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Ruthenium(II)-Catalyzed sp^3 C−H Bond Arylation of Benzylic Amines Using Aryl Halides

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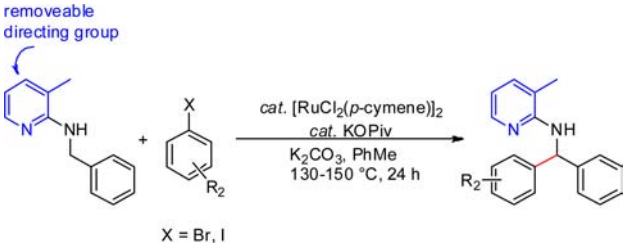
ABSTRACT



A ruthenium(II)-catalyzed protocol for the direct arylation of benzylic amines was developed. Employing 3-substituted pyridines as directing groups, arylation was achieved using aryl bromides or aryl iodides as the aryl source. Potassium pivalate proved to be an important additive in this transformation. The arylation took place selectively in the benzylic sp^3 position, and no significant competitive sp^2 arylation was observed. Arylated imines were observed as byproducts in minor amounts. Additionally, reaction conditions for cleaving the pyridine group were established, enabling access to bis-arylated methylamines.

Molecules with a diarylmethylamine subunit represent a promising class of pharmaceutically active compounds.[1] They received significant recent interest owing to diverse biological activities as antihistaminics (e.g., Cetirizine),[2] antimalarials[3] and antidepressants (e.g., Tianeptine).[4] Different strategies were proposed in the literature for synthesizing this structural motif, ranging from nucleophilic substitution to asymmetric imine arylation.[5] Metal catalyzed C−H activation evolved in recent years as an attractive and atom efficient method for the formation of new C−C or also C−heteroatom bonds.[6] In our quest to develop new methods for catalytic sp^3 bond C−H activation, we recently reported a Ru(0)-catalyzed chelation-assisted method for the direct sp^3 C−H bond arylation of benzylic amines.[7] Within this previous study, 3-substituted pyridines were used as directing group, giving access to bisarylated methylamines. The method required the application of boronic acid esters as aryl donor. Although many boronic esters are already commercially available or can be easily prepared from the corresponding boronic acids, aryl halides are a more conveniently employable aryl source.

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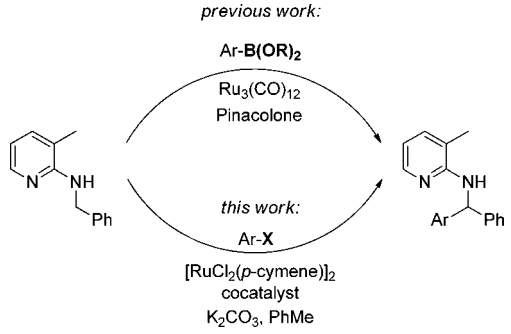
A significantly larger number of structurally diverse halides are commercially available at present, usually at a substantially lower price. Hence, our goal was to develop an alternative method that would allow the application of aryl halides as aryl donors. Herein, we report the Ru(II)-catalyzed direct arylation of benzylic amines with aryl bromides, again taking advantage of 3-substituted pyridines as crucial directing groups to facilitate selectivity (Scheme 1).

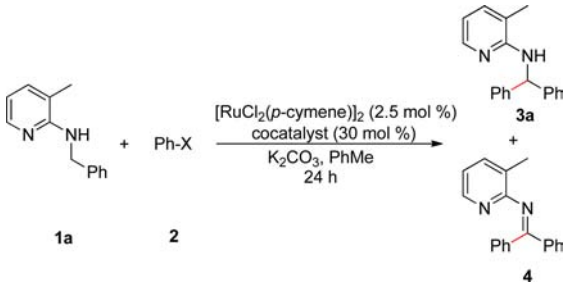
In our previously disclosed protocol, we had already established that pyridines bearing a bulky and inert substituent in the 3-position could effectively direct a metal catalyst toward the C−H bond to be arylated. Preliminary computational studies indicated that a certain steric bulk at this position of the directing group is necessary to stabilize the required conformation in which the C−H bond in question is in close proximity to the pyridine ligated metal catalyst (unpublished results). Furthermore, we could develop a method for the cleavage of the 3-substituted pyridine group, enabling access to the Boc protected or the free amine. On the basis of this rationale, we decided to maintain these advantageous properties of the directing group and set out to identify a suitable catalytic system for our purpose. Initially, different Pd-, Rh-, and Ru-catalysts were tested. Among the investigated complexes, only $[RuCl_2(p\text{-cymene})]_2$ showed promising results.

Scheme 1. Ru-Catalyzed Direct Arylation of Benzylic Amines



The $[RuCl_2(p\text{-cymene})]_2$ catalyst has attracted much attention for the direct chelation-assisted functionalization of sp^2 C−H bonds during recent years.[8,9] However, to the best of our knowledge, there is no report about sp^3 C−H bond arylation using this system. In our initial experiment, substrate **1a** was reacted with bromobenzene using $[RuCl_2(p\text{-cymene})]_2$ as catalyst in toluene at 120 °C, which yielded a moderate 21% of the desired product **3a** together with its imine derivative **4** in a 6:1 ratio (Table 1, entry 1). The $[RuCl_2(p\text{-cymene})]_2$/carboxylate system is a prominent method for the direct arylation of sp^2 C−H bonds, and a variety of catalytic reactions were developed during the last years.[6a] These carboxylate assisted C−H bond transformations are proposed to proceed via a concerted deprotonation metalation (CMD) mechanism. To increase the yield of our reaction, different carboxylates were screened as cocatalyst (Table 1), indicating a substantially beneficial effect of KOPiv (Table 1, entry 7; 46% yield). While the ratio of **3a**:**4** was not affected when using bromobenzene (6:1), a further increase in the formation of **3a** was observed when employing iodobenzene (entry 9; 53% yield, 15:1 ratio **3a**:**4**). Chlorobenzene was not suitable for this transformation (Table 1, entry 8). Finally, by increasing the temperature to 140 °C (Table 1, entry 11), we could achieve a reasonable GC yield of 75% using bromobenzene as phenyl source. This Ru(II) mediated protocol offers the additional benefit of a lower catalyst loading of

Table 1. Optimization Studies for the Direct Arylation of Benylic Amine **1a**[a]



entry	cocatalyst	X	T [°C]	**3a**:**4**[b]	yield of **3a**[c] (%)
1		Br	120	6:1	21
2	AcOH	Br	120	2:1	34
3	KOAc	Br	120	2:1	32
4	$AdCO_2H$	Br	120	4:1	34
5	$AdCO_2K$	Br	120	6:1	43
6	PivOH	Br	120	2:1	42
7	KOPiv	Br	120	6:1	46
8	KOPiv	Cl	120		2
9	KOPiv	I	120	15:1	53
10	KOPiv	Br	130	6:1	66
11	**KOPiv**	**Br**	**140**	**6:1**	**75**
12		Br	140	6:1	42
13	KOPiv	I	140	30:1	57
14	KOPiv	Br	150	6:1	74

[a] Reaction conditions: **1a** (0.5 mmol), PhX (0.75 mmol), $[RuCl_2(p\text{-cymene})]_2$ (2.5 mol %), cocatalyst (30 mol %), K_2CO_3 (1.5 mmol), and PhMe (2 mL). [b] Ratio based on GC analysis. [c] Yield determined by GC analysis with respect to **1a** (dodecane as internal standard).

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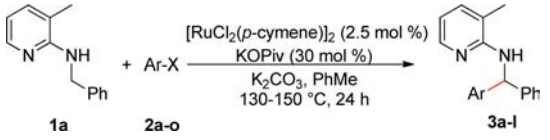
2.5 mol % (compared to 5 mol % required previously); this corresponds to only 5 mol % ruthenium present (dimeric catalyst) as opposed to 15 mol % (trimeric catalyst).[7] Interestingly, iodobenzene gave lower yields at higher temperature due to the more pronounced formation of unidentified byproducts. Formation of imine **4** as side product was observed in all experiments, which was not the case in the previously reported $Ru_3(CO)_{12}$/phenylboronic acid ester system.[7] In the absence of a substituent in position 3 of pyridine, only small amounts (< 10%) of arylated product were observed.

In the next step, we investigated the scope of the reaction (Table 2). In agreement with the $Ru_3(CO)_{12}$ protocol, this method is also sensitive to electronic and steric properties of the aryl donor. Electron neutral and donating groups such as 4-methyl (**3e**, 65%), 4-*t*-butyl (**3f**, 64%), 4-*n*-butyl (**3g**, 67%) or 4-methoxy (**3h**, 63%) resulted in good yields, while electron withdrawing groups such as 4-Cl (**3k**, 51%) or 4-CO_2Et (**3l**, 33%) decreased the yield and required higher reaction temperatures. Strong electron withdrawing groups (e.g., 4-CN, 4-NO_2, 4-Ac) and heterocylic halides (e.g., pyridine or thiophene), were not accepted. The catalyst tolerates substituents in the para and meta (3-Me, **3c**, 55%) positions, but ortho substituents (2-Me, **3b**) slowed down the reaction significantly. Bromide aryl sources usually performed slightly better compared to the corresponding iodo derivatives at the same reaction temperature (Table 2, entries 10 and 13).

Table 2. Scope of Direct Arylations with Aryl Halides **2**

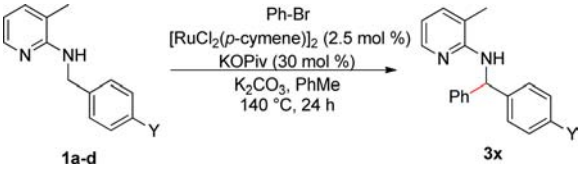


entry		X	Ar	T [°C]	yield[a] (%)
1	**3a**	Br	Ph	140	69
2	**3a**	I	Ph	140	48
3	**3b**	Br	2-Me-C_6H_4	140	n.i.[b]
4	**3c**	Br	3-Me-C_6H_4	140	55
5	**3d**	Br	3-MeO-C_6H_4	140	60
6	**3e**	Br	4-Me-C_6H_4	140	65
7	**3f**	Br	4-*t*-Bu-C_6H_4	140	64
8	**3g**	Br	4-*n*-Bu-C_6H_4	140	67
9	**3h**	Br	4-MeO-C_6H_4	140	63
10	**3h**	I	4-MeO-C_6H_4	140	61
11	**3i**	Br	4-Me_2N-C_6H_4	130	50
12	**3j**	Br	4-F-C_6H_4	150	61
13	**3j**	I	4-F-C_6H_4	150	55
14	**3k**	Br	4-Cl-C_6H_4	150	51
15	**3l**	Br	4-EtO_2C-C_6H_4	150	33

[a] Isolated yield. [b] n.i. = not isolated. GC shows 18% conversion, but the product could not be isolated because of sideproducts.

Next, the influence of the electronic properties of the benzylic position on the direct arylation was investigated (Table 3). To exclude any additional steric effect, reactions were conducted with para substituents at the benzylic group of the substrate only. The best result was achieved with the unsubstituted phenyl group. Electron donating (e.g., Me, OMe) groups are obviously slowing down the reaction significantly, whereas the system tolerated the electron withdrawing CO_2Me group, providing comparable conversion and yield to the unsbustituted substrate.

Table 3. Influence of the Electronic Properties of the Benzylic Group on the Direct Arylation



entry		Y	conv[a] (%)	yield[b] (%)
1	**3h**	OMe	49	28
2	**3e**	Me	77	48
3	**3a**	H	96	69
4	**3m**	CO_2Me	88	57

[a] Conversion based on GC analysis with respect to **1a**–**d** (dodecane as internal standard). [b] Isolated yield.

To investigate the mechanism of the reaction, we performed competitive kinetic isotope effect experiments (Scheme 2).

For the intermolecular competition experiment, 1 equiv of starting material **1a** and 1 equiv of the corresponding deuterated compound **5** were reacted under the optimized reaction conditions in the presence of only 1 equiv of bromobenzene. Finally, the mixture of products was isolated, and the ratio of **3a**:**6** was determined by ^{1}H NMR. A KIE of 1.3 was found, indicating that C−H insertion of the metal is not the rate determining step in this reaction since otherwise a much higher KIE could be expected.[10,11] This result is in contrast to our previously reported $Ru_3(CO)_{12}$/phenylboronic acid ester protocol displaying a KIE of 3.3.[7] Consequently, we also carried out an intramolecular competition experiment with compound **7**. Here, the KIE was found to be 1, again in contrast to the $Ru_3(CO)_{12}$ protocol (KIE = 0.43)[7] indicating again that C−H insertion is not rate determining.

On the basis of our experimental studies and the literature[12] we propose the Ru(II)-complex **8** to undergo an oxidative addition with the aryl halide, forming complex **9**.

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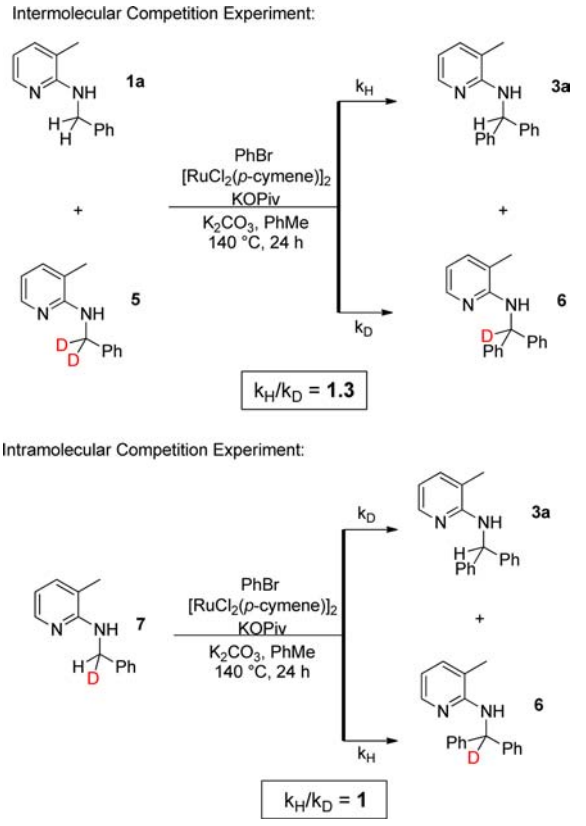
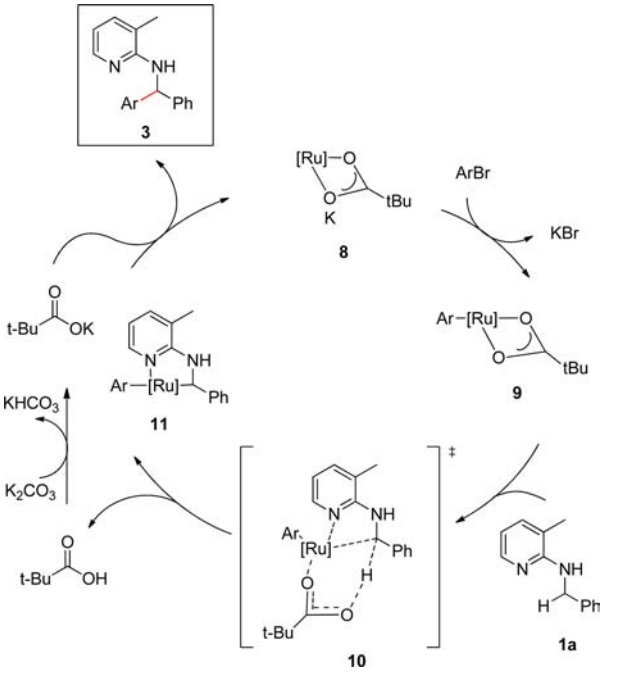
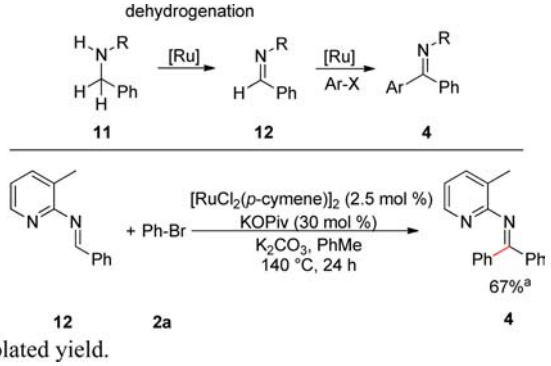
Scheme 2. Competitive Deuterium-Labeling Experiments



Scheme 3. Proposed Mechanism



Scheme 4. Possible Explanation for Imine Formation



[a]Isolated yield.

The metal is subsequently inserted into the benzylic C−H bond of amine **1a**, delivering intermediate **10** via a concerted metalation−deprotonation (CMD) mechanism. The proton is transferred to the potassium carbonate, and reductive elimination ultimately yields amine **3** (Scheme 3).

Formation of the imine product **4** can be tentatively assigned to ruthenium-catalyzed oxidative dehydrogenation.[13] The so formed imine can then again be arylated, which was also demonstrated by subjecting **12** to our arylation conditions, giving **4** in 67% isolated yield. Subjecting substrate **1a** to the reaction conditions in the absence of halide gave formation of the corresponding imine only in small amounts. Additionally, imine **4** was only produced in trace amounts within a control experiment employing **3a** in the presence of catalyst and PivOK (Scheme 4). Hence, we believe that the dehydrogenation occurs from an intermediate complex of type **10** or **11**.

In summary, we have demonstrated that the $[RuCl_2(p\text{-cymene})]_2$/aryl halide/carboxylate system is also suitable for the direct arylation of benzylic amines. This method is compatible with a variety of functional groups, delivering moderate to good yields. The pyridine directing group can be cleaved taking advantage of our previously reported conditions. Moreover, preliminary data presented so far suggests a distinctly different reaction mechanism to the $Ru_3(CO)_{12}$/arylboronic acid ester system. Further investigations aiming at elucidating the mechanism in more detail are underway in our laboratory.

Acknowledgment. We acknowledge the Austrian Science Foundation (FWF, Project P21202−N17) for financial support of this work.

Supporting Information Available. Experimental procedures, characterization data, and ^1H and ^{13}C NMR spectra for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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The authors declare no competing financial interest.