provided.

^{1}H-NMR (400 MHz, DMSO-d_6): δ (ppm) = 11.30 (s, NH), 9.72 (s, NH), 7.74 + 7.73 (s, 1H), 7.37-7.31 (m, 4H), 7.28-7.16 (m, 4H), 6.98 (d, ^3J= 8.1 Hz, 1H), 6.92 (d, ^3J= 8.3 Hz, 1H), 3.79 + 3.76 (s, 3H), 2.59 + 2.54 (t, ^3J= 7.4 Hz, 2H), 1.99 (s, 3H), 1.64 + 1.59 (sext, ^3J= 7.5, 2H), 0.94 + 0.90 (t, ^3J= 7.2 Hz, 3H).

^{13}C{^{1}H}-NMR (151 MHz, DMSO-d_6): = 167.48 (s, C_{quat}), 158.64 (s, C_{quat}), 157.64 (s, C_{quat}), 141.33 (s, C_{quat}), 139.63 (s, C_{quat}), 134.48 (s, C_{quat}), 134.30 (s, C_{quat}), 132.83 (s, C_{quat}),, 132.59 (s, C_{quat}), 132.57 (s, C_{quat}), 132.11 (s, C_{quat}), 132.08 (s, C_{quat}), 130.80 (s, C_{quat}), 130.02 (s, C_{quat}),, 129.50 (s, CH), 129.23 (s, CH), 128.55 (s, CH), 128.40 (s, CH), 128.25 (s, C_{quat}), 128.05 (s, C_{quat}),, 127.68

(s, CH), 127.58 (s, CH), 124.93 (s, C_{quat}), 115.39 (s, C_{quat}), 115.17 (s, C_{quat}), 114.14 (s, CH), 113.94 (s, CH), 112.66 (s, CH), 112.28 (s, CH), 111.02 (s, CH), 110.95 (s, CH), 108.84 (s, CH), 108.74 (s, CH), 55.12 (s, CH_3), 55.02 (s, CH_3), 37.05 (s, CH_2), 36.94 (s, CH_2), 24.05 (s, CH_2), 23.89 (s, CH_2), 13.81 (s, CH_3), 13.71 (s, CH_3).

***N*-(2,3-diethyl-1*H*-indol-5-yl)benzamide (178m'k)**



Following general procedure **5**, using *N*-(4-nitrophenyl)acetamide **174m'** (0.50 mmol, 90.1 mg) and hex-3-yne **164k** (0.60 mmol, 49.2 mg). The crude mixture was purified by SiO_2 gel column chromatography hexane/ethyl acetate (1:1). Isolated yield: 46.1 mg, 0.20 mmol, 41%.

^{1}H-NMR (600 MHz, DMSO-d_6): δ (ppm) = 10.53 (s, NH), 9.65 (s, NH), 7.68-7.67 (m, 1H), 7.19-7.09 (m, 2H), 2.66 (q, ^3J= 7.6 Hz, 2H), 2.59 (q, ^3J= 7.4 Hz, 2H), 2.01 (s, 3H), 1.21 (t, ^3J= 7.6 Hz, 3H), 1.19 (t, ^3J= 7.4 Hz, 3H).

^{13}C{1H}-NMR (151 MHz, DMSO-d_6): δ (ppm) = 167.41 (s, C_{quat}), 137.37 (s, C_{quat}), 132.00 (s, C_{quat}), 130.72 (s, C_{quat}), 127.56 (s, C_{quat}), 113.59 (s, CH), 111.11 (s, C_{quat}), 110.12 (s, CH), 108.39 (s, CH), 23.91 (s, CH_3), 18.83 (s, CH_2), 16.89 (s, CH_2), 15.91 (s, CH_3), 14.66 (s, CH_3).

ESI-HRMS: $[M+H]^+$ m/z: calculated for $[C_{14}H_{18}N_2ONa]^+$ 253.13113, found 253.13130.

IR (neat, cm-1): $\tilde{\upsilon}$: 3276, 2961, 2867, 1652, 1545, 1468, 1370, 1269, 1129, 1013, 869, 801, 746, 662.

5 References

[1] C.-H. Zhou, Y. Wang, *Curr. Med. Chem.* **2012**, *19*, 239.

[2] Ş. G. Küçükgüzel, S. Şenkardeş, *Eur. J. Med. Chem.* **2015**, *97*, 786.

[3] L. M. Blair, J. Sperry, *J. Nat. Prod.* **2013**, *76*, 794.

[4] E. Merino, *Chem. Soc. Rev.* **2011**, *40*, 3835.

[5] C. Roullier, M. Chollet-Krugler, P. van de Weghe, F. L.-L. Devehat, J. Boustie, *Bioorg. Med. Chem. Lett.* **2010**, *20*, 4582.

[6] Q. Zhang, A. Mándi, S. Li, Y. Chen, W. Zhang, X. Tian, H. Zhang, H. Li, W. Zhang, S. Zhang et al., *Eur. J. Org. Chem.* **2012**, *2012*, 5256.

[7] Paul Ehrlich, *Berl. Klin. Wochenschr.* **1907**, *9*, 232.

[8] Hunger K. Mischke P. Rieper W. Raue R. Kunde K. Engel A, *2000*.

[9] C. M. Michener, E. C. Kohn, *Carboxyamidotriazole, an Inhibitor of Nonvoltage-Operated Calcium Entry*.

[10] P. Walden, *Geschichte der organischen Chemie seit 1880*, Springer Berlin Heidelberg, Berlin, Heidelberg, s.l., **1941**.

[11] W. Strober, *Curr. Protoc. Immunol.* **2001**, *Appendix 3*, Appendix 3B.

[12] Q. Zhang, A. Mándi, S. Li, Y. Chen, W. Zhang, X. Tian, H. Zhang, H. Li, W. Zhang, S. Zhang et al., *Eur. J. Org. Chem.* **2012**, *2012*, 5256.

[13] "Hydrazin - RÖMPP, Thieme", can be found under https://roempp.thieme.de/lexicon/RD-08-02134?searchterm=hydrazin, **2011**.

[14] P. S. Dendage, D. B. Sarwade, S. N. Asthana, H. Singh, *J. Energ. Mater.* **2001**, *19*, 41.

[15] H. Hayashi, *Catal. Rev.* **1990**, *32*, 229.

[16] F. Raschig, *Berichte der deutschen chemischen Gesellschaft* **1907**, *40*, 4580.

[17] Jean-Pierre Schirmann, Paul Bourdauducq.

[18] J.-P. Schirmann, F. Weiss, *Tetrahedron Lett.* **1972**, *13*, 633.

[19] G. H. Coleman, *Org. Synth.* **1922**, *2*, 71.

[20] B. Pieber, S. T. Martinez, D. Cantillo, C. O. Kappe, *Angew. Chem. Int. Ed.* **2013**, *52*, 10241.

[21] E. Mitscherlich, *Ann. Phys. Chem.* **1834**, *107*, 625.

[22] C. Glaser, *Ann. Chem. Pharm.* **1867**, *142*, 364.

[23] J. Wang, J. He, C. Zhi, B. Luo, X. Li, Y. Pan, X. Cao, H. Gu, *RSC Adv.* **2014**, *4*, 16607.

[24] M. Barbero, I. Degani, S. Dughera, R. Fochi, P. Perracino, *Synthesis* **1998**, *1998*, 1235.

[25] W. H. Nutting, R. A. Jewell, H. Rapoport, *J. Org. Chem.* **1970**, *35*, 505.

[26] C. Zhang, N. Jiao, *Angew. Chem. Int. Ed.* **2010**, *49*, 6174.

[27] a) James Forrest, David A. Liddell, S. Horwood Tucker, *J. Chem. Soc.* **1946**, 454; b) H. Wieland, S. Gambarjan, *Ber. Dtsch. Chem. Ges.* **1906**, *39*, 1499.

[28] Y. Zhu, Y. Shi, *Org. Lett.* **2013**, *15*, 1942.

[29] a) G. Bringmann, S. Tasler, H. Endress, J. Kraus, K. Messer, M. Wohlfarth, W. Lobin, *J. Am. Chem. Soc.* **2001**, *123*, 2703; b) M.-L. Louillat, F. W. Patureau, *Org. Lett.* **2013**, *15*, 164.

[30] B. R. Rosen, E. W. Werner, A. G. O'Brien, P. S. Baran, *J. Am. Chem. Soc.* **2014**, *136*, 5571.

[31] C. Yu, J. Sanjosé-Orduna, F. W. Patureau, M. H. Pérez-Temprano, *Chem. Soc. Rev.* **2020**, *49*, 1643.

[32] a) C. Nozaki, C. G. Lugmair, A. T. Bell, T. D. Tilley, *J. Am. Chem. Soc.* **2002**, *124*, 13194; b) S. Tripathi, S. N. Singh, L. D. S. Yadav, *RSC Adv.* **2016**, *6*, 14547; c) M. K. Eberhardt, *Tetrahedron Lett.* **1984**, *25*, 3663.

[33] A. W. Jones, M.-L. Louillat-Habermeyer, F. W. Patureau, *Adv. Synth. Catal.* **2015**, *357*, 945.

[34] B. Özkaya, H. Kelm, F. W. Patureau, *CCDC 2209643 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/structures* **2022**.

[35] a) T. Flessner, S. Doye, *J. Prakt. Chem.* **1999**, *341*, 186; b) R. Rabie, M. M. Hammouda, K. M. Elattar, *Res. Chem. Intermed.* **2017**, *43*, 1979; c) F. Lehmann, *Synlett* **2004**, 2447.

[36] O. H. Wheeler, *Can. J. Chem.* **1958**, *36*, 667.

[37] M. C. Ryan, J. R. Martinelli, S. S. Stahl, *J. Am. Chem. Soc.* **2018**, *140*, 9074.

[38] Z.-S. Huang, H. Meier, D. Cao, *J. Mater. Chem. C* **2016**, *4*, 2404.

[39] M. J. Ohlow, B. Moosmann, *Drug. Discov. Today* **2011**, *16*, 119.

[40] X. Pan, C. Fang, M. Fantin, N. Malhotra, W. Y. So, L. A. Peteanu, A. A. Isse, A. Gennaro, P. Liu, K. Matyjaszewski, *J. Am. Chem. Soc.* **2016**, *138*, 2411.

[41] Y.-N. Zhou, J.-J. Li, Y.-Y. Wu, Z.-H. Luo, *Chem. Rev.* **2020**, *120*, 2950.

[42] Z. Iqbal, W.-Q. Wu, D.-B. Kuang, L. Wang, H. Meier, D. Cao, *Dyes Pigm.* **2013**, *96*, 722.

[43] S. Revoju, S. Biswas, B. Eliasson, G. D. Sharma, *Phys. Chem. Chem. Phys.* **2018**, *20*, 6390.

[44] J. K. Salunke, F. L. Wong, K. Feron, S. Manzhos, M. F. Lo, D. Shinde, A. Patil, C. S. Lee, V. A. L. Roy, P. Sonar et al., *J. Mater. Chem. C* **2016**, *4*, 1009.

[45] S. Kumar, M. Singh, J.-H. Jou, S. Ghosh, *J. Mater. Chem. C* **2016**, *4*, 6769.

[46] R. Grisorio, B. Roose, S. Colella, A. Listorti, G. P. Suranna, A. Abate, *ACS Energy Lett.* **2017**, *2*, 1029.

[47] P. Guttman, P. Ehrlich, *Berl. Klin. Wochenschr.* **1891**, 953.

[48] "World Health Organization Model List of Essential Medicines. 21st List 2019", can be found under https://www.who.int/medicines/publications/essentialmedicines/en/.

[49] M.-L. Louillat-Habermeyer, R. Jin, F. W. Patureau, *Angew. Chem. Int. Ed.* **2015**, *54*, 4102.

[50] R. Jin, F. W. Patureau, *Org. Lett.* **2016**, *18*, 4491.

[51] R. Jin, C. L. Bub, F. W. Patureau, *Org. Lett.* **2018**, *20*, 2884.

[52] C. Friedel, J. M. Crafts, *J. Chem. Soc.* **1877**, *32*, 725.

[53] J. Clayden, N. Greeves, S. G. Warren, *Organic chemistry*, Oxford University Press, Oxford, **2012**.

[54] M. Rueping, B. J. Nachtsheim, *Beilstein J. Org. Chem.* **2010**, *6*, 6.

[55] T. Tsuchimoto, K. Tobita, T. Hiyama, S. Fukuzawa, *J. Org. Chem.* **1997**, *62*, 6997.

[56] T. Tsuchimoto, K. Tobita, T. Hiyama, S. Fukuzawa, *Synlett* **1996**, *1996*, 557.

[57] a) M. Rueping, B. J. Nachtsheim, W. Ieawsuwan, *Adv. Synth. Catal.* **2006**, *348*, 1033; b) M. Rueping, B. J. Nachtsheim, T. Scheidt, *Org. Lett.* **2006**, *8*, 3717.

[58] L. N. Lewis, J. F. Smith, *J. Am. Chem. Soc.* **1986**, *108*, 2728.

[59] S. Murai, F. Kakiuchi, S. Sekine, Y. Tanaka, A. Kamatani, M. Sonoda, N. Chatani, *Nature (London)* **1993**, *366*, 529.

[60] a) J.-J. Brunet, D. Neibecker, K. Philippot, *J. Chem. Soc., Chem. Commun.* **1992**, 1215; b) J.-J. Brunet, G. Commenges, D. Neibecker, K. Philippot, *J. Organomet. Chem.* **1994**, *469*, 221.

[61] D. R. Coulson, *Tetrahedron Lett.* **1971**, *12*, 429.

[62] M. Rueping, B. J. Nachtsheim, *Beilstein J. Org. Chem.* **2010**, *6*, 6.

[63] M. Beller, O. R. Thiel, H. Trauthwein, *Synlett* **1999**, *2*, 243.

[64] Z. Dong, Z. Ren, S. J. Thompson, Y. Xu, G. Dong, *Chem. Rev.* **2017**, *117*, 9333.

[65] D. A. Colby, R. G. Bergman, J. A. Ellman, *Chem. Rev.* **2010**, *110*, 624.

[66] F. Kakiuchi, S. Murai, *Acc. Chem. Res.* **2002**, *35*, 826.

[67] a) T. Matsubara, N. Koga, D. G. Musaev, K. Morokuma, *J. Am. Chem. Soc.* **1998**, *120*, 12692; b) T. Matsubara, N. Koga, D. G. Musaev, K. Morokuma, *Organometallics* **2000**, *19*, 2318.

[68] F. Dénès, A. Pérez-Luna, F. Chemla, *Chem. Rev.* **2010**, *110*, 2366.

[69] D. W. Stephan, G. Erker, *Angew. Chem. Int. Ed.* **2015**, *54*, 6400.

[70] a) J. Zhu, M. Pérez, C. B. Caputo, D. W. Stephan, *Angew. Chem. Int. Ed.* **2016**, *55*, 1417; b) Y. Soltani, L. C. Wilkins, R. L. Melen, *Angew. Chem. Int. Ed.* **2017**, *56*, 11995; c) S. Tamke, Z.-W. Qu, N. A. Sitte, U. Flörke, S. Grimme, J. Paradies, *Angew. Chem. Int. Ed.* **2016**, *55*, 4336; d) L. Süsse, M. Vogler, M. Mewald, B. Kemper, E. Irran, M. Oestreich, *Angew. Chem. Int. Ed.* **2018**, *57*, 11441.

[71] X. Hu, D. Martin, M. Melaimi, G. Bertrand, *J. Am. Chem. Soc.* **2014**, *136*, 13594.

[72] Y. Uchimaru, *Chem. Commun.* **1999**, 1133.

[73] M. Pérez, T. Mahdi, L. J. Hounjet, D. W. Stephan, *Chem. Commun.* **2015**, *51*, 11301.

[74] a) M. Dryzhakov, M. Hellal, E. Wolf, F. C. Falk, J. Moran, *J. Am. Chem. Soc.* **2015**, *137*, 9555; b) M. Dryzhakov, J. Moran, *ACS Catal.* **2016**, *6*, 3670.

[75] a) S. Quideau, D. Deffieux, C. Douat-Casassus, L. Pouységu, *Angew. Chem. Int. Ed.* **2011**, *50*, 586; b) M. Weber, M. Weber, V. Weber, 1; c) A. G. Pinkus, *J. Am. Chem. Soc.* **1997**, *119*, 5991; d) Z. Huang, J.-P. Lumb, *ACS Catal.* **2019**, *9*, 521; e) H. Zeng, Z. Qiu, A. Domínguez-Huerta, Z. Hearne, Z. Chen, C.-J. Li, *ACS Catal.* **2017**, *7*, 510; f) M. Tobisu, N. Chatani, *Top. Curr. Chem.* **2016**, *374*, 41; g) T. Mesganaw, N. K. Garg, *Org. Process Res. Dev.* **2013**, *17*, 29.

[76] a) S. Sato, R. Takahashi, T. Sodesawa, K. Matsumoto, Y. Kamimura, *J. Catal.* **1999**, 180; b) J. W. Walton, J. M. J. Williams, *Angew. Chem. Int. Ed.* **2012**, *51*, 12166; c) A. Kolka, J. Napolitano, G. Ecke, *J. Org. Chem.* **1956**, *21*, 712; d) G. Evano, C. Theunissen, *Angew. Chem. Int. Ed.* **2019**, *58*, 7202.

[77] G. Wang, L. Gao, H. Chen, X. Liu, J. Cao, S. Chen, X. Cheng, S. Li, *Angew. Chem. Int. Ed.* **2019**, *58*, 1694.

[78] Z. Yu, Y. Li, J. Shi, B. Ma, L. Liu, J. Zhang, *Angew. Chem. Int. Ed.* **2016**, *55*, 14807.

[79] J. N. Bentley, C. B. Caputo, *Organometallics* **2018**, *37*, 3654.

[80] a) D. Gillingham, N. Fei, *Chem. Soc. Rev.* **2013**, *42*, 4918; b) X. Guo, W. Hu, *Acc. Chem. Res.* **2013**, *46*, 2427.

[81] A. J. Boyington, M.-L. Y. Riu, N. T. Jui, *J. Am. Chem. Soc.* **2017**, *139*, 6582.

[82] N. A. Romero, D. A. Nicewicz, *Chem. Rev.* **2016**, *116*, 10075.

[83] a) C. K. Prier, D. A. Rankic, D. W. C. MacMillan, *Chem. Rev.* **2013**, *113*, 5322; b) Q.-Q. Zhou, Y.-Q. Zou, L.-Q. Lu, W.-J. Xiao, *Angew. Chem. Int. Ed.* **2019**, *58*, 1586.

[84] C. P. Seath, N. T. Jui, *Synlett* **2019**, *30*, 1607.

[85] a) K. D. Hesp, M. Stradiotto, *ChemCatChem* **2010**, *2*, 1192; b) M. Patel, R. K. Saunthwal, A. K. Verma, *Acc. Chem. Res.* **2017**, *50*, 240.

[86] Christian Karlheinz Rank, *Entwicklung einzigartiger Methoden zur Synthese aromatischer und heteroaromatischer Verbindungen*, RWTH Aachen University, Aachen, **2022**.

[87] K. P. C. Vollhardt, N. E. Schore, *Organische Chemie*, Wiley-VCH, Weinheim, **2020**.

[88] C. K. Rank, B. Özkaya, F. W. Patureau, *Org. Lett.* **2019**, *21*, 6830.

[89] a) M. D. Greenhalgh, A. S. Jones, S. P. Thomas, *ChemCatChem* **2015**, *7*, 190; b) D. Wei, X. Zhu, J.-L. Niu, M.-P. Song, *ChemCatChem* **2016**, *8*, 1242; c) G. Fang, X. Cong, G. Zanoni, Q. Liu, X. Bi, *Adv. Synth. Catal.* **2017**, *359*, 1422.

[90] M. Goswami, A. Konkel, M. Rahimi, M.-L. Louillat-Habermeyer, H. Kelm, R. Jin, B. de Bruin, F. W. Patureau, *Chem.—Eur. J.* **2018**, *24*, 11936.

[91] a) A. Bernthsen, *Ber. Dtsch. Chem. Ges.* **1883**, *16*, 1025; b) A. Bernthsen, *Ann. Pharm.* **1885**, *230*, 73.

[92] W. Zhu, Q. Sun, Y. Wang, D. Yuan, Y. Yao, *Org. Lett.* **2018**, *20*, 3101.

[93] a) Sigma-Aldrich, "Tris(pentafluorophenyl)<WBR>borane 442593", can be found under https://www.sigmaaldrich.com/catalog/product/aldrich/442593?lang=de&region=DE, **2021**; b) "Triphenylmethylium tetrakis(perfluorophenyl)borate | CAS No. 136040-19-2 | Sigma-Aldrich", can be found under https://www.sigmaaldrich.com/catalog/buildingblock/product/ambeedinc/ambh2d6f6db0?lang=de&region=DE, **2021**; c) Sigma-Aldrich, "Silber-<WBR>tetrafluoroborat 208361", can be found under https://www.sigmaaldrich.com/catalog/product/aldrich/208361?lang=de&region=DE&gclid=Cj0KCQjwwOz6BRCgARIsAKEG4FWoAWrJkDDYt6YxeqUBCCWwL0uSDnTInTV2uWPIEKQCeB34Vcd3lxwaAmZbEALw_wcB, **2021**; d) Sigma-Aldrich, "Tetrafluoroborsäure Diethylether Komplex 400068", can be found under https://www.sigmaaldrich.com/catalog/product/aldrich/400068?lang=de&region=DE, **2021**.

[94] W. R. ACOSTA, *PHARMACOLOGY FOR HEALTH PROFESSIONALS*, JONES & BARTLETT LEARNING, [S.l.], **2020**.

[95] a) J.-H. Lee, J. Lee, *FEMS Microbiol. Rev.* **2010**, *34*, 426; b) A. J. Kochanowska-Karamyan, M. T. Hamann, *Chem. Rev.* **2010**, *110*, 4489; c) M. Ishikura, T. Abe, T. Choshi, S. Hibino, *Nat. Prod. Rep.* **2013**, *30*, 694; d) Gerald Booth (Ed.) *ULLMANN'S Encyclopedia of Industrial Chemistry // Ullmann's encyclopedia of industrial chemistry*. *Nitro Compounds, Aromatic*, Wiley‐VCH Verlag GmbH & Co. KGaA.; Wiley, Chichester, **2000** *//* **2010**.

[96] F. Auld, E. L. Maschauer, I. Morrison, D. J. Skene, R. L. Riha, *Sleep. Med. Rev.* **2017**, *34*, 10.

[97] a) D. J. McKenna, G. Towers, F. Abbott, *J. Ethnopharmacol* **1984**, *10*, 195; b) T. M. Carbonaro, M. B. Gatch, *Brain. Res. Bull.* **2016**, *126*, 74.

[98] G. R. Humphrey, J. T. Kuethe, *Chem. Rev.* **2006**, *106*, 2875.

[99] M. Inman, C. J. Moody, *Chem. Sci.* **2013**, *4*, 29.

[100] E. Fischer, O. Hess in *Untersuchungen über Triphenylmethanfarbstoffe Hydrazine und Indole* (Eds.: E. Fischer, M. Bergmann), Springer Berlin Heidelberg, Berlin, Heidelberg, **1924**, pp. 454–462.

[101] E. Fischer, O. Hess, *Ber. Dtsch. Chem. Ges.* **1884**, *17*, 559.

[102] B. Robinson, *Chem. Rev.* **1963**, *63*, 373.

[103] R. C. Larock, E. K. Yum, *J. Am. Chem. Soc.* **1991**, *113*, 6689.

[104] R. C. Larock, E. K. Yum, M. D. Refvik, *J. Org. Chem.* **1998**, *63*, 7652.

[105] D. R. Stuart, M. Bertrand-Laperle, K. M. N. Burgess, K. Fagnou, *J. Am. Chem. Soc.* **2008**, *130*, 16474.

[106] Y. Hoshino, Y. Shibata, K. Tanaka, *Adv. Synth. Catal.* **2014**, *356*, 1577.

[107] a) G. Song, F. Wang, X. Li, *Chem. Soc. Rev.* **2012**, *41*, 3651; b) N. Kuhl, N. Schröder, F. Glorius, *Adv. Synth. Catal.* **2014**, *356*, 1443.

[108] G. N. Hermann, C. L. Jung, C. Bolm, *Green Chem.* **2017**, *19*, 2520.

[109] a) K. Morimoto, T. Dohi, Y. Kita, *Synlett* **2017**, *28*, 1680; b) S. Tang, L. Zeng, A. Lei, *J. Am. Chem. Soc.* **2018**, *140*, 13128; c) S. Guo, P. S. Kumar, M. Yang, *Adv. Synth. Catal.* **2017**, *359*, 2; d) C. S. Yeung, V. M. Dong, *Chem. Rev.* **2011**, *111*, 1215.

[110] K.-S. Ju, R. E. Parales, *Microbiol. Mol. Biol. Rev.* **2010**, *74*, 250.

[111] A. Reissert, *Ber. Dtsch. Chem. Ges.* **1897**, *30*, 1030.

[112] C. Granchi, S. Roy, C. Giacomelli, M. Macchia, T. Tuccinardi, A. Martinelli, M. Lanza, L. Betti, G. Giannaccini, A. Lucacchini et al., *J. Med. Chem.* **2011**, *54*, 1599.

[113] G. Bartoli, G. Palmieri, M. Bosco, R. Dalpozzo, *Tetrahedron Lett.* **1989**, *30*, 2129.

[114] A. Dobbs, *J. Org. Chem.* **2001**, *66*, 638.

[115] a) K. Knepper, S. Bräse, *Org. Lett.* **2003**, *5*, 2829; b) R. Dalpozzo, G. Bartoli, *Curr. Org. Chem.* **2005**, *9*, 163; c) L. Wylie, P. Innocenti, D. K. Whelligan, S. Hoelder, *Org. Biomol. Chem.* **2012**, *10*, 4441.

[116] a) *The MAK‐Collection for Occupational Health and Safety: Annual Thresholds and Classifications for the Workplace*. *Methylzinnverbindungen [MAK Value Documentation in German language, 2014]*, Wiley-VCH Verl., Germany, **2002**; b) "Organozinnverbindungen in verbrauchernahen Produkten - Aktualisierte Stellungnahme Nr.034/2011 des BfR vom 2. August 2011", can be found under https://mobil.bfr.bund.de/cm/343/organozinnverbindungen_in_verbrauchernahen_produkten.pdf; c) *The MAK‐Collection for Occupational Health and Safety: Annual Thresholds and Classifications for the Workplace*. *Phenylzinnverbindungen [MAK Value Documentation in German language, 2010]*, Wiley-VCH Verl., Germany, **2002**.

[117] A. Penoni, K. M. Nicholas, *Chem. Commun.* **2002**, 484.

[118] F. Ragaini, A. Rapetti, E. Visentin, M. Monzani, A. Caselli, S. Cenini, *J. Org. Chem.* **2006**, *71*, 3748.

[119] a) S. Murru, A. A. Gallo, R. S. Srivastava, *ACS Catal.* **2011**, *1*, 29; b) S. Murru, A. A. Gallo, R. S. Srivastava, *Eur. J. Org. Chem.* **2011**, *11*, 2035; c) G. Zhang, H. Yu, G. Qin, H. Huang,

Chem. Commun. **2014**, *50*, 4331; d) H. Yan, H. Wang, X. Li, X. Xin, C. Wang, B. Wan, *Angew. Chem. Int. Ed.* **2015**, *54*, 10613; e) Z. Zhou, G. Liu, Y. Chen, X. Lu, *Adv. Synth. Catal.* **2015**, *357*, 2944; f) L. L. Anderson, M. A. Kroc, T. W. Reidl, J. Son, *J. Org. Chem.* **2016**, *81*, 9521.

[120] a) N. Ono, H. Feuer (Eds.) *The Nitro Group in Organic Synthesis*, John Wiley & Sons, Inc, New York, USA, **2001**; b) R. Parry, S. Nishino, J. Spain, *Nat. Prod. Rep.* **2011**, *28*, 152.

[121] T. Kahl, K.-W. Schröder, F. R. Lawrence, W. J. Marshall, H. Höke, R. Jäckh.

[122] a) Antoine Béchamp, *Annales de chimie et de physique* **1854**, 186; b) N. Zinin, *J. Prakt. Chem.* **1842**, *27*, 140.

[123] Z. Wang **2010**, 284.

[124] E. Breitmaier, G. Jung, *Organische Chemie*. *Grundlagen, Verbindungsklassen, Reaktionen, Konzepte, Molekülstruktur, Naturstoffe ; 133 Tabellen*, Thieme, Stuttgart, **2009**.

[125] N. Shen, C. W. Cheung, J.-A. Ma, *Chem. Commun.* **2019**, *55*, 13709.

[126] S. Zhao, N. P. Mankad, *Org. Lett.* **2019**, *21*, 10106.

[127] C. W. Cheung, M. Leendert Ploeger, X. Hu, *Chem. Sci.* **2018**, *9*, 655.

[128] L. Ling, C. Chen, M. Luo, X. Zeng, *Org. Lett.* **2019**, *21*, 1912.

[129] S. Suárez-Pantiga, R. Hernández-Ruiz, C. Virumbrales, M. R. Pedrosa, R. Sanz, *Angew. Chem. Int. Ed.* **2019**, *58*, 2129.

[130] C. W. Cheung, X. Hu, *Nat. Commun.* **2016**, *7*, 12494.

[131] M. Rauser, R. Eckert, M. Gerbershagen, M. Niggemann, *Angew. Chem. Int. Ed.* **2019**, *58*, 6713.

[132] C. W. Cheung, M. L. Ploeger, X. Hu, *Nat. Commun.* **2017**, *8*, 14878.

[133] M. Rauser, C. Ascheberg, M. Niggemann, *Angew. Chem. Int. Ed.* **2017**, *56*, 11570.

[134] M. Rauser, C. Ascheberg, M. Niggemann, *Chem.—Eur. J.* **2018**, *24*, 3970.

[135] a) S. D. Roughley, A. M. Jordan, *J. Med. Chem.* **2011**, *54*, 3451; b) J. S. Carey, D. Laffan, C. Thomson, M. T. Williams, *Org. Biomol. Chem.* **2006**, *4*, 2337.

[136] R. M. Lanigan, T. D. Sheppard, *Eur. J. Org. Chem.* **2013**, *33*, 7453.

[137] J. M. Hoerter, K. M. Otte, S. H. Gellman, Q. Cui, S. S. Stahl, *J. Am. Chem. Soc.* **2008**, *130*, 647.

[138] P. Acosta-Guzmán, A. Mateus-Gómez, D. Gamba-Sánchez, *Molecules (Basel, Switzerland)* **2018**, *23*.

[139] C. W. Cheung, M. L. Ploeger, X. Hu, *ACS Catal.* **2017**, *7*, 7092.

[140] C. W. Cheung, J.-A. Ma, X. Hu, *J. Am. Chem. Soc.* **2018**, *140*, 6789.

[141] J. Gui, C.-M. Pan, Y. Jin, T. Qin, J. C. Lo, B. J. Lee, S. H. Spergel, M. E. Mertzman, W. J. Pitts, T. E. La Cruz et al., *Science (New York, N.Y.)* **2015**, *348*, 886.

[142] a) C. Lu, Z. Su, D. Jing, S. Jin, L. Xie, L. Li, K. Zheng, *Org. Lett.* **2019**, *21*, 1438; b) H. Song, Z. Yang, C.-H. Tung, W. Wang, *ACS Catal.* **2020**, *10*, 276.

[143] J. Liu, C. Zhang, Z. Zhang, X. Wen, X. Dou, J. Wei, X. Qiu, S. Song, N. Jiao, *Science (New York, N.Y.)* **2020**, *367*, 281.

[144] L. Caron, L.-C. Campeau, K. Fagnou, *Org. Lett.* **2008**, *10*, 4533.

[145] M. Orlandi, D. Brenna, R. Harms, S. Jost, M. Benaglia, *Org. Process Res. Dev.* **2018**, *22*, 430.

[146] D. Lapointe, K. Fagnou, *Chem. Lett.* **2010**, *39*, 1118.

[147] a) P. Ruiz-Castillo, S. L. Buchwald, *Chem. Rev.* **2016**, *116*, 12564; b) D. W. Old, J. P. Wolfe, S. L. Buchwald, *J. Am. Chem. Soc.* **1998**, *120*, 9722; c) D. S. Surry, S. L. Buchwald, *Chem. Sci.* **2011**, *2*, 27; d) A. Fihri, P. Meunier, J.-C. Hierso, *Coord. Chem. Rev.* **2007**, *251*, 2017; e) I. Kostas, *Curr. Org. Synth.* **2008**, *5*, 227; f) C. Kaes, A. Katz, M. W. Hosseini, *Chem. Rev.* **2000**, *100*, 3553; g) R. Ziessel, *Coord. Chem. Rev.* **2001**, *216-217*, 195; h) D. A. Colby, A. S. Tsai, R. G. Bergman, J. A. Ellman, *Acc. Chem. Res.* **2012**, *45*, 814.

[148] a) D. J. Dixon, O. Pando Morejón, 479; b) D. Formenti, F. Ferretti, F. K. Scharnagl, M. Beller, *Chem. Rev.* **2019**, *119*, 2611; c) I. D. Entwistle, A. E. Jackson, R. A. W. Johnstone, R. P. Telford, *J. Chem. Soc., Perkin Trans. 1* **1977**, 443.

[149] C. Berti, L. Greci, M. Poloni, G. D. Andreetti, G. Bocelli, P. Sgarabotto, *J. Chem. Soc., Perkin Trans. 2* **1980**, 339.

[150] A. P. Walsh, W. D. Jones, *Organometallics* **2015**, *34*, 3400.

[151] a) M. Lafrance, K. Fagnou, *J. Am. Chem. Soc.* **2006**, *128*, 16496; b) Y. Tanji, N. Mitsutake, T. Fujihara, Y. Tsuji, *Angew. Chem. Int. Ed.* **2018**, *57*, 10314.

[152] Y. Hoshino, Y. Shibata, K. Tanaka, *Adv. Synth. Catal.* **2014**, *356*, 1577.

[153] M. Fukui, Y. Hoshino, T. Satoh, M. Miura, K. Tanaka, *Adv. Synth. Catal.* **2014**, *356*, 1638.

[154] Y. Shibata, K. Tanaka, *Angew. Chem.* **2011**, *123*, 11109.

[155] "Zinkstaubdestillation - RÖMPP, Thieme", can be found under https://roempp.thieme.de/lexicon/RD-26-00405, **2020**.

[156] S. Rej, N. Chatani, *Angew. Chem. Int. Ed.* **2019**, *58*, 8304.

[157] a) S. Kotha, K. Lahiri, D. Kashinath, *Tetrahedron* **2002**, *58*, 9633; b) A. Taheri Kal Koshvandi, M. M. Heravi, T. Momeni, *Appl. Organometal. Chem.* **2018**, *32*, e4210.

[158] "Niclosamid - RÖMPP, Thieme", can be found under https://roempp.thieme.de/lexicon/RD-14-01132, **2020**.

[159] *Index nominum 2000*. *International Drug Directory*, Medpharm Scientific Pub, Stuttgart, **2000**.

[160] Christina Kercher (geb. Bub), *Development of oxidative, redox-neutral and reductive C-N bond forming coupling reactions*, RWTH Aachen University, Aachen, **2021**.

[161] B. Özkaya, C. L. Bub, F. W. Patureau, *Chem. Commun.* **2020**, *56*, 13185.

[162] J. Vicente, J. A. Abad, F. J. Lahoz, F. J. Plou, *J. Chem. Soc., Dalton Trans.* **1990**, 1459.

[163] a) N. Guimond, S. I. Gorelsky, K. Fagnou, *J. Am. Chem. Soc.* **2011**, 6449; b) J. Li, Z. Qiu, *J. Org. Chem.* **2015**, 10686; c) Y.-F. Yang, K. N. Houk, Y.-D. Wu, *J. Am. Chem. Soc.* **2016**, 6861; d) J. Jayakumar, K. Parthasarathy, Y.-H. Chen, T.-H. Lee, S.-C. Chuang, C.-H. Cheng, *Angew. Chem. Int. Ed.* **2014**, 9889.

[164] S. Grecian, A. D. Wrobleski, J. Aubé, *Org. Lett.* **2005**, *7*, 3167.

[165] K. Park, G. Bae, J. Moon, J. Choe, K. H. Song, S. Lee, *J. Org. Chem.* **2010**, *75*, 6244.

6 Acknowledgments

My first and special thanks go to Prof. Dr. Frederic W. Patureau, who already supported me during my studies and the diploma thesis. Thank you very much for the opportunity to do research with you and for giving me the chance to do my doctorate. I have always appreciated and enjoyed the scientific freedom, the associated creativity and the trust placed in me. I would also like to thank you for the numerous scientific and non-scientific discussions and your mentorship.
I would like to thank Prof. Dr. Carsten Bolm for writing the second opinion. I would also like to thank Prof. Dr. Iris Oppel and Prof. Dr. Markus Albrecht, who were available as the third examiner and as examination chair.

Of course, a very special thank you goes to all the staff of the Department of Chemistry at the TU Kaiserslautern, as well as the staff of the IOC at the RWTH Aachen.
I would like to thank Dr. Harald Kelm for preparing crystal structures, his support with NMR-spectroscopy and the numerous scientific and non-scientific discussions. Furthermore, I would like to thank Dr. Uwe Bergsträßer, Dr. Irina Kemptner, Ruth Maria Bergsträßer, Christiane Müller, as well as Ludvik Napast and his team. Thank you very much for your support in the daily work. Another special thanks goes to Cornelia Vermeeren, who supported me especially in procurement processes, analytical questions and their implementation. I would also like to take this opportunity to thank our secretaries Gabriele Bertrand and Britta Steudel for their help with administrative work. Furthermore, I would like to thank the analytical department of the IOC for measuring the samples, as well as Dr. Christoph Räuber for measuring the NMR samples and supporting me with the evaluation.
A big thank you also goes to the current and former members of the Patureau working group. In particular, I would like to thank Vinzenz Thönnißen, Dr. Christina Kercher, Dr. Christian Rank and Dr. Congjun Yu for their support and the wonderful moments in the lab.
I would also like to thank my colleagues at the TU Kaiserslautern, especially Dr. Pascal Weingart, Dr. Marcel Jung, Dr. Philipp Kramer and Dr. Patrick Jost.

The biggest thank you goes to the people I met and grew fond of at the IOC. Thank you for the excellent working atmosphere, scientific discussions, the coffee breaks, beer and barbecue evenings and for your friendship. You made my time in Aachen unforgettable and I always felt at

home. In particular, I would like to thank Dr. Vinzenz Thönnißen, Dr Felix Krauskopf, Dr. Steven Terhorst, Dr. Christina Kercher, Dr. Anne-Katrin Bachon, Dr. Francesco Pucceti, Dr. Marc Calin, Dr. Plamena Staleva, Dr. Maximilian Bremerich, Marco Passia and Dr Jan-Hedrik Schöbel, Dr. Victoria Pfennig, Dr. Christian Schuhmacher to name a few. Thanks again to those who proofread this thesis.

The last thanks, of course, goes to my family, especially my parents and my brother, and friends from my studies. Thank you so much for your support and encouragement during this time. Without you, this would not have been possible. In particular, I would like to thank Stefan Mattern, who has always supported me for 12 years and has become part of my family. I would also like to thank Maximiliane Engelhardt, who has always been a reliable and wonderful support during our time together.