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Directed Additions of 2-Arylpyridines and Related Substrates to Cyclic Imines through Rhodium-Catalyzed C−H Functionalization

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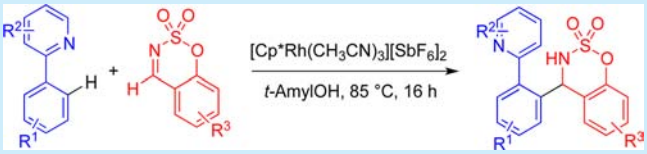
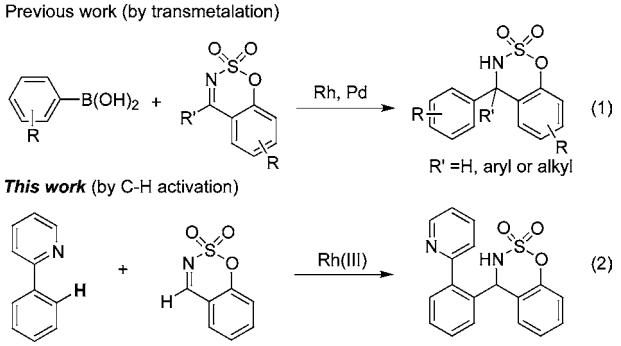
Supporting Information

ABSTRACT: Rhodium-catalyzed C−H functionalizations have been used for *ortho*-directed additions of 2-arylpyridines and (hetero)aryl-substituted pyrimidines, isoquinolines, and benzo[*h*]quinolones to cyclic imines. The resulting amino-functionalized products are formed in good to high yields.



The addition of organometallic reagents to polar electrophiles (aldehydes, imines, etc.) is a traditional method for the formation of new C−C bonds.[1] Unfortunately, most of the required organometallic reagents are air and moisture sensitive and have to be prepared at low temperature under an inert atmosphere to avoid decomposition. In addition, due to their high reactivity the functional group tolerance of many organometallic reagents is rather limited. A valuable alternative is the use of arylboronic acids in addition to aldehydes, imines, and nitriles.[2] Mechanistically these C−C bond forming processes are different as they involve transition metal catalysts that undergo oxidative additions or transmetalations before adding to the polar electrophiles. Unfavorable is the fact that this approach implies the formation of significant amounts of salts and organic waste. To circumvent these disadvantages metal-catalyzed C−H activations and subsequent additions of the resulting organometallic species to the polar double bond have emerged as an attractive alternative. The reaction systems are generally highly atom economical as well as environmentally benign. As early as 2006, Kuninobu and Takai reported rhenium-catalyzed additions of aldimines to isocyanates and alkynes through C−H activations.[3] To date, rhodium(III) complexes play a dominant role in this field.[4] Most of these studies have focused on *ortho*-directed C−H functionalizations through additions of metal-activated intermediates to alkynes, alkenes, and allenes.[4] Only a few reports refer to analogous reactions with polar electrophiles such as imines, aldehydes, isocyanides, and nitrosobenzenes.[5] Catalytic C−H bond activations with other metals have also been investigated. For example, Cheng and co-workers reported ruthenium(II)-catalyzed *ortho*-directed amidations of 2-arylpyridines with isocyanates,[6] and a cationic high-valent Cp*-cobalt(III) complex was introduced by Matsunaga and Kanai for analogous additions of 2-arylpyridines to imines.[7,8] However, to the best of our knowledge, such metal-catalyzed C−H bond activations have never been utilized in additions to cyclic imines, which is surprising considering the fact that related reactions involving transmetalations from arylboronic acids are well investigated (Scheme 1, eq 1).[9] Here, we fill this synthetic gap and report on applications of rhodium(III) catalysts in insertion reactions of *ortho*-directing substrates into C═N bonds of cyclic imines (Scheme 1, eq 2).[10]

Scheme 1. Metal-Catalyzed Aryl Additions to Cyclic Imines



For the optimization study 2-phenylpyridine (**1a**) and cyclic imine **2a** were selected as representative substrates. The best conditions for obtaining C−H addition product **3a** (in 88% yield) involved the use of $[Cp^*Rh(CH_3CN)_3][SbF_6]_2$ (5.0 mol %) in *t*-AmylOH at 85 °C for 16 h (Table 1, entry 1). The analogous rhodium complex with BF_4^- as a counterion was less effective giving **3a** in 65% yield (entry 2). Whereas, with $[RhCp^*Cl_2]_2$, only a trace of the product was observed (entry 3), the combination of $[RhCp^*Cl_2]_2$ and $AgSbF_6$ led to an active catalyst providing **3a** in 76% yield (entry 4). Similar combinations with other metal complexes were less effective (entries 5−8). Instead of *t*-AmylOH a variety of other solvents could be applied, but in all cases the yields of **3a** were lower (Table 1, entries 9−14).

The evaluation of the substrate scope was initiated by reacting various 2-aryl-substituted pyridines (**1b−h**) with cyclic imine **2a** under the optimized reaction conditions. The results are summarized in Table 2. Substrates with 4-methyl, 4-chloro-, 4-fluoro-, and 4-phenyl substituents on the arene (**1b−e**) reacted smoothly with **2a** giving the corresponding C−H addition products **3b−e** in yields ranging from 72% to 83%

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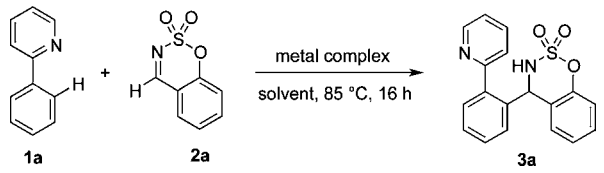
Table 1. Effect of Catalyst and Solvent on the Addition of 2-Phenylpyridine (1a) to Cyclic Imine 2a after C−H Activation[a]



1a 2a 3a

entry	catalyst	solvent	yield (%)
1	**$[Cp^*Rh(CH_3CN)_3][SbF_6]_2$**	***t*-AmylOH**	**88**
2	$[Cp^*Rh(CH_3CN)_3][BF_4]_2$	*t*-AmylOH	65
3	$[RhCp^*Cl_2]_2$	*t*-AmylOH	trace
4[b]	$[RhCp^*Cl_2]_2/AgSbF_6$	*t*-AmylOH	76
5[b]	$Rh(PPh_3)_3Cl/AgSbF_6$	*t*-AmylOH	0
6[b]	$[RhCl(COD)]_2/AgSbF_6$	*t*-AmylOH	0
7[b]	$[IrCl(COD)]_2/AgSbF_6$	*t*-AmylOH	0
8[b]	$[RuCl_2(p\text{-cymene})]_2/AgSbF_6$	*t*-AmylOH	48
9	$[Cp^*Rh(CH_3CN)_3][SbF_6]_2$	DCE	80
10	$[Cp^*Rh(CH_3CN)_3][SbF_6]_2$	DME	74
11	$[Cp^*Rh(CH_3CN)_3][SbF_6]_2$	THF	69
12	$[Cp^*Rh(CH_3CN)_3][SbF_6]_2$	CH_3CN	51
13	$[Cp^*Rh(CH_3CN)_3][SbF_6]_2$	EtOH	64
14	$[Cp^*Rh(CH_3CN)_3][SbF_6]_2$	toluene	72

[a]Reaction conditions: 2-phenylpyridine (**1a**, 0.30 mmol), **2a** (0.34 mmol), catalyst (5 mol %), and solvent (2 mL) at 85 °C for 16 h. [b]$AgSbF_6$ (20 mol %) were used.

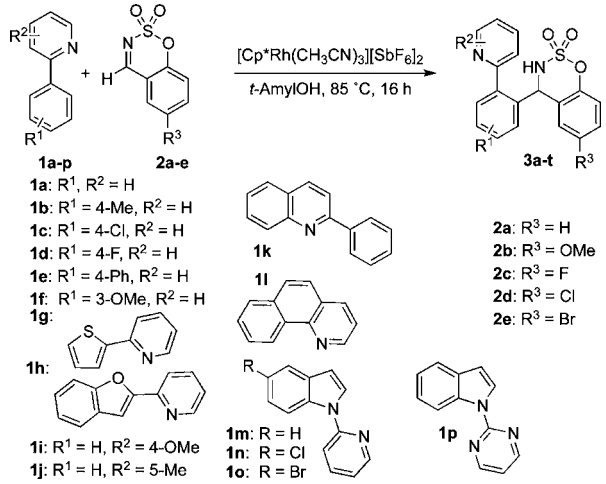
(entries 2−5). 2-(3-Methoxyphenyl)pyridine (**1f**) underwent a selective C−H activation/addition reaction with **2a** affording **3f** in 81% yield (entry 6). Noteworthy is the fact that out of the two *ortho* C−H bonds of **1f** that could react (at C2 and C6) only the sterically less hindered one at C6 was activated. Also 2-thienyl- and 2-benzofurylpyridines (**1g** and **1h**) reacted well affording the corresponding addition products **3g** and **3h** in yields of 97% and 77%, respectively (entries 7−8). Substituents at the 4 or 5 position of the pyridine ring did not significantly affect the catalysis as exemplified by the product formations of **3i** and **3j**, which were obtained in almost the same yields (72% and 74%, entries 9 and 10). A reduction in yield was observed in the conversions of 2-phenyl-isoquinoline (**1k**) and benzo[*h*]quinolone (**1l**), which led to the corresponding products **3k** and **3l** in 56% and 27% yield, respectively (entries 11 and 12).

The reactions of *N*-pyridin-2-yl indoles **1m−o** and *N*-pyrimidin-2-yl indole (**1p**) with **2a** revealed that also a less explored C2-functionalization of the indole core was possible. As a result, products **3m−p** were obtained in yields ranging from 70% to 80% (entries 13−16).

The scope of the C−H addition reaction was further extended to differently functionalized cyclic imines. The application of 5-methoxy-, 5-fluoro-, 5-chloro-, and 5-bromo-substituted cyclic imines **2b−e** in reactions with **1a** gave **3q−t** in good to high yields (entries 17−20).

With previous work on metal-catalyzed directing group assisted C−H bond activation reactions providing guidance,[4,5,10,11] a mechanistic proposal could be derived that accounted for the presented catalysis. In Scheme 2 it is summarized for the rhodium-catalyzed reaction between **1a** and **2a**. The first step involves coordination of the pyridine nitrogen of **1a** to the rhodium complex, which is followed by insertion of the metal into the *ortho* C−H bond. This transformation is rate-determining as demonstrated by an intermolecular

Table 2. Results of the Reactions of 2-Arylpyridines and Related Substrates with Cyclic Imines[a]



1a-p 2a-e 3a-t

1a: R^1, R^2 = H
1b: R^1 = 4-Me, R^2 = H
1c: R^1 = 4-Cl, R^2 = H
1d: R^1 = 4-F, R^2 = H
1e: R^1 = 4-Ph, R^2 = H
1f: R^1 = 3-OMe, R^2 = H
1g:
1h:
1i: R^1 = H, R^2 = 4-OMe
1j: R^1 = H, R^2 = 5-Me
1k
1l
1m: R = H
1n: R = Cl
1o: R = Br
1p

2a: R^3 = H
2b: R^3 = OMe
2c: R^3 = F
2d: R^3 = Cl
2e: R^3 = Br

entry	1	2	product 3	yield (%)
1	1a	2a	**3a**: R^1 = H	88
2	1b	2a	**3b**: R^1 = Me	81
3	1c	2a	**3c**: R^1 = Cl	79
4	1d	2a	**3d**: R^1 = F	83
5	1e	2a	**3e**: R^1 = Ph	72
6	1f	2a	**3f**	81
7	1g	2a	**3g**	97
8	1h	2a	**3h**	77
9	1i	2a	**3i**	72
10	1j	2a	**3j**	74
11	1k	2a	**3k**	56
12	1l	2a	**3l**	27

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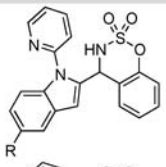
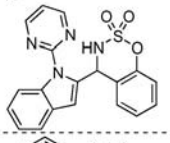
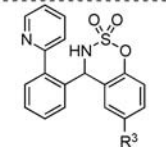
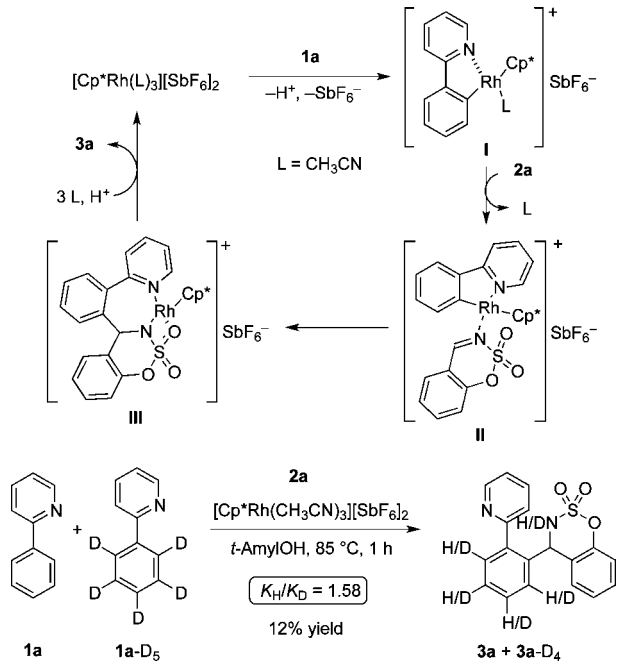
Table 2. continued

entry	1	2	product 3		yield (%)
13	1m	2a		3m: R = H	80
14	1n	2a		3n: R = Cl	77
15	1o	2a		3o: R = Br	70
16	1p	2a		3p	74
17[b]	1a	2b		3q: R^3 = OMe	69
18	1a	2c		3r: R^3 = F	74
19	1a	2d		3s: R^3 = Cl	81
20	1a	2e		3t: R^3 = Br	83

[a]Reaction conditions: 2-arylpyridine **1** (0.50 mmol), **2** (0.54 mmol), $[Cp^*Rh(CH_3CN)_3][SbF_6]_2$ (5 mol %), and *t*-AmylOH (3 mL) at 85 °C for 16 h. [b]Use of only 0.50 mmol of **2b** (instead of 0.54 mmol).

Scheme 2. Proposed Mechanism for the Addition of 2-Phenylpyridine (1a) to Cyclic Imine 2a by Metal-Catalyzed C−H Activation; Determination of a Kinetic Isotope Effect



competition experiment involving **2a** and a 1:1 mixture of **1a** and **1a-D$_5$**, which showed a kinetic isotopic effect (KIE) of 1.58 for k_H/k_D. By loss of a proton, five-membered rhodacycle **I** is formed. Coordination of the cyclic imine leads to intermediate **II**, which inserts the C═N portion of **2a** into the rhodium−carbon bond to give seven-membered rhodacycle **III**. Finally, protonation of **III** affords addition product **3a** and regenerates the active rhodium species for the next catalytic cycle.[12]

In summary, we utilized the rhodium-catalyzed *ortho*-directed C−H bond functionalization of 2-arylpyridines and related compounds for the synthesis of amino derivatives resulting from trapping of the organometallic intermediates with cyclic imines. The substrate range is broad, the functional group tolerance is high, and the products are obtained in good yields. A mechanistic scheme has been proposed which is supported by the observed kinetic isotopic effect. Further mechanistic studies and applications in natural product syntheses are in progress.

■ ASSOCIATED CONTENT

Supporting Information

General experimental procedure and characterization details. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(12) As indicated by the ^{1}H NMR spectra, the proton (deuterium) at the amide group of **3a** (and its deuterated analog) undergoes a rapid (H/D) exchange.