Exploiting the C-H bond in metal-catalyzed C-C bond-forming reactions

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Dedicated to the memory of Prof. Alan R. Katritzky

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Abstract

This account summarizes our work in the field of direct C-H bond functionalization. We have explored methods in the area of directing group assisted C(sp^2)-H and C(sp^3)-H activation and investigated arylation as well as deuteration reactions. In these transformations either ruthenium or palladium catalysts were applied. In case of C(sp^2)-H activation, we developed a protocol for the synthesis of ortho arylated anilines and disclosed the first method for a direct arylation in a continuous flow reactor. Additionally, we applied a direct arylation in the synthesis of compounds which can accelerate cell differentiation. In the field of C(sp^3)-H activation we developed a protocol for the selective mono-arylation of piperidine and three different arylation protocols for acyclic amines employing either aryl chlorides, aryl bromides, aryl iodides, or arylboronic acid esters as the aryl donor.

Keywords: C-H activation, direct arylation, deuteration, concerted metalation deprotonation, palladium, ruthenium

Table of Contents

1. Introduction

The field of organic synthesis can be considered as well established and matured with great achievements throughout its history.[1] Today it is believed that we can synthesize almost any given molecule (which is thermodynamically stable) no matter whether it is a simple synthetic small molecule or a complex natural product. This statement might be largely true (with some exceptions) but it does not include information on the efficiency of a synthetic sequence. Nowadays, any new transformation developed is looked at also from the viewpoint of efficiency regarding various aspects. For a new method to be of use and to be accepted and applied in the synthetic community it has to offer advantages over established protocols such as replacement of a toxic or otherwise hazardous reagent, substitution of an environmentally problematic solvent by e.g. water, the possibility to use milder reaction conditions, an increase in functional group tolerance and generality of a protocol, or avoidance of elaborate workup and purification procedures to mention only a few. Also the use of reagents in a catalytic fashion is highly attractive for increasing efficiency of synthetic reactions. Here, metal catalyzed cross-coupling reactions[2,3] have been very successful during the last decades, which were recognized by the Nobel Prize in chemistry 2010 for Akira Suzuki,[4,5] Ei-ichi Negishi,[6,7] and Richard Heck[8] for their achievements in this field.

As it is generally known, most of the cross-coupling reactions take advantage of an organometal reagent and a halide or pseudohalide (e.g. triflate) component for the C-C bond formation process (Figure 1).[2] Neither of these two functional groups remains in the final product and has to be considered as “waste” in these reactions.

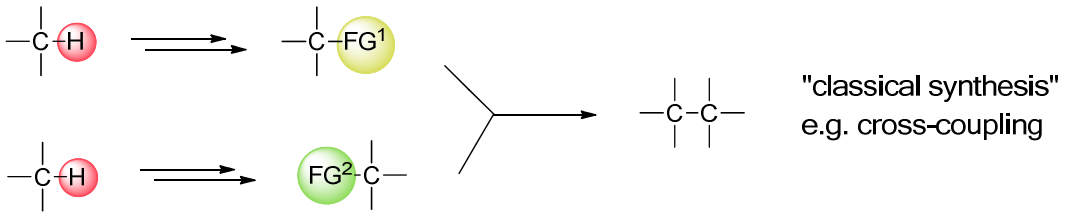


Figure 1

Two cross-coupling reactions show a noteworthy difference towards others. The Heck[9] and the Sonogashira[10] reaction, usually listed as cross-coupling reactions, do not rely on an

organometal species but react a C-H bond with a halide species. Hence, they show all aspects of a C-H activation reaction and their listing as cross-coupling reactions can be explained by the historical context of the times in which they were developed.

So actually, metal catalyzed C-C bond forming reactions which can rely on only one pre-functionalized coupling partner were reported already early on. However, only since the beginning of the new millennium the potential of such methods was fully recognized and the field started to expand rapidly. A C-H activation reaction,[11-17] as we understand the term nowadays, can be generalized as shown in Figure 2. Elimination of one functional group from the starting materials (as compared to a cross-coupling reaction) can greatly contribute to increased reaction efficiency.

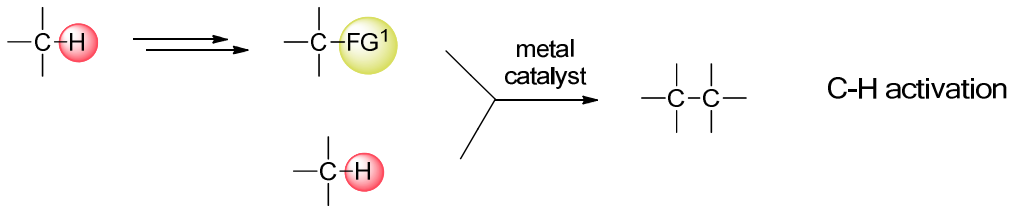


Figure 2

For this type of reactions, the term *C-H activation* has become generally accepted vocabulary among the community of synthetic organic chemists. Within this account we present our research efforts in this field.

2. Discussion

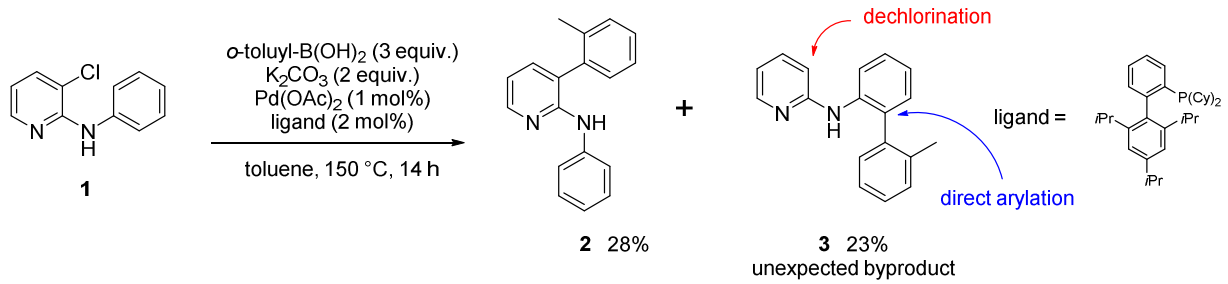
The field of C-H activation chemistry is a very diverse one. It starts already with the type of C-H bond to be activated, since these can be sp, sp^2 or sp^3 hybridized. Furthermore, residues to be introduced can be selected from a wide range of different moieties and functional groups, and different methods have been reported to achieve C-H functionalization. Furthermore, a certain method might have different mechanistic pathways through which it can proceed. This is also reflected in our work in this area, in which we investigated C(sp^2)-H and C(sp^3)-H activation reactions via one-site C-H functionalization methods where we could show that the very same products can be formed via different reaction mechanisms. Besides method development, we were also aiming to apply our chemistry to the synthesis of biologically relevant molecules. In the following subchapters these topics are discussed in detail.

2.1. Investigations of C(sp^2)-H activation

Direct arylation of arenes ortho to a directing group is an efficient method for the synthesis of biaryl motifs. The groups of Miura and Murai pioneered research on direct arylation protocols initially focusing on palladium catalysis,[18-19] and later extending to ruthenium.[20] Already in 1996 Miura disclosed the arylation of 2-phenyl-phenol in ortho position of the phenol ring as a side

note in a paper on aldehyde C-H activation towards benzophenone derivatives.[18a] Since these early examples, the field of metal catalyzed direct arylation of arenes ortho to a directing group has expanded almost exponentially and reviews on the matter have been published regularly.[21-22] The directing group most frequently applied is pyridine, even though it cannot be removed after the arylation step in many cases.[23-28] Still, 2-phenylpyridine is often the first substrate to be tested for a certain set of reaction conditions since a new method can be compared with a number of existing protocols. Also we have taken advantage of pyridine as a directing group, however we focused on protocols which allow cleavage of the directing group after arylation took place.

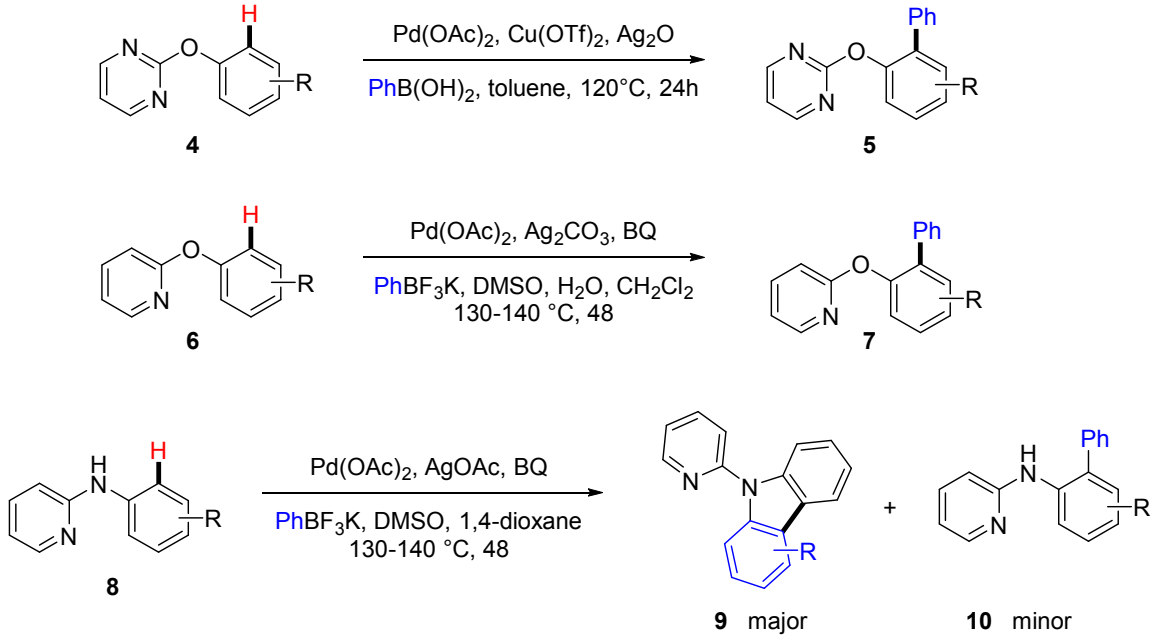
2.1.1. Pyridine directed C(sp^2)-H activation of arenes towards ortho-arylated anilines.[29] Our first entry in the field of pyridine directed arylation was initiated by a side reaction we observed in another research program. For some time we were investigating different aspects of cross-coupling reactions on pyridine derivatives.[30-33] In an effort to synthesize *N*-arylated-4-arylpyridin-2-amines we investigated Suzuki-Miyaura cross-coupling between a series of arylboronic acids and *N*-aryl-3-chloropyridin-2-amines. When 2-methylphenylboronic acid was the coupling partner, side product **3** was formed besides the desired product **2** (Scheme 1).[30] Obviously, **3** was formed via a direct arylation reaction, which was in this case accompanied by a dechlorination of pyridine as well.



Scheme 1

The direct arylation of this substrate was remarkable due to the geometry of the palladacycle which should be formed in the C-H activation step. In the observed case the reaction has to proceed via a 6-membered palladacycle, since pyridine is not directly attached to the arene to be arylated, as it is the case in most literature examples where a 5-membered metallacycle is formed. This increased ring size is due to the "amine linker" present in our substrate. When checking the literature for similar transformations, we found that just two pyridine directed arylations were reported which have a heteroatom linker between pyridine and the aryl ring to be functionalized (Scheme 2) at the moment we started our research on this topic. In these papers phenoxypyrimidines **4**[34] and phenoxypyridines **6**[35] were applied as substrates. An example for an amine linker was not published at that time, but was disclosed later when we were already preparing our manuscript. In that case *N*-phenylpyridinamines **8**[36] were used as substrates which

were first arylated ortho to the amine group and then further cyclized to *N*-pyridin-2-yl carbazoles **9**. The ortho-arylated non-cyclized product **10** was only isolated in small amounts as byproduct.

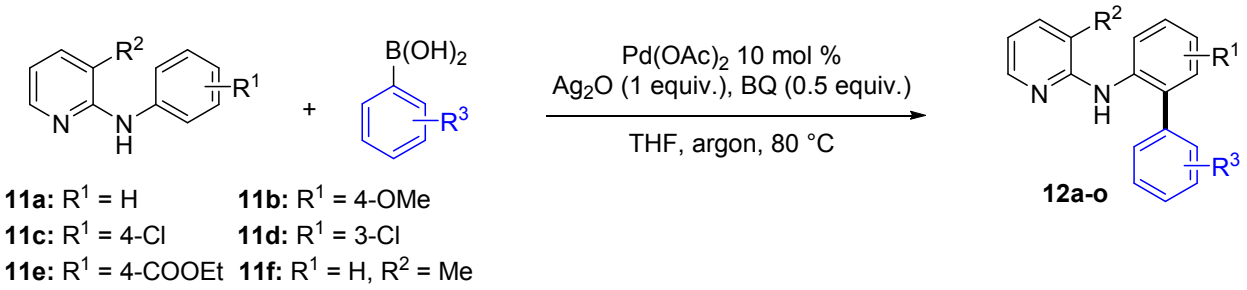


Scheme 2

We wanted to develop this side reaction in a useful protocol for the ortho arylation of anilines. Hence, two prerequisites had to be fulfilled: 1.) the former side reaction should become the major process; 2) in the end, cleavage of the pyridine directing group had to be achieved.

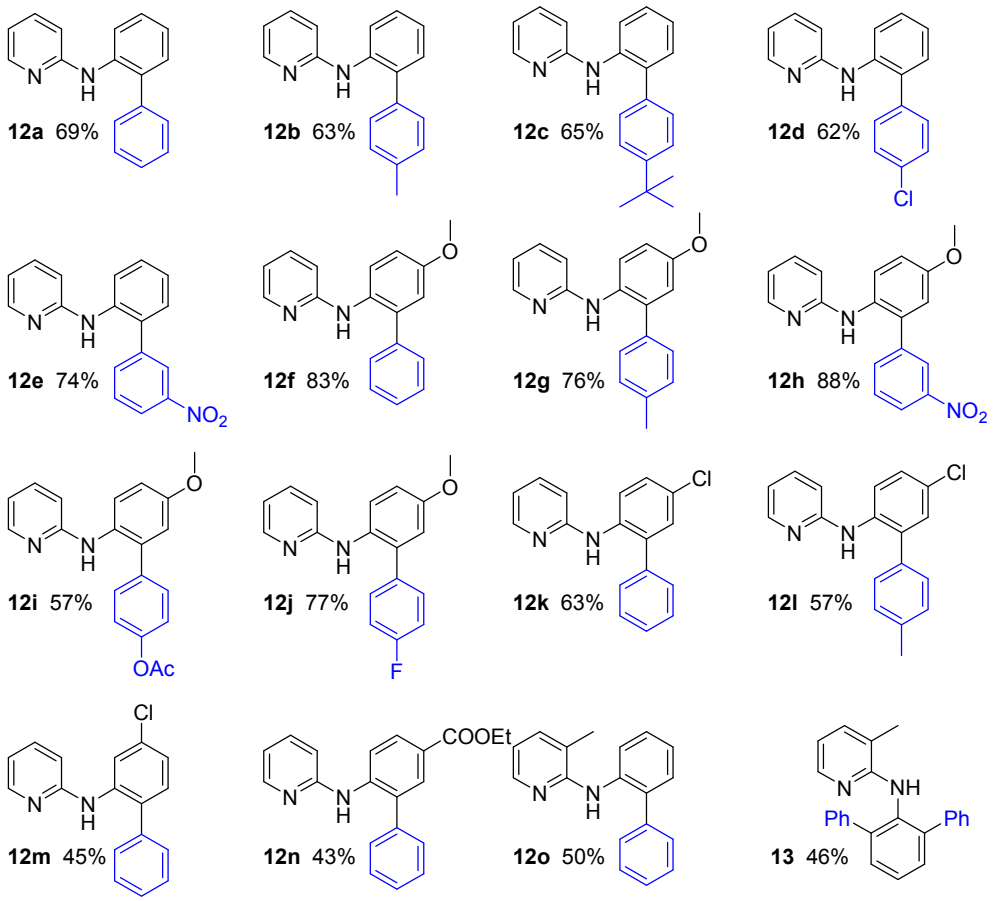
As starting point for reaction optimization we used our Suzuki-Miyaura coupling conditions and the two protocols for arylation of **4** and **6**. In the arylation of **4** and **6** (and also of **8**) an oxidant had to be added in order to get good conversion and yield. Additionally, high reaction temperature was required. In case of substrates **6** a complex mixture of solvents had to be applied which makes this transformation less convenient in handling. After extensive screening of reaction conditions we identified a protocol which could address these shortcomings (Scheme 3).

We could use THF as the sole solvent at 80 °C, a considerably lower temperature compared to literature protocols which required up to 140 °C.[34-36] Ag_2O and benzoquinone (BQ) were required as additives, both acting as oxidants and in case of BQ as ligand as well most likely. When carrying out the reaction in absence of Ag_2O the reaction still gave conversion even though to a lower extent. In absence of benzoquinone the reaction was shut down completely, demonstrating that BQ must have another effect besides just being an oxidant.



11a: R^1 = H **11b:** R^1 = 4-OMe
11c: R^1 = 4-Cl **11d:** R^1 = 3-Cl
11e: R^1 = 4-COOEt **11f:** R^1 = H, R^2 = Me

Scheme 3

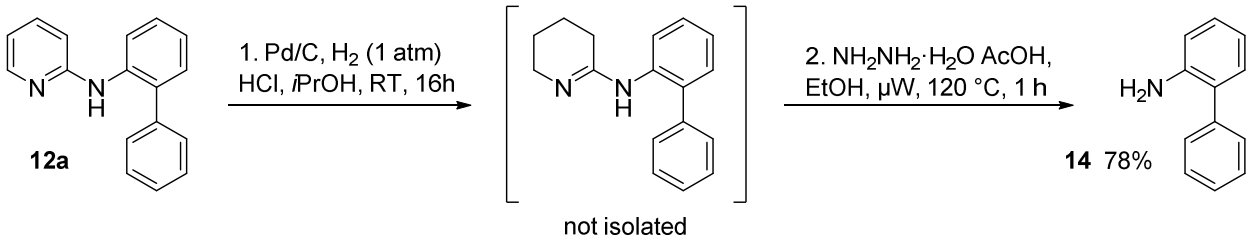


Scheme 4

The substrate scope proved to be substantial, both with respect to the substrate **11** as well as to the boronic acid coupling partner (Scheme 4). It can be seen that electron-donating and electron-withdrawing substituents on the boronic acid were well tolerated (Scheme 4, examples **12a-e**). In case of substrate **11b**, which carries a methoxy group in para position to the amine, even higher yields were obtained (Scheme 4, **12f-j**). A para-chloro substituent did not show this yield increasing effect and arylation of **11c** gave similar yields as compared to the unsubstituted

11a. A meta-chloro substituent as in **11d** or a para-COOEt substituent as in **11e** showed significantly lower yield (Scheme 4, **12m**). In all these examples only mono-arylation took place, which is actually remarkable for a pyridine directing group since often no selectivity between mono- or bis-arylation is observed. However, substrate **11f** which carries a methyl group in position 3 of the pyridine directing group gave a mediocre yield of 50%. In this case bisarylation to **13** was observed as well, which explains the lower yield. Increasing the amount of phenylboronic acid to 6 equivalents in the reaction with **11f** led to a 1:1 mixture of **12o** and **13** in 45% and 46% respectively. The methyl group seems to enable a conformation in which the second ortho-position points towards the pyridine ring enabling a second arylation to occur.

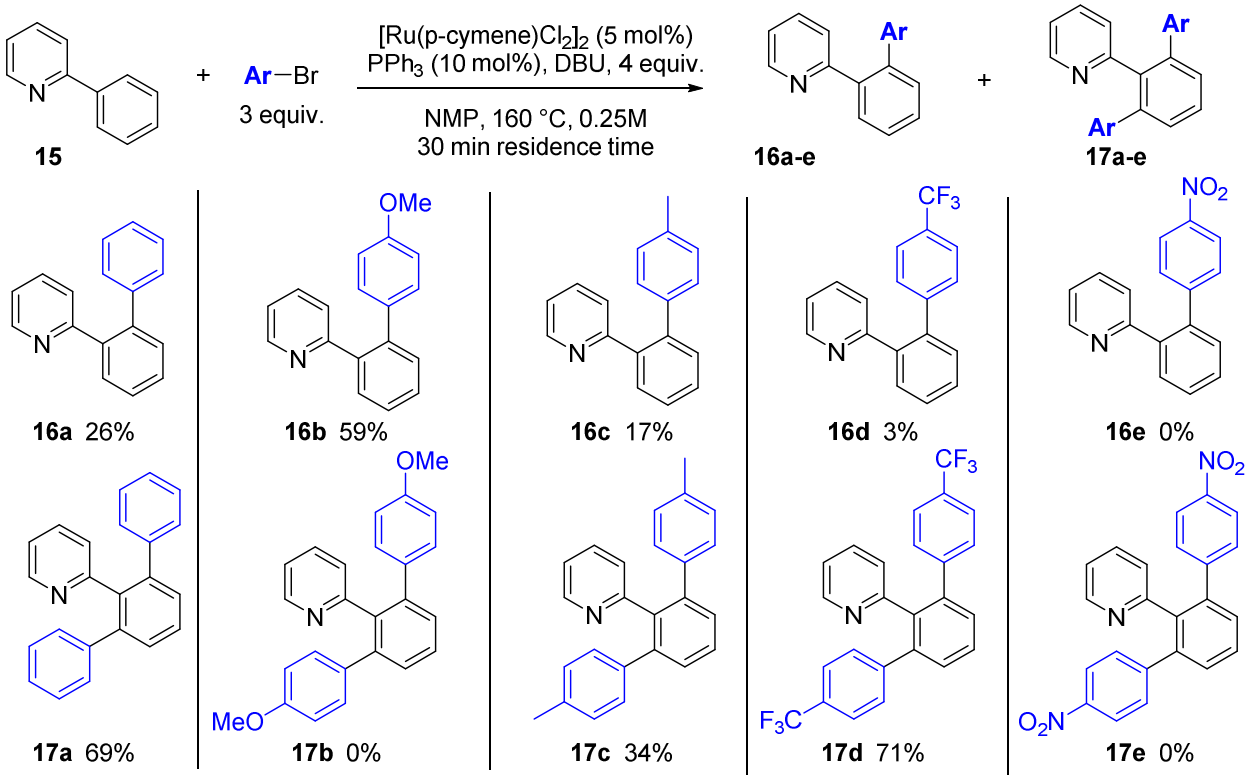
Finally, we could demonstrate the cleavability of the pyridine directing group via a protocol established by Maes and coworkers.[37] Initial reduction of the pyridine followed by hydrolysis led to 2-phenyl aniline **14** in 78% yield (Scheme 5).



Scheme 5

2.1.2. Direct arylation of 2-phenylpyridine in continuous flow.[38] Synthesis in continuous flow has emerged as a very active research field in recent years with series of organic reactions carried out under such conditions. Additionally, complete reaction sequences towards complex molecules have been carried out under flow conditions.[39-41] However, direct arylations have not been included in this reaction portfolio so far. Hence we set out to develop such a protocol.[38] As substrate we picked 2-phenylpyridine since many reaction conditions for directly arylating this system have been disclosed and we were confident to be able to identify conditions which would enable direct arylation under continuous flow conditions. We quickly realized that a method taking advantage of a heterogeneous catalyst was inefficient since we observed considerable leaching of the metal in all cases (e.g. from PdEnCat or Pd/C). Hence we shifted our attention to a protocol under homogeneous conditions. One restriction in flow chemistry is the residence time in the reactor which cannot be extended to many hours in most cases. Hence a protocol was required which could be performed within a short period of time. Screening literature conditions, we identified a ruthenium (II) catalyzed method which could be modified in a way that it fulfilled our requirements.[42,43] There, NMP was used as solvent at 120 °C in combination with $[RuCl_2(h^6\text{-}C_6H_6)]_2$ as catalyst. Even though the reaction time was 20h, NMP as solvent would allow us to increase the temperature significantly in order to accelerate the reaction.

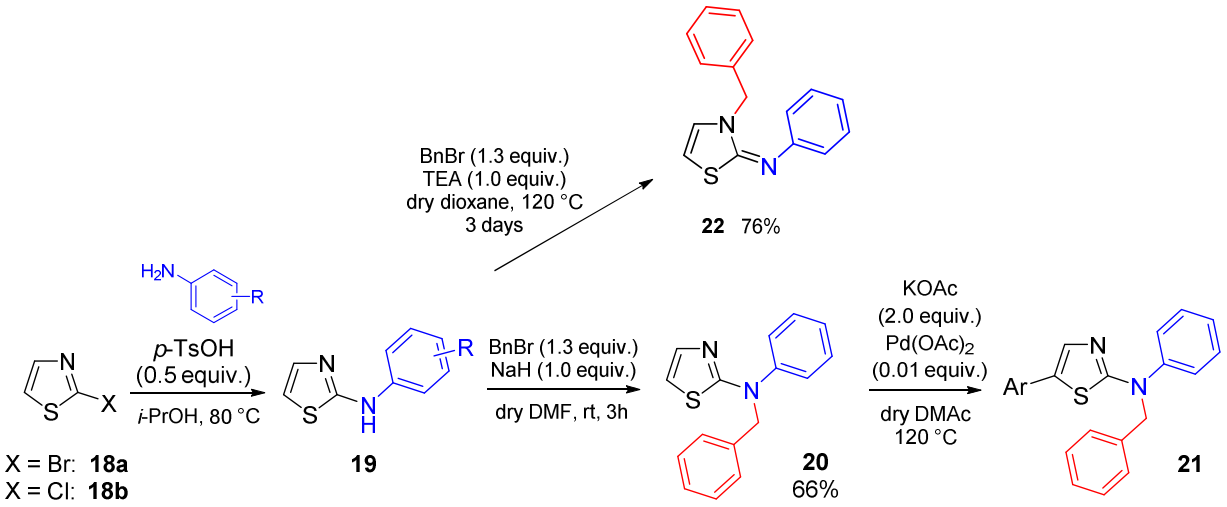
In our case, it was important to use an organic base in order to avoid precipitation of formed salts and a high boiling solvent in order to increase the reaction temperature to a value which allowed a rapid reaction. We identified DBU as suitable base and NMP as solvent at 160 °C. Our results are summarized in Scheme 6. As it was expected, mixtures of mono- and bis-arylated products were formed in some cases, which is usually the case when substrate **15** is directly arylated. Noteworthy, the ratio between the monoarylated product **16** and the bisarylated product **17** correlated with the electronic effects of the aryl bromide coupling partner. A strong electron-donating substituent (*p*-methoxy) gave mono-arylation exclusively (**16b**) whereas a strongly electron-withdrawing substituent (*p*-CF_3) led to almost exclusive formation of bisarylated product **17d**. Neutral or weakly donating substituents led to various ratios of the two products. In case of **16c** and **17c** the products were obtained as an inseparable mixture and yields were determined by NMR analysis of the mixture. A nitro group was not tolerated, most likely due to the metal coordinating ability of the nitro group, which renders the catalyst unable to carry out the direct arylation reaction.



Scheme 6

2.1.3. Direct arylation of thiazole-2-amines towards cell differentiation accelerators.[44] Besides method development in C-H activation chemistry we also aim to apply these methods in the synthesis of functional molecules. We had identified a compound class which showed interesting activity in the field of cell differentiation modulators.[45] More precisely, *N*-

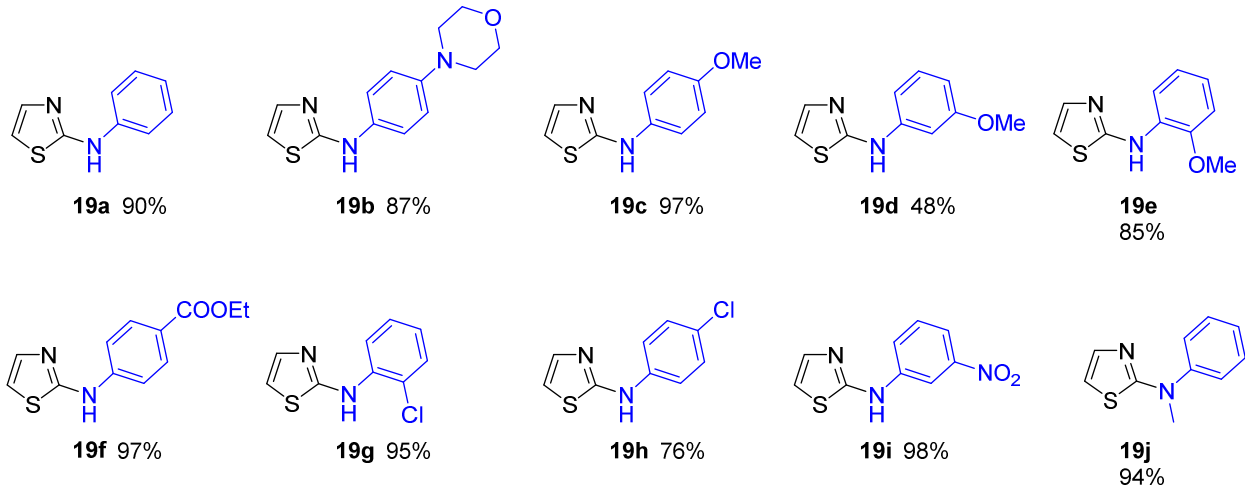
phenylthiazoleamines of the general structure **21** showed an accelerating effect on cell differentiation of C2C12 cells, a lineage committed mouse cell line which forms skeletal muscle cells. When C2C12 cells were treated with compounds of type **21**, the differentiation to skeletal muscle cells was significantly accelerated (for details see reference 43). Even though we have gained significant experience in Stille and Suzuki-Miyaura cross-coupling of thiazoles over the years,[46-50] we decided to use a palladium catalyzed direct arylation reaction in the final step of the synthesis since we could avoid pre-functionalization of the thiazole system. Hence, we envisioned an overall synthetic sequence as depicted in Scheme 7.



Scheme 7

Initially, the arylamine should be introduced in position 2 of thiazoles **18a,b** via a nucleophilic substitution of either Br or Cl with aniline derivatives to give intermediate **19**. Then, the benzyl group should be attached to the exocyclic nitrogen to the key building block **20**. Finally, the aryl group in position 5 should be introduced via a direct arylation reaction towards the target compounds **21**. The first step, the nucleophilic substitution gave excellent yields (Scheme 8) in a number of examples, however it required very long reaction time (up to 3 weeks). The robustness of this first step is demonstrated by the fact that electron-rich anilines (**19b-e**), electron-deficient ones (**19f,i**) and especially also sterically demanding ones (**19e,g**) were well tolerated.

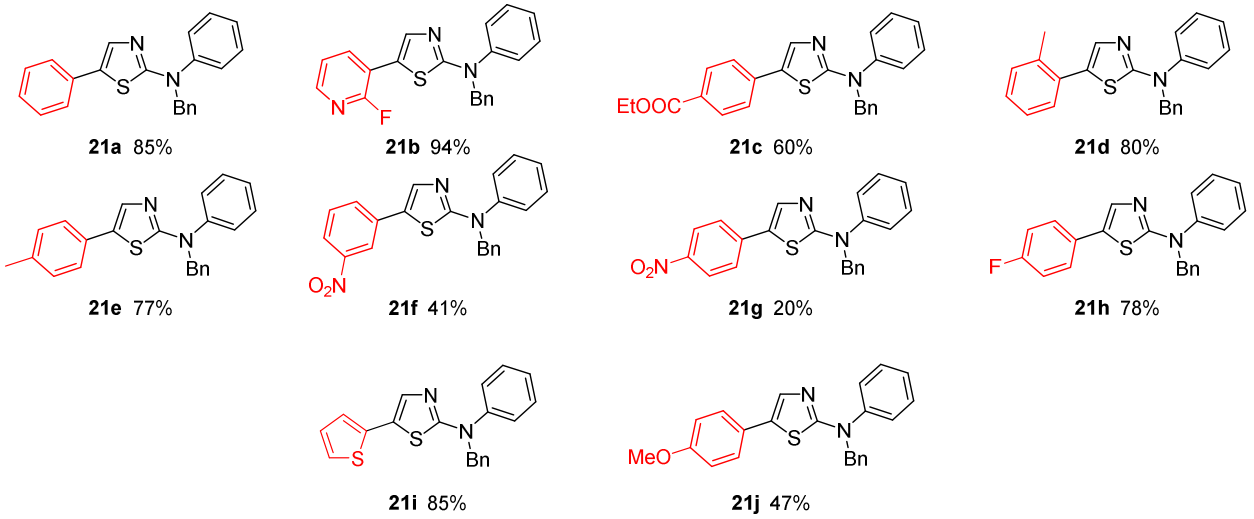
The benzylation step proved to be less straight forward as expected since not only the exo- but also the endocyclic nitrogen was benzylated to give byproduct **22**. However, we succeeded in developing two complementary protocols for synthesizing either the one or the other predominantly. Using triethylamine as weaker base the endocyclic nitrogen was benzylated preferentially (Scheme 7, **22**, 76%), when using as stronger base NaH the exocyclic nitrogen was the preferred center of reaction (Scheme 7, **20** R = H, 66%).



Scheme 8

With Intermediate **20** in hand we set out to investigate the direct arylation in position 5 of thiazole. Based on a protocol reported by Dixneuf and coworkers,[51] we developed a method which led to the target molecules in good yields using aryl iodides as the aryl donors. The final conditions used 1 mol% of $Pd(OAc)_2$ and no additional ligand. KOAc was used as base (2 equiv.) in dry DMAc at 120 °C. The procedure proved to be very robust since a number of arenes and also heteroarenes could be introduced in good yields (Scheme 9). Iodobenzene gave a good yield of 85% (**21a**) and also the heterocyclic examples **21b** and **21i** were obtained in good to excellent yield. Again steric bulk was well tolerated (**21b,d**) and also residues with no M effect (**21e,h**). However, a nitro group either in meta or para position gave significantly lower yield (**21f,g**) and also a para-MeO group led to a drop in yield below 50% (**21j**).

Reports on the biological results can be found in our original publication.[43]

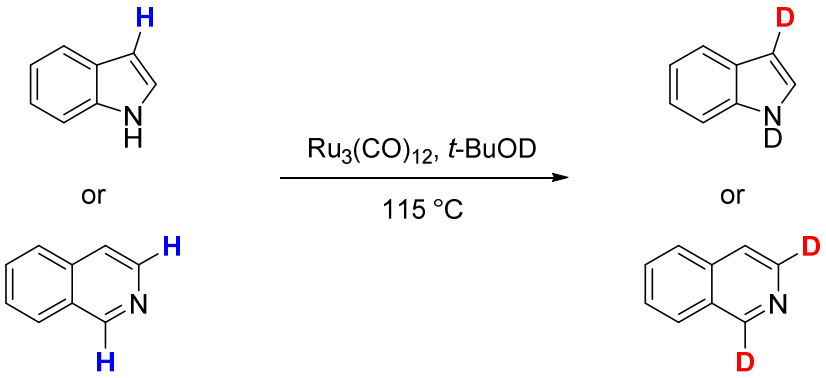


Scheme 9

2.2. Ruthenium catalyzed hydrogen-deuterium exchange of aliphatic and aromatic systems[52]

So far we discussed only arylation reactions under palladium catalysis. However, other transition metals are very successful as well in C-H activation chemistry, one of them being ruthenium. When someone wants to develop a method for the direct functionalization of a C-H bond, it can be of great use to find out whether the catalyst in use can insert into the C-H bond in question. We thought this could be most easily checked by exposing a given substrate to a metal catalyst in presence of a deuterium source. If C-H insertion can occur (and if it is reversible), an equilibrium between protonated and deuterated compound should be seen which could be tracked in NMR easily. Another reason to investigate in metal catalyzed H-D exchange reactions is the fact that deuterated compounds are of immense importance for kinetic studies of organic reactions.[53,54] Hence, their efficient synthesis is also important.

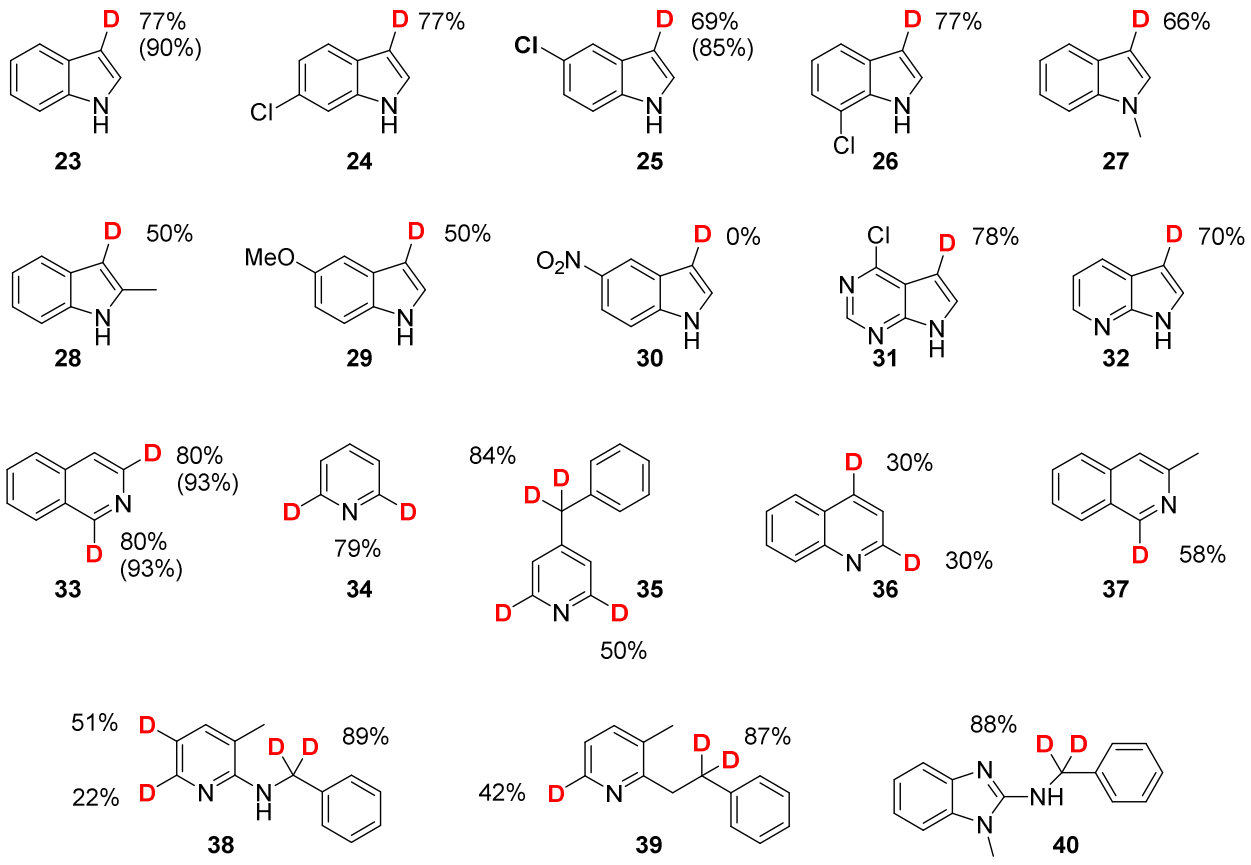
$Ru_3(CO)_{12}$ was reported to be able to undergo C-H insertion in a series of C-H bonds, mainly of aliphatic systems.[55] Hence this catalyst seemed to be well suited for a first study in this direction. As deuterium source should serve a deuterated protic solvent and we selected deuterated *t*-butanol (*t*-BuOD). We started with 5 equivalents of this solvent (per exchangeable position) which should lead to a maximum of 83.3% deuterium incorporation in case C-H cleavage is a reversible process.[56] As model substrates indole and isoquinoline were chosen and we expected H-D exchange in positions 1 and 3 in both cases (Scheme 10).



Scheme 10

Indeed, in case of indole we isolated the product with a deuterium incorporation of 77% in position 3 whereas the N-D was quickly transformed back to N-H by small amounts of water (e.g. present in the NMR solvent). In case of isoquinoline it was expected that C1 and C3, the positions adjacent to the ring nitrogen, would be prone to C-H insertion and subsequent H-D exchange. Also in this case the reaction worked well and we isolated 1,3-bisdeuterated isoquinoline with 80% deuterium incorporation in both positions. In order to increase the deuteration degree we stripped of the solvent, added fresh *t*-BuOD, and subjected the two products to a second round of deuteration again using 5 equivalents of deuterium source per

exchangeable position. In case of indole this led to a deuteration degree of 90% in position 3 and in case of isoquinoline to an even higher deuterium incorporation of 93%, the theoretical value being 96.8%.[52] With these protocols in hand we explored the substrate scope of the deuteration reaction and the results are summarized in Scheme 11 (deuteration degrees in brackets correspond to the two step protocol). As can be seen, indole substrates were nicely deuterated close to the theoretical value in most cases (**23-27**), one exception being 5-nitroindole **30**, which did not react at all. Such an effect of a nitro group we have seen throughout all our ruthenium catalyzed reactions as will be shown in the upcoming sections. A significant decrease in deuterium incorporation was also seen in case of 2-methylindole **28** and 5-methoxyindole **29**. This deuteration reaction is not limited to indole since also 7-azapurine **32** and deazapurine **31** worked well. Additionally, 6-membered nitrogen heterocycles such as isoquinoline **33** and pyridine **34** showed high deuterium incorporation. Interestingly, quinoline **36** gave a significantly worse result and also 3-methylisoquinoline did not reach similar high deuterium content as isoquinoline. We also investigated systems in which C(sp^3)-H and C(sp^2)-H bonds can be exchanged. Interestingly, in all these examples we found the highest deuterium content in the aliphatic positions (**35**, **38-40**). Additionally, indole derivatives can be deuterated under microwave irradiation as well, which shortens the reaction time from 3 hours to 15 minutes.[48]



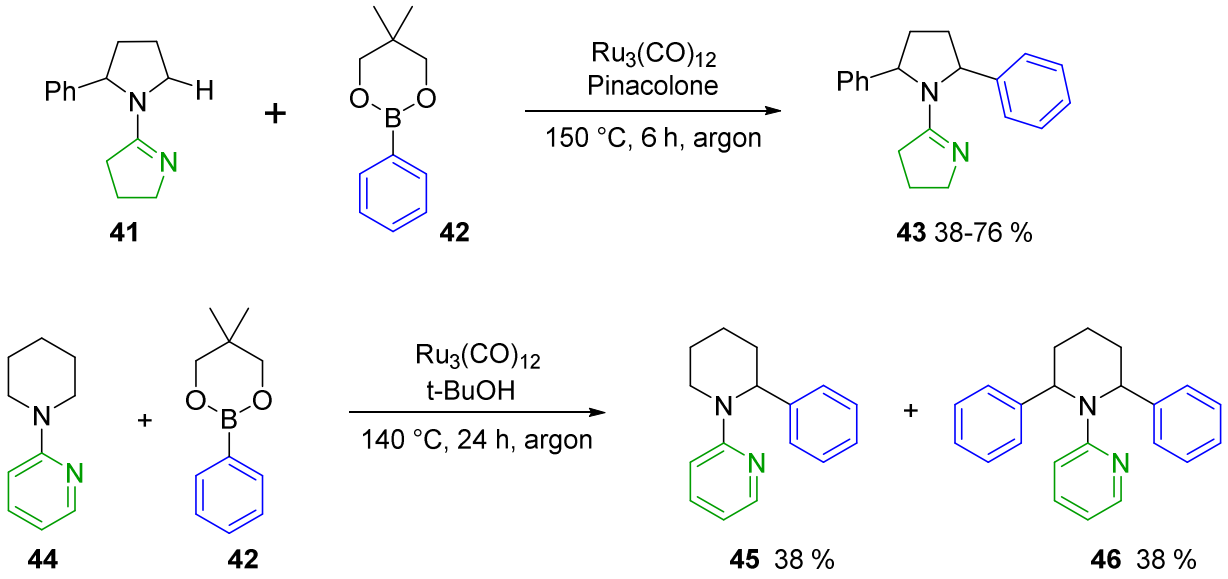
Scheme 11

It has to be mentioned that our protocol can be exploited for tritiation reactions as well which we showed in a proof of principal experiment: CF_3COOT is commercially available and should be convertible to *t*-BuOT easily. We demonstrated this by mixing CF_3COOD with *t*-BuONa which gave us CF_3COONa and *t*-BuOD, which we used in our deuteration reaction successfully.

2.3. Investigations of C(sp^3)-H activation

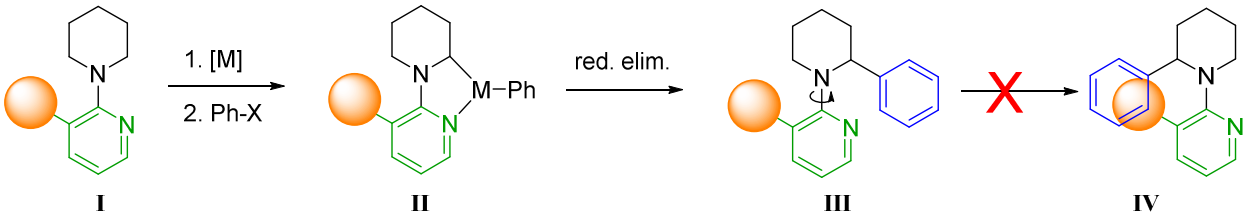
Besides our efforts in C(sp^2)-H activation we dedicated our research to C(sp^3)-H activation early on. This area is much more challenging since it turned out that aliphatic C-H bonds are much harder to activate in a selective manner as compared to aromatic ones.[57-59] This is reflected in literature as well where much more contributions on C(sp^2)- rather than C(sp^3)-H activation are reported. Our focus was on direct arylation methods of cyclic and acyclic amines and we have contributed to this field with several protocols.

2.3.1. Selective mono-arylation of cyclic amines under neutral conditions.[60] The direct arylation of cyclic amines, especially pyrrolidines was pioneered by the group of Sames.[61] They used $Ru_3(CO)_{12}$ as catalyst and boronic acid esters as the arylating reagent. As directing group a cyclic imine was used, which could be cleaved after the arylation as well (Scheme 12). One problem the authors observed was that a selective monoarylation of pyrrolidine could not be achieved. If both positions α to the pyrrolidine nitrogen were unsubstituted mixtures of mono- and bisarylated products were obtained. Hence, they used substrates which carried a substituent in one of the α-positions already and introduced only the second substituent via their methodology.



Scheme 12

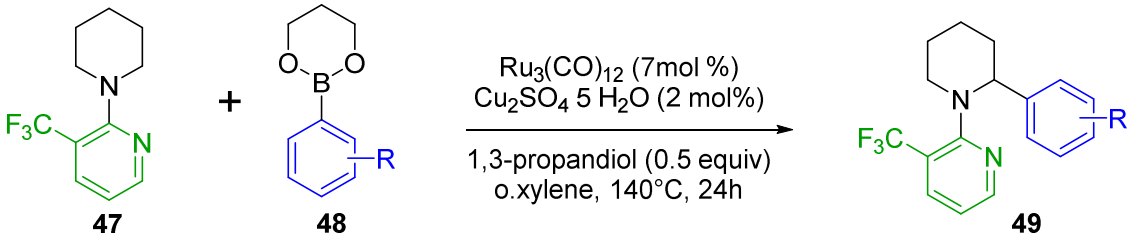
Later, Maes and coworkers published a study dedicated to the direct arylation of piperidines, this time directed by pyridine.[37] They observed the same problems with competing bisarylation as the group of Sames did on the pyrrolidine system. We wanted to address this shortcoming and hypothesized that a suitable directing group would allow for a selective mono-arylation. Our idea was to introduce steric bulk to the directing group which should disfavor after the first arylation a conformation of the intermediate which would allow a second arylation step. Our concept is displayed in Scheme 13. If the directing group applied carries a bulky substituent in the position ortho to the piperidine as in **I**, the first arlation towards **III** via **II** should be facile. For a second arylation, a rotation around the pyridine C2 and the piperidine N bond by 180° would be required to get to the conformer **IV** which could undergo a second direct arylation. However, this should be prevented by the bulky group and hence only monoarylation should take place.



Scheme 13

We decided to use pyridine as directing group since it proved to be efficient in the example of Maes. As blocking group CF_3 was chosen, since the very same directing group proved to be efficient in a related research topic we investigated (see Sections 2.3.2–2.3.4). Already from the beginning of our optimization efforts we never detected any bisarylation product and only monoarylation was observed demonstrating the validity of our hypothesis. However, conversion and GC yield of the product was unsatisfactory at the beginning. Initially we used $Ru_3(CO)_{12}$ as catalyst but only reached conversion just above 50%. An improvement came by the addition of metal salts as co-catalysts. We tested several Pd, Fe, and Cu salts and finally identified $Cu(II)SO_4.5H_2O$ as best performing one giving 87% conversion (69% GC yield) and 60% isolated yield in our test reaction (Table 1, entry 1). Using these conditions we set out to investigate the substrate scope of our protocol. It turned out that this transformation was very delicate regarding electronic influences since either electron donating or electron-withdrawing substituents led to a decrease in yield (Table 1, entries 2-6). Also substituents on the piperidine ring were not well tolerated. Hence, the yields are mediocre but still they are in the same range or even better as compared to the protocol reported by Maes.[56] Additionally, purification is simple since substrate and monoarylated product can be separated easily. On the other hand, separation of mono- and bisarylated products is difficult as reported in literature.[56]

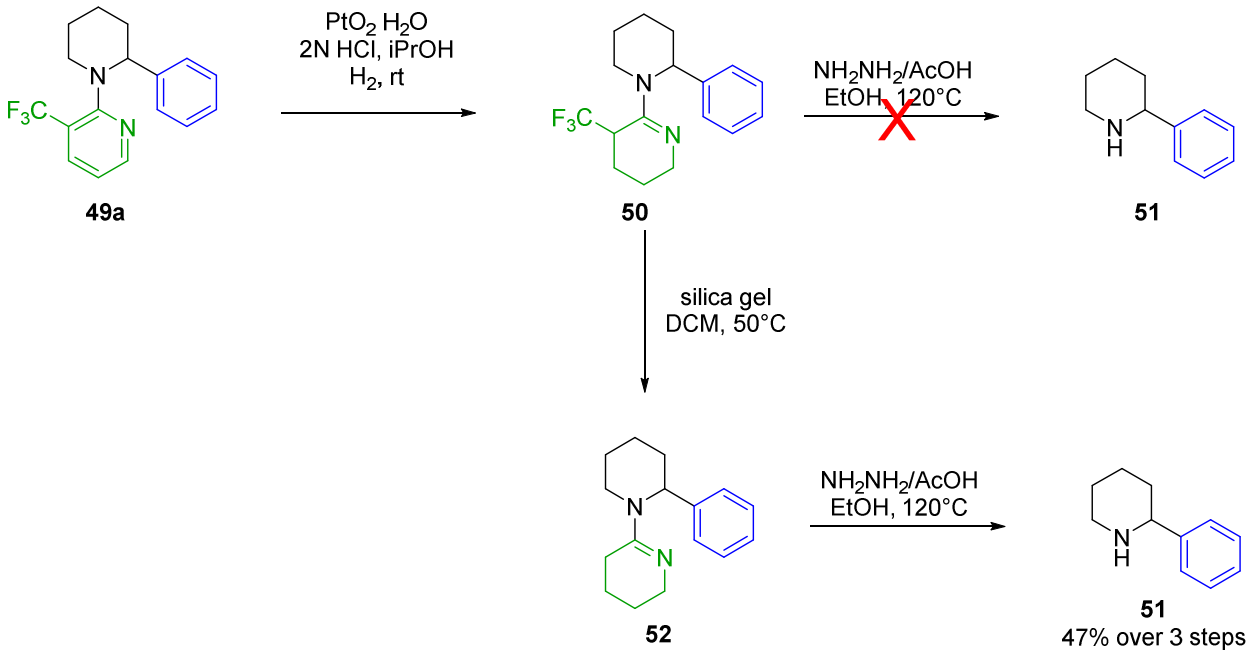
Table 1



Entry	Product	R	Conversion	Yield [%]
1	**49a**	H	82%	60%
2	**49b**	4-CH_3	65%	47%
3	**49c**	4-*t*Bu	75%	50%
4	**49d**	4-CF_3	61%	40%
5	**49e**	4-F	74%	43%
6	**49f**	3-CH_3	71%	49%

Finally, cleavage of the directing group was investigated which led to surprising results. Initially we believed that we could cleave the directing group by simple hydrogenation and subsequent hydrolysis as reported previously (Scheme 14).[56] However, it was found that after the hydrogenation the hydrolysis did not work and led to decomposition and only small amounts of deprotected product. In these experiments we always tried to carry out the two steps required for deprotection in a one pot fashion. Since hydrolysis was identified as the problematic step, we wanted to isolate the reduced intermediate and to investigate the hydrolysis step in detail. To our surprise, after column chromatography of the intermediate the CF_3 group was not present in the molecule anymore! This indicates cleavage of the CF_3 group in presence of silica gel. Hence, we stirred intermediate **50** in presence of silica gel and indeed observed complete detrifluoromethylation within 2.5 hours at 50 °C. To the best of our knowledge such a CF_3 cleavage has not been reported in literature previously. Luckily this served our purpose perfectly since the resulting product **50** can be easily hydrolyzed using literature conditions. Additionally, the three steps hydrogenation, detrifluoromethylation and hydrolysis can be carried out without isolation of the intermediates giving 2-phenylpiperidine **51** in 47% over all three steps. This is exactly the same yield as reported for deprotection of unsubstituted pyridine which indicates that cleavage of the CF_3 group is quantitative.

Overall we developed a competitive protocol for selective monoarylation of piperidine which is in spite of mediocre yields still competitive in comparison to other methods published so far,[56] especially due to facile isolation of the monoarylated products.



Scheme 14

2.3.2. Arylation of acyclic amines under neutral conditions.[62-63] A relatively neglected research topic was the direct arylation of acyclic amines. Hence we decided to work in this field and selected benzylamine as initial test system since the structural motif of α,α-bisarylated amines occurs in a number of biologically active compounds (Figure 3).[64-66]

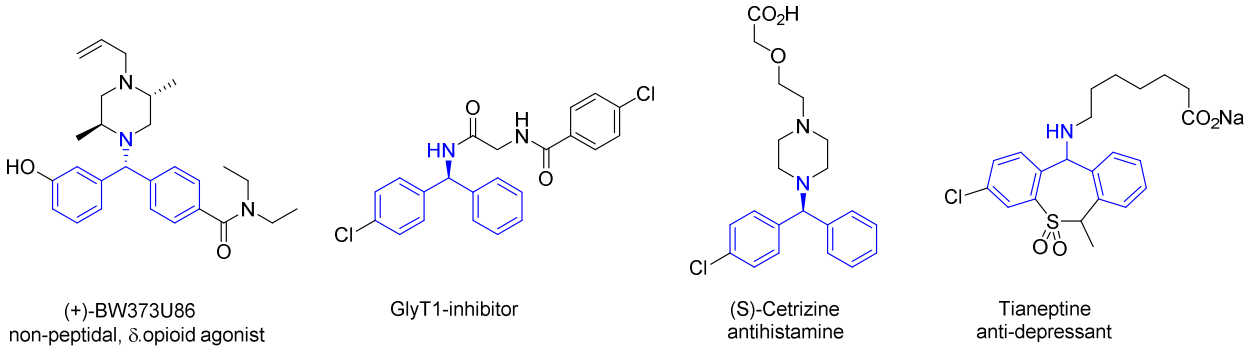
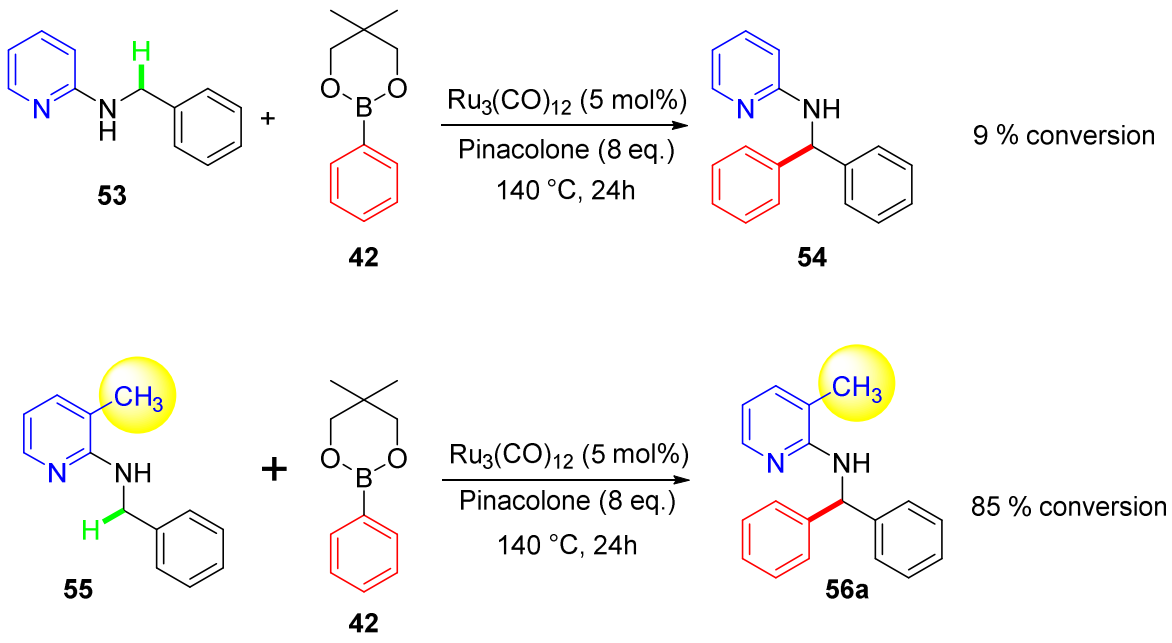


Figure 3

For a first test reaction we choose benzylamine carrying a directing group on the amine group. Amongst the many groups we tested, only pyridine gave a low conversion of 9% towards **54** starting from **53**. However, with a small change in the directing group, i.e. introduction of a methyl group in position 3 (substrate **55**), we could improve conversion to **56a** to 85% (Scheme 15).



Scheme 15

The same effect was already observed in alkenylation reactions of the same substrates. The rational for this tremendous change in conversion by such a small modification is that in presence of the methyl group a different conformation of the substrate is favored as compared to the unsubstituted directing group. The steric bulk of the methyl group introduced favors a conformation where the pyridine nitrogen points towards the benzylic CH_2 group to be arylated (Figure 4, bottom left). Only then the ruthenium catalyst is close enough to the C-H bond which shall be cleaved and the reaction can proceed. We carried out DFT calculations and found that in presence of the methyl group the conformation which enables C-H insertion is 4.4 kcal/mol lower in energy, which explains the much higher conversion. In absence of the methyl group (numbers in brackets) the difference is actually negligible with 0.5 kcal/mol only.

With suitable reaction conditions in hand we carried out substrate scope investigations. First, the effect of substituents on the boronic acid ester coupling partner was investigated (Scheme 16). It turned out that electron-neutral substituents were most efficient (**56a-c,h**). Electron-donating (**56d,f,i**) and electron-withdrawing substituents (**56e,g**) were less efficient. Strongly electron-withdrawing groups with free electron pairs were especially unsuited for this reaction, most likely due to competitive complexation of the catalyst (CN, NO_2). Also heterocyclic coupling partners (thiophene or pyridine) and steric bulk (o-toluylboronic acid ester or 1-naphthylboronic acid ester) were not well tolerated.

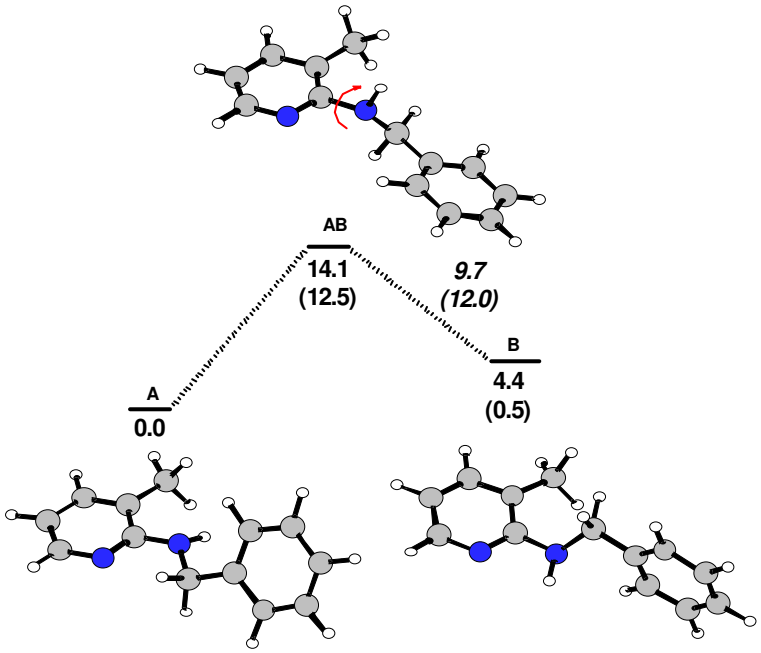
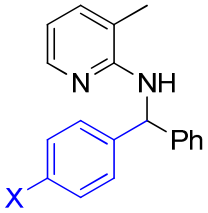
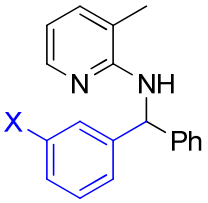


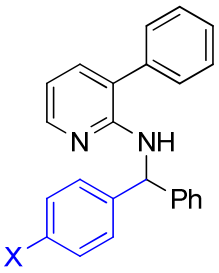
Figure 4



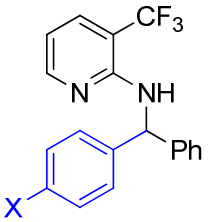
56a: X = H: 64%
56b: X = Me: 62%
56c: X = *t*-Bu: 64%
56d: X = MeO: 39%
56e: X = F: 66%
56f: X = Cl: 33%
56g: X = CF_3: 41%



56h: X = Me: 61%
56i: X = Cl: 38%



57a: X = H: 90%
57b: X = Me: 85%
57c: X = *t*-Bu: 96%
57d: X = F: 69%
57e: X = CF_3: 31%
57f: X = Cl: 64%
57g: X = COMe: 52%

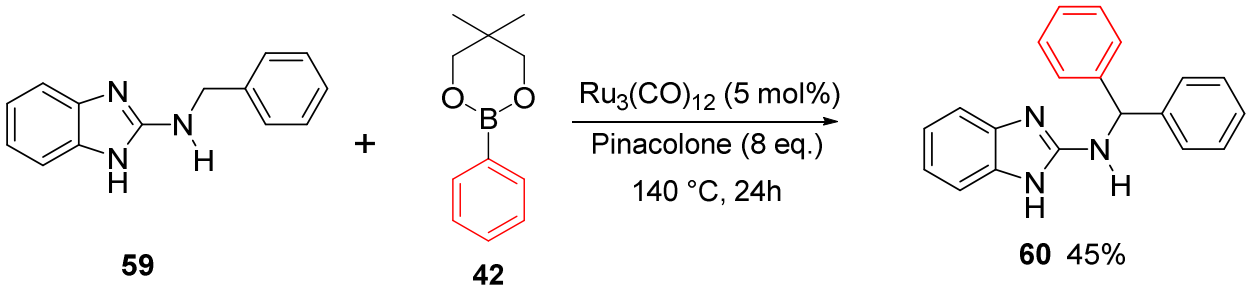


58a: X = H: 78%
58b: X = Me: 77%
58c: X = MeO: 61%
58d: X = *t*-Bu: 70%
58e: X = F: 51%

Scheme 16

In terms of the directing group, there is flexibility in the nature of the substituent in position 3. Besides methyl, also CF_3 (compounds **58**) and phenyl (compounds **57**) were well tolerated. The latter one actually gave the best results amongst the three tested substituents. Chlorine in position three of the pyridine directing group led to low conversion again since obviously the steric bulk is not large enough.

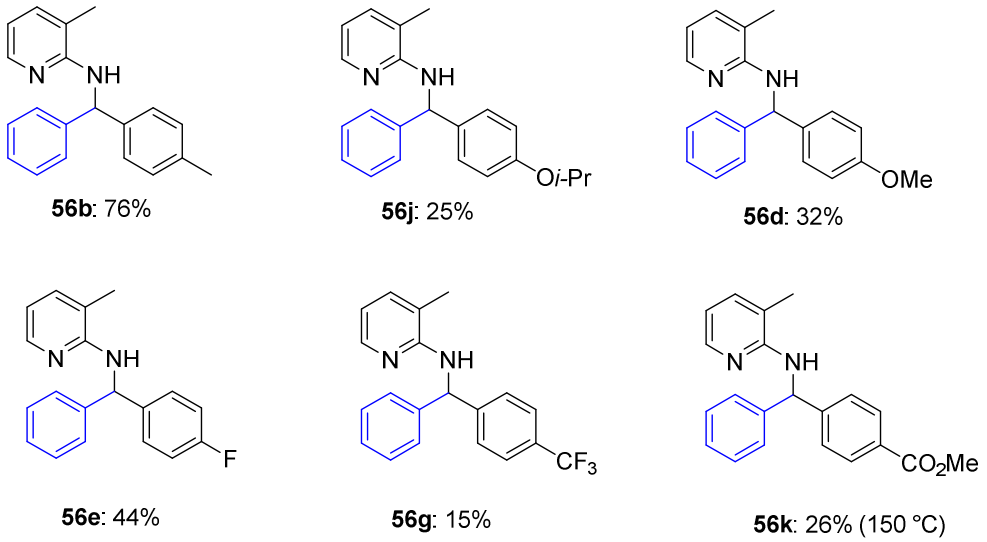
We also tested a directing group not based on pyridine, namely *N*-methylbenzimidazole derivative **59** (Scheme 17). Also in this case the reaction worked with 62% conversion and 45% yield of **60**. Due to the lower yield we decided to stick with 3-substituted pyridines.



59 **42** **60** 45%

Scheme 17

Further substrate scope investigations were directed towards elucidation of the effects of a substituent already present in the benzylamine substrate (Scheme 18). Also in this case electron-neutral substituents gave the best results (**56b**) and with both, electron-donating (**56j,d**) and electron-withdrawing ones (**56e,g,k**) the yield dropped.



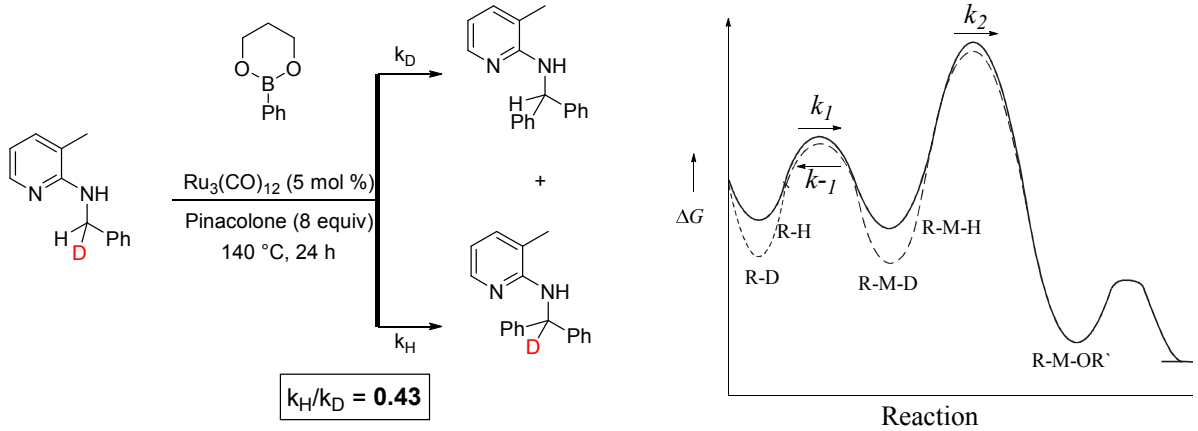
56b: 76% **56j**: 25% **56d**: 32%

56e: 44% **56g**: 15% **56k**: 26% (150 °C)

Scheme 18

An interesting result was observed when carrying out kinetic isotope effect studies. In an intermolecular competition experiment we measured a large KIE of 3.3 which is commonly observed in C-H activation reactions. However, in an intramolecular experiment a KIE of 0.43 was observed (Scheme 19), which means that the deuterated substrate reacts faster than the protonated one. This can be explained by a reversible C-H activation step and the corresponding KIE is referred to as inverse equilibrium isotope effect.[67] Scheme 19 explains this finding with the help of a hypothetical energy profile of such a reaction.

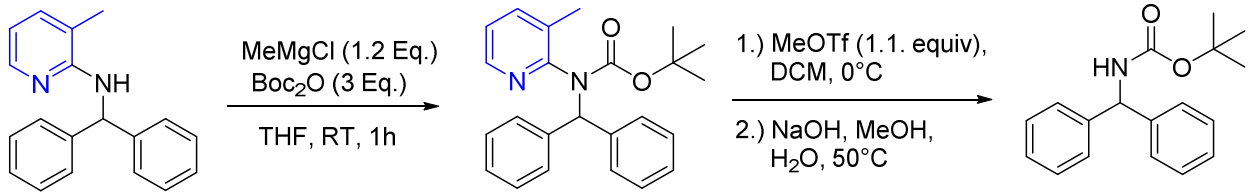
Intramolecular Competition Experiment:



Scheme 19

The C-D bond (dashed line in Scheme 19) is of course more stable than the C-H bond. Hence, insertion into the C-H bond is faster. However, it has to be taken into account that the product after C-D insertion, the metal deuteride R-M-D, is again more stable than the metal hydride species R-M-H. If the rate determining step is now after C-H insertion and C-H insertion is reversible, the metal deuteride complex can accumulate (since it is lower in energy) and react more often in the end, which explains the observed inverse KIE. This is a nice example showing that it is dangerous to draw conclusions on the rate determining step of a C-H activation reaction from a single KIE experiment.[68] Solely looking at the intermolecular experiment would have pointed towards C-H activation being rate determining, which is certainly not the case in this transformation.

Finally, we demonstrated the cleavage of the directing group as well, which we believe to be of crucial importance for this type of chemistry since the possibility to cleave the directing group gives more flexibility in synthesis and increases the applicability of a given protocol.



56a **61** 92 % yield **62** 91 %

Scheme 20

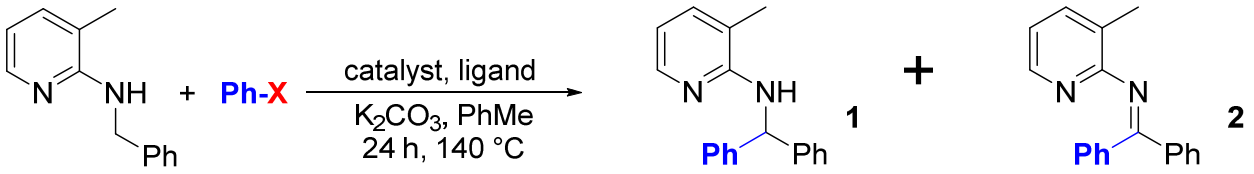
The protocol developed by Maes[56] was certainly not applicable in our case since it would rather cleave the C-N bond between the methylene group and the amine function (benzylic deprotection). Hence, an alternative protocol had to be applied. Based on literature precedence,[69]

the amine was Boc protected to **61** followed by methylation of the pyridine nitrogen leading to a pyridinium species which could then be hydrolyzed easily to **62**. Both steps proceed in high yield and diarylmethylamines are made accessible via our arylation protocol.

2.3.3. Ruthenium (II) catalyzed arylation of acyclic amines using aryl bromides and aryl iodides.[70,71] To use neutral conditions for a direct arylation is certainly very attractive. However, one little flaw of that protocol is that boronic acid esters are used as aryl source. Even though many of these compounds are commercially available already, they cannot compete with the corresponding halides regarding availability and cost. Hence, a protocol using aryl halides instead would be highly attractive.

It was quite clear that Ru(0) would not be suitable for this type of reaction and that the addition of a base would be necessary in order to quench the acid equivalent formed. We screened Ru(I), Ru(II), Ru(III), and Rh(III) catalysts and identified $[RuCl_2(p\text{-cymene})]_2$ as the most effective one. In presence of K_2CO_3 as base and KOPiv as additive, this set of reaction conditions allowed the direct arylation of **55** using aryl bromides and aryliodies as aryl donors. It has to be mentioned that besides the arylated aliphatic amine **56a** also the corresponding imine product **63** was observed. In case of the test reaction with bromobenzene, the ratio between **56a** and **63** was 6:1 at all reaction temperatures investigated (120 °C, 130 °C, 140 °C, and 150 °C). Since at 140 °C the yield was highest (75% GC-yield of **56a**) this temperature was chosen for substrate scope investigations. The reaction with iodobenzene gave a better amine to imine ratio (30:1 at 140 °C) but the yield was considerably lower (57% GC-yield of **56a**).

Table 2

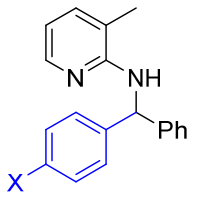


55 **56a** **63**

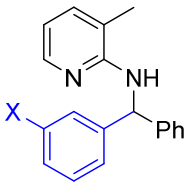
Entry	Catalyst	Ligand	X	Conv	**56a:63**	Yield of **1**
1	$[RuCl_2(p\text{-cymene})]_2$	--	Br	59	4.0	34
2	$RuCl_3\cdot(H_2O)_n$	--	Br	28	3.5	17
3	$RuCl_2(PPh_3)_3$	--	Br	47	2.4	27
4	$[RuCl_2(p\text{-cymene})]_2$	KOPiv	Br	98	6.0	75
5	$[RuCl_2(p\text{-cymene})]_2$	PPh_3	Br	85	4.6	51
6	$[RuCl_2(p\text{-cymene})]_2$	KOPiv	Cl	8	n.d.	4
7	$[RuCl_2(p\text{-cymene})]_2$	KOPiv	I	88	30	57

n.d.: not determined

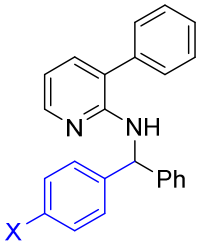
With the optimized reaction conditions in hand the substrate scope was investigated. It proved to be similar to that of the $Ru_3(CO)_{12}$ catalyzed protocol and the same effects of substituents were observed (Scheme 21), however less pronounced. Electron-neutral substituents in para position were well tolerated (**56a-c,l**) and also a para-MeO (**56d**) and para-F (**56e**) substituents gave good yield. With para-Me_2N (**56m**) and para-Cl (**56f**) the yield dropped, but only by ~10%. A carboxylic acid ester in the same position was not well tolerated and only 33% of **56n** were isolated. In meta position chlorine was less well tolerated giving only 37% of **56i** but Me (**56h**) and MeO (**56o**) gave good yields still.



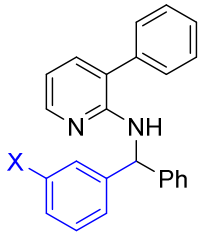
56a: X = H: 69% (Br)
56a: X = H: 48% (I)
56b: X = Me: 65%
56c: X = *t*-Bu: 64%
56l: X = *n*-Bu: 67%
56d: X = MeO: 63% (Br)
56d: X = MeO: 61% (I)
56m: X = Me_2N: 50%
56e: X = F: 61% (Br)
56e: X = F: 55% (I)
56f: X = Cl: 51%
56n: X = COOEt: 33%



56h: X = Me: 55%
56o: X = MeO: 60%
56i: X = Cl: 37%



57a: X = H: 70%
57b: X = Me: 67%
57c: X = *t*-Bu: 72%
57h: X = *n*-Bu: 69%
57g: X = COMe: 41%
57f: X = Cl: 59%
57i: X = COOEt: 42%



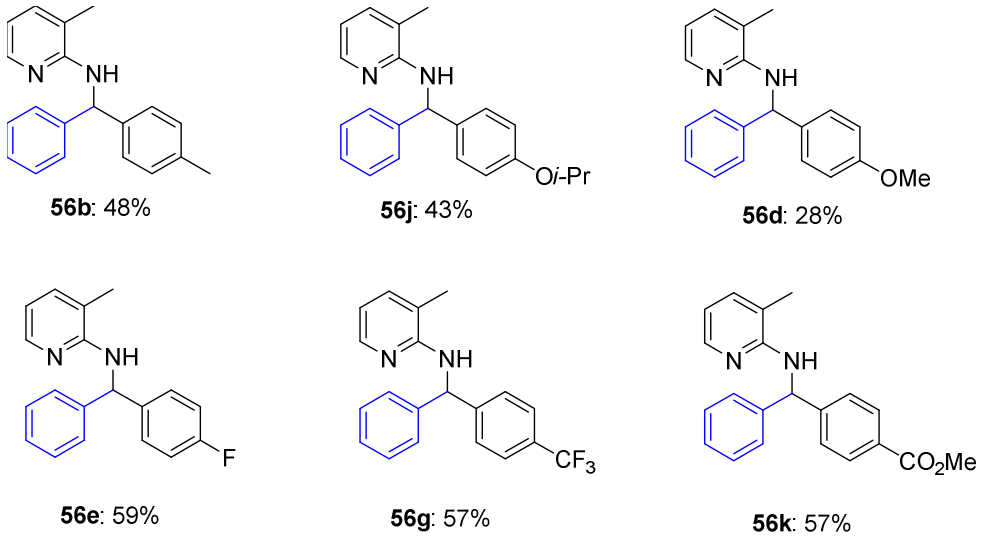
57j: X = Me: 68%
57k: X = MeO: 64%

Scheme 21

Besides substrate **55** with the methyl group in position 3, the corresponding starting material carrying a phenyl group instead was investigated as well. This substrate gave generally higher yields (Scheme 21, products **57**). The most important example is the acetyl substituted product **57g** which was isolated in 41%. The corresponding product with a methyl instead of a phenyl group was only observed in GC with low conversion (15%) and was not isolated. Strongly electron-withdrawing groups that additionally have the potential to coordinate the catalyst, did not show any conversion (NO_2, CN). Also heterocyclic halides (2-bromothiophene and 3-bromopyridine) were not tolerated.

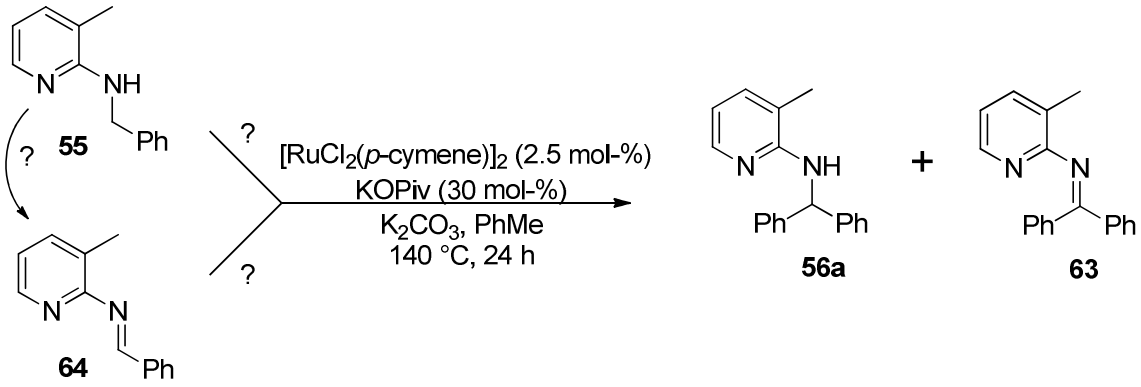
Starting from in para position of the benzylamine substituted compounds (Scheme 22) the trend is a bit different to the one observed for the Ru(0) catalyzed protocol (Scheme 18). There, electron-donating and electron-withdrawing substituent led to significantly lower yields in the

phenylation reaction. In the Ru(II) catalyzed protocol only electron-donating groups led to reduced yields (**56b,d,j**) and electron-withdrawing ones had little effect (**56e,g,k**).



Scheme 22

Again we carried out mechanistic investigations. Due to the reaction conditions applied it is quite clear that a concerted metalation deprotonation[72] mechanism is operable. However, due to the formation of the imine side product **63** it was unclear whether the arylation proceeds via the imine substrate **64**, or directly on the amine substrate **55**, and the imine product **63** is formed via a different pathway or via dehydrogenation of the amine product **56a**.



Scheme 23

We obtained results which support either of the two possibilities. First of all, we never observed the imine substrate **64** in the reaction mixture. This speaks against a pathway which involves initial imine formation. However, an imine species formed could remain bound to the

catalyst and then could be arylated immediately which would explain its absence in the reaction mixture. Next it was tested whether imine substrate **64** can be arylated under the applied reaction conditions, which was actually the case and imine product **63** was isolated in 67% yield. The rate of imine arylation is almost identical to the rate of arylation starting from amine substrate **55**. So if the arylation proceeds via the imine, its formation has to be fast (i.e. not rate determining), and also the reduction of the imine product **63** to the amine product **56a** has to be fast. Whether the imine is formed as intermediate should be tested by subjecting **55** to the reaction conditions in absence of aryl halide. However, we did not observe significant amounts of the imine intermediate **64**. The same experiment was carried out by adding the catalytic system to the amine product **56a**. Also in this case no significant amount of imine product **63** was detected. These results speak against a mechanism via the imine. However, substrates which cannot undergo imine formation (Figure 5) did not show any conversion to the corresponding products.

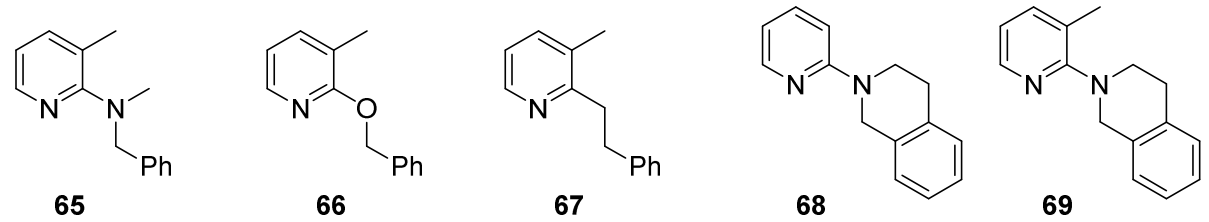
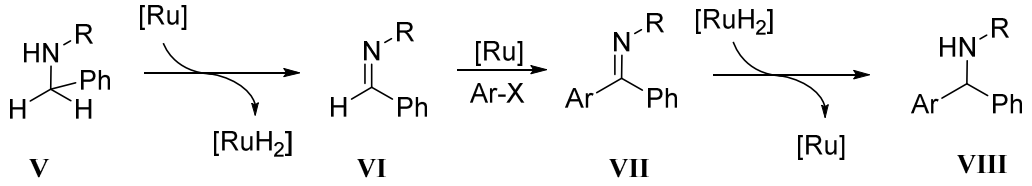


Figure 5

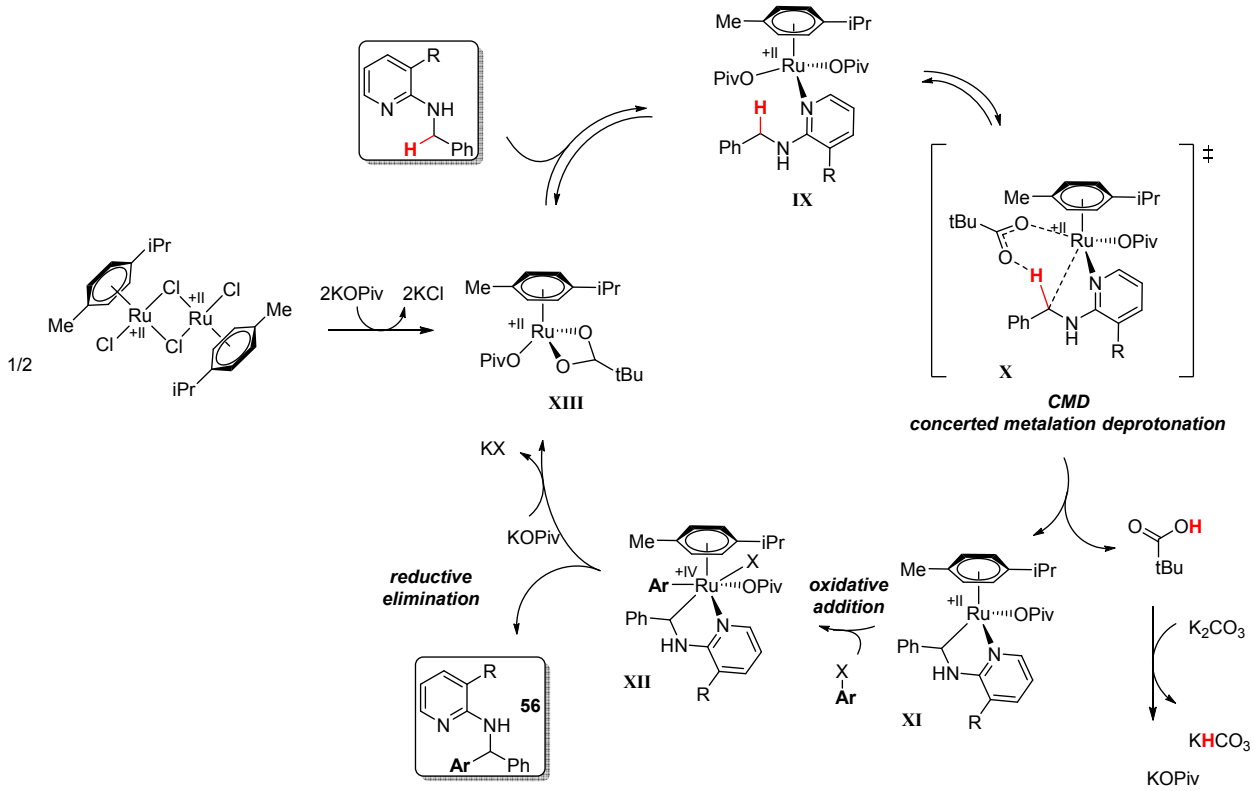
Based on these results we cannot suggest a definitive mechanism. The mechanism via an imine intermediate can be generalized as shown in Scheme 24. Dehydrogenation of **V** in presence of ruthenium catalyst leads to an imine species **VI** (which must stay closely associated to the catalyst) and a ruthenium dihydride species. Then arylation takes place and the corresponding imine product **VII** is reduced by the ruthenium dihydride species to the corresponding amine product **VIII**.



Scheme 24

On the other hand, arylation of the amine could proceed via a classical CMD mechanism as shown in Scheme 25. Initially a ruthenium pivalate complex **XIII** is formed which coordinates to the substrate to give **IX** and enables the crucial CMD step via **X** to give **XI**. Then oxidative

addition takes place towards **XII** and subsequent reductive elimination delivers the final product **56**.



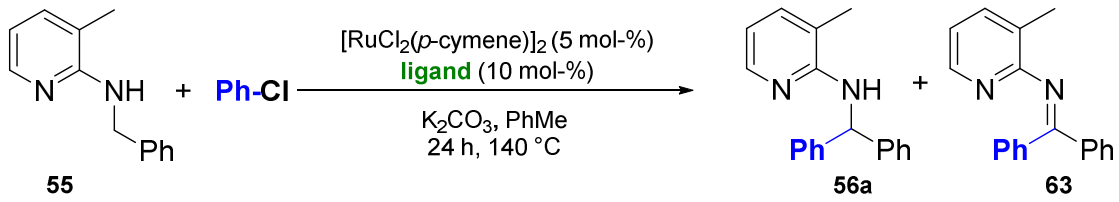
Scheme 25

2.3.4. Ruthenium (II) catalyzed arylation of acyclic amines using aryl chlorides.[65] In the protocol reported above, aryl chlorides were inefficient. Still, it was tried to expand this reaction to aryl chlorides since they are again cheaper as the corresponding bromides and iodides and a vast number of them is readily available.

As shown previously, the reaction conditions applied for aryl bromides and aryl iodides gave only 8% conversion when chlorobenzene was applied (Table 3, Entry 1). Interestingly, in absence of KOPiv the conversion was increased significantly to 34% (Entry 2). This suggests that no CMD mechanism is operable in this case. Unfortunately the amine to imine product ratio was low (1.8 : 1) which explains the low isolated yield of amine product (12%). Next, different phosphine ligands were tested (Entries 3-6) and simple PPh_3 (Entry 3) had the most positive effect improving conversion to 81% with 38% GC-yield of **56a**, but still a low amine to imine ratio of 1.9 : 1. Hence, it was tested whether the imine product could be reduced in situ to the corresponding amine. For that purpose secondary alcohols were added since it was hypothesized that they would deliver the hydrogen required for reduction being oxidized themselves to the corresponding ketones. This was indeed the case and in presence of *i*-PrOH solely amine product

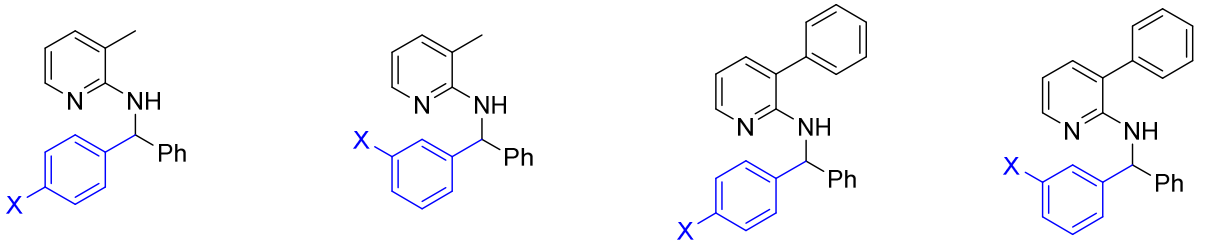
was obtained but now again with low conversion (Entry 7). Cyclohexanol proved to be significantly better giving 49% conversion and GC-yield (Entry 8). The final breakthrough came when the temperature was increased to 160 °C which led to almost full conversion and 70% isolated yield of amine product **56a** (Entry 9).

Table 3



Entry	Ligand	Additive	Conv	**56a:63**	Yield of **1**
1	KOPiv	-	8	--	4
2	--	-	34	1.8	12
3	PPh_3	-	81	1.9	38
4	$P(Cy)_3$	-	60	1.5	28
5	XPhos	-	62	2.1	30
6	JohnPhos	-	51	2.9	26
7	PPh_3	*i*-PrOH	17	>100	12
8	PPh_3	cyclohexanol	49	>100	38
9	PPh_3	cyclohexanol	93	12	79 (70)

With the optimized conditions in hand the substrate scope of this protocol was investigated. Regarding yields and electronic effects of substituents it was similar again to the Ru(0) and the Ru(II) protocol using aryl bromides or aryl iodides (Scheme 26).



56a: X = H: 70%
56b: X = Me: 79%
56d: X = MeO: 64%
56e: X = F: 56%
56f: X = CF_3: 30%

56h: X = Me: 72%

57a: X = H: 48%
57b: X = Me: 39%
57c: X = *t*-Bu: 55%
57h: X = *n*-Bu: 47%

57j: X = Me: 58%
57k: X = MeO: 61%

Scheme 26

Since in this case phosphines had a beneficial influence and no pivalate is present the reaction must proceed via yet another mechanism. This is quite interesting since three methods for the direct arylation of the same system were developed all showing the same scope and limitations even though proceeding via different mechanisms. Investigations to determine this third mechanism are ongoing.

Conclusions

In the presented research program C(sp^2)-H and C(sp^3)-H activation reactions were investigated. We were able to develop a facile method for the ortho arylation of anilines using pyridine as directing group. Additionally, the first direct arylation of 2-phenylpyridine in continuous flow was developed. Furthermore we demonstrated the utility of direct arylations by synthesizing 5-arylated thiazole-2-amines which act as cell differentiation accelerators. Another important development was our ruthenium catalyzed deuteration protocol which can be used to test whether C-H activation is possible at a certain position and to prepare deuterated substrates for KIE studies. We showed also that the protocol can be used for tritiation reactions as well in principal, which is important for studies in biological systems.

In C(sp^3)-H activation the first direct arylation of piperidine leading selectively to monoarylated products was developed. Additionally an interesting detrifluoromethylation reaction was observed which could be exploited to cleave the pyridine directing group. Finally, three protocols for the direct arylation of benzylamines were developed using the most common arylsources, namely arylboronic acid esters, aryl chlorides, aryl bromides, and aryl iodides. It was shown that all of these transformations proceed via distinctively different mechanisms.

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Michael Schnürch was born in Klagenfurt, Austria in 1978. He started to study chemistry in Vienna in 1996 and carried out his diploma and PhD thesis in the group of Professor Peter Stanetty. In 2005 he received his PhD from Vienna University of Technology (VUT). During his

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