C–H Activation

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Rhodium-Catalyzed Direct C–H Amination of Benzamides with Aryl Azides: A Synthetic Route to Diarylamines**

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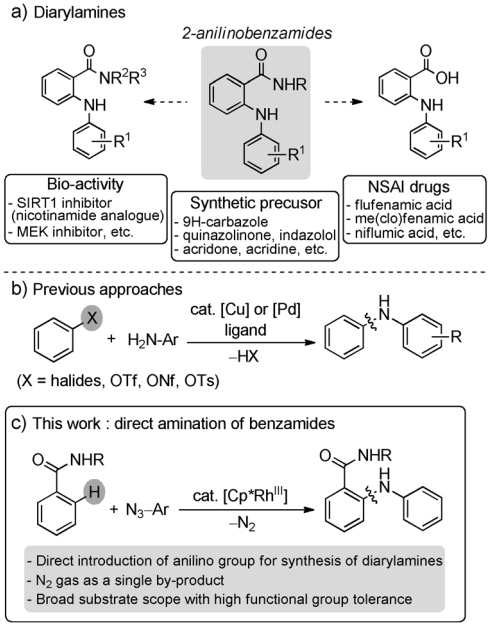
Dedicated to Professor Chang Kiu Lee

Diarylamines are widely present in biologically active natural products, and are also an important synthetic unit in numerous pharmaceuticals, agrochemicals, dyes, and functional materials.[1] Among the diarylamines, derivatives bearing an *ortho*-carbonyl group serve as important pharmacophores and are key components in a wide range of bioactive compounds (Scheme 1a).[2,3] Furthermore, they are easily converted into various heterocycles of high synthetic utility.[4] Conventional methods for the preparation of diarylamines rely on the Cu-mediated coupling between aryl halides and anilines,[5] and generate stoichiometric amounts of copper waste. The subsequent development of catalytic methods for this *N*-arylation has been predicated upon the choice of suitable ligands (Scheme 1b).[6,7]



Scheme 1. Utility and synthesis of diarylamines.

In recent years, new research has been focused on metal-catalyzed direct C–H amination (or amidation) of (hetero)-arenes without the need for pre-functionalized aryl halides.[8] Although this approach is highly promising, it still generates stoichiometric amounts of by-products from the external oxidants,[9] halide salts, or bases employed;[10] the substrate scope is also often rather limited.

In our continuing efforts to develop highly efficient amination reactions,[11] we recently reported a Rh-catalyzed direct arene C–H amidation using sulfonyl azides as the amine source.[12] It proceeds without external oxidants and releases N_2 as a single by-product. This result led us to attempt the direct amination of arenes with aryl azides, which can be readily prepared with wide diversity, to afford diarylamines.[13] In particular, we were interested in the direct installation of an amino group onto benzamides to afford 2-anilinobenzamides (Scheme 1c). Although some elegant examples of catalytic C–H amination were previously reported using aryl- or vinyl azides, they were mainly limited to intramolcular conversions.[14,15] In contrast, only a few examples of intermolecular reactions are known, primarily for the amination of allylic or benzylic sp^3 C–H bonds.[14,16,17] It is in this context that we herein describe a highly efficient and selective Rh-catalyzed direct intermolecular C–H amination of benzamides and ketoximes using aryl azides.

At the outset of our study, we searched for optimal C–H amination conditions (Table 1). All reactions were catalyzed by a cationic Rh^{III} species, which was generated in situ by treating $[\{RhCp^*Cl_2\}_2]$ with a silver salt. No conversion was observed with primary or tertiary benzamides (entries 1 and 2) or with *N*-pivaloyloxy benzamide (entry 3), whereas amination of *N*-methylbenzamide with 4-nitrophenyl azide (**2a**) was found to proceed, albeit with moderate yield (entry 4). We were pleased to observe that high yield was obtained when *N*-*tert*-butylbenzamide (1.8 equiv relative to **2a**) was applied, even with a lower loading of the rhodium catalyst (2.5 mol%), when conducted at 85 °C in 1,2-dichloroethane (1,2-DCE; entry 5). Reactions at lower temperatures resulted in decreased reactivity (entries 6 and 7). Other catalytic systems tested were largely ineffective under these conditions (entries 8 and 9). Other carbonyl groups, including ketone, ester, or carboxylic acids, were not found to be viable for direct amination (entries 10–12).

With the optimal conditions established, we next investigated the substrate scope of various aryl amides in the reaction with 4-nitrophenyl azide (Scheme 2). The reaction

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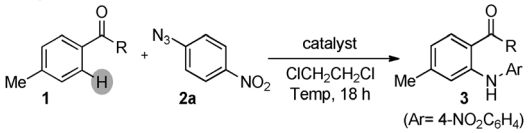
Table 1: Optimization studies.[a]



Entry	R	Catalyst (mol%)	*T* [°C]	Yield [%][b]
1	NH_2	[{RhCp*Cl_2}$_2$] (4)/$AgSbF_6$ (16)	85	<5
2	NMe_2	[{RhCp*Cl_2}$_2$] (4)/$AgSbF_6$ (16)	85	<5
3	NHOPiv	[{RhCp*Cl_2}$_2$] (4)/$AgSbF_6$ (16)	85	<5
4	NHMe	[{RhCp*Cl_2}$_2$] (4)/$AgSbF_6$ (16)	85	40
5	NH*t*Bu	[{RhCp*Cl_2}$_2$] (2.5)/$AgSbF_6$ (10)	85	85(80)
6	NH*t*Bu	[{RhCp*Cl_2}$_2$] (2.5)/$AgSbF_6$ (10)	70	73
7	NH*t*Bu	[{RhCp*Cl_2}$_2$] (2.5)/$AgSbF_6$ (10)	50	49
8	NH*t*Bu	[$Rh_2(O_2CCF_3)_4$] (4)	85	<5
9[c]	NH*t*Bu	[{Ru(*p*-cymene)Cl_2}$_2$] (4)	85	<5
10	Me	[{RhCp*Cl_2}$_2$] (4)/$AgSbF_6$ (16)	85	<1
11	OMe	[{RhCp*Cl_2}$_2$] (4)/$AgSbF_6$ (16)	85	<1
12	OH	[{RhCp*Cl_2}$_2$] (4)/$AgSbF_6$ (16)	85	<1

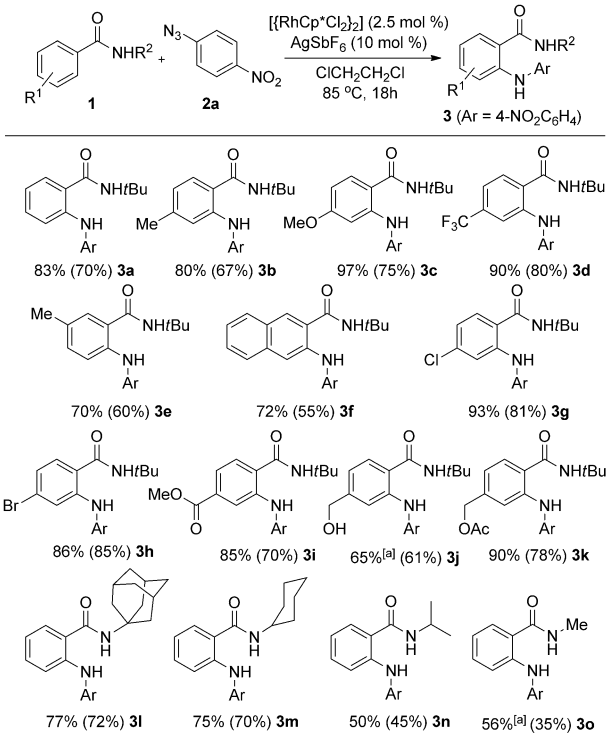
[a] Conditions: **1** (0.36 mmol) and **2a** (0.2 mmol) in 1,2-dichloroethane (0.5 mL). [b] Yield determined by ^{1}H NMR spectroscopy; yield of isolated product shown in parentheses. [c] KPF_6 (16 mol%) as an additive. Cp* = pentamethylcyclopentadiene, Piv = pivaloyl.

was effective irrespective of variation in the electronic nature of the benzamides (**3a**–**3d**).

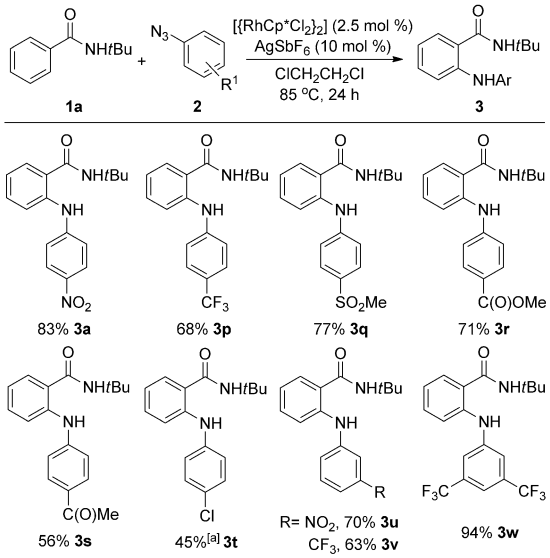
It should be mentioned that the use of benzamides as the limiting reagent (**1**/**2a** = 1:1.5) afforded products in slightly lower yields (numbers in parentheses), but still at a synthetically acceptable level, thus the present method is highly flexible. Substrates having a *meta*-substituent (**1e**) underwent the amination only at the sterically more accessible C–H bond. Likewise, 2-naphthamide was aminated exclusively at the 3-position (**3f**). The present amination was highly compatible with various functional groups. For example, substrates bearing a chloro (**1g**), bromo (**1h**), or ester group (**1i**) were all smoothly aminated in high yields. Notably, a free hydroxy group was tolerated under the present conditions, producing product **3j**. A highly functionalized arene compound was also obtained in excellent yield (**3k**). Steric bulk on the *N*-alkyl portion of the secondary amides was found to have a dramatic influence on the amination efficiency. For instance, reactions of benzamides bearing bulkier *N*-alkyl groups such as adamantyl (**1l**) or cyclohexyl (**1m**) provided higher product yields than those bearing isopropyl (**1n**) or methyl (**1o**) groups.[18]

The scope of aryl azides was then examined in the amination of *N*-*tert*-butylbenzamide **1a** (Scheme 3). Phenyl azides substituted with trifluoromethyl (**2p**), sulfonyl (**2q**), ester (**2r**), ketone (**2s**), or chloro (**2t**) groups in the *para* position were all viable for this direct amination, although only moderate product yields were obtained in reactions with **2s** and **2t**. Phenyl azides bearing *meta* substituents (**2u** and **2v**) also readily participated in the amination reaction, providing products in satisfactory yields. The best result was obtained with 3,5-bis(trifluoromethyl)phenyl azide to afford the corresponding aminated product (**3w**) in excellent yield. As in the case of benzamides, a broad range of functional groups on the aryl azides were tolerated, thus allowing for high diversity in the synthesis of diarylamines.

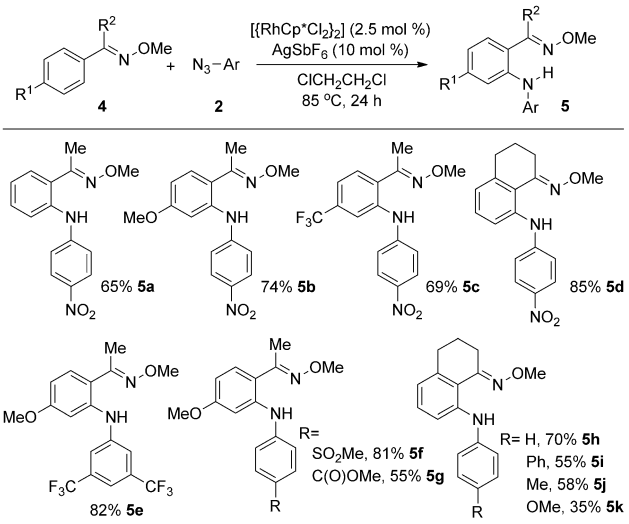
Encouraged by the successful results in the amination of benzamides, we turned our attention to additional substrates bearing synthetically useful directing groups (Scheme 4). We



Scheme 2. Aromatic amide substrate scope. Conditions: **1** (0.36 mmol) and **2a** (0.2 mmol) in 1,2-DCE (0.5 mL); yields given are of isolated products. Yields in parentheses were obtained from reactions with **1**/**2a** = 1:1.5. [a] Reaction run for 48 h.



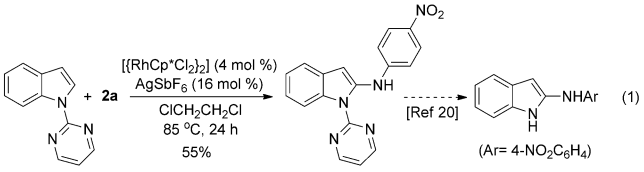
Scheme 3. Aryl Azide substrate scope. Conditions: **1a** (0.36 mmol), **2**, (0.2 mmol) in 1,2-DCE (0.5 mL); yields given are of isolated products. [a] Reaction run for 48 h.



Scheme 4. Aromatic Ketoxime substrate scope. Conditions: **4** (0.2 mmol), **2** (0.3 mmol) in 1,2-DCE (0.5 mL); yields given are of isolated products.

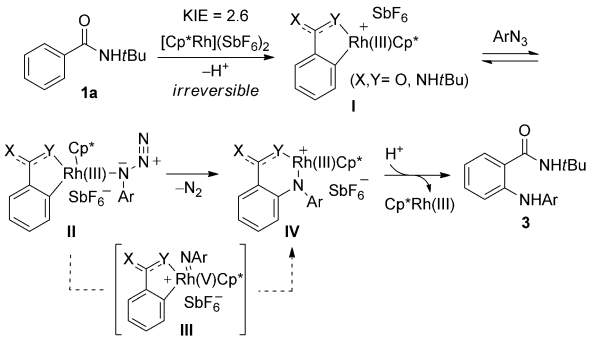
were pleased to observe that ketoximes also worked well to facilitate direct amination with aryl azides. Electronically modified aryl ketoximes were smoothly aminated with 4-nitrophenyl azide (**2a**) to give **5a**–**5c**. A bicyclic ketoxime derived from α-tetralone also successfully underwent amination to give **5d**. Variation with regard to aryl azides was also feasible in the present amination. In particular, it was noted that phenyl azides bearing not only electron-withdrawing substituents, but also electron-neutral and even electron-donating groups were all viable for this amination, emphasizing the generality of this method.

The direct amination of indole[19] was also performed with the same catalyst system [Eq. (1)]. Using a pyrimidyl group as an easily installable and readily removable directing group,[20] the reaction inserted an anilino unit selectively at the C2 position of the indole skeleton.



To gain insight into the reaction mechanism, preliminary isotopic experiments were conducted. Analysis of the aminated products and recovered starting material showed negligible H/D-scrambling, thus implying the irreversible nature of the C–H activation step. A competition reaction between *N-tert*-butylbenzamide **1a** and [D_5]**1a** showed a kinetic isotopic effect (KIE) of 2.6, which indicates that the C–H bond cleavage is most likely the rate-limiting step (see the Supporting Information for details).[21]

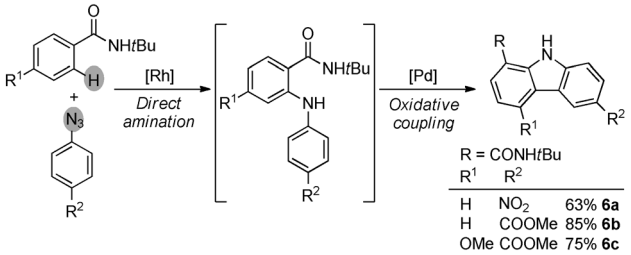
The proposed pathway for this amination reaction is shown in Scheme 5. A cyclometalation process through C–H bond activation delivers 5-membered rhodacycle intermediate **I**.[12,22] Irrespective of the exact structure of rhodacycle **I**, it



Scheme 5. Proposed reaction pathways.

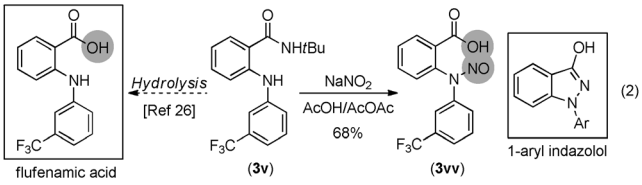
will then bind to aryl azides, leading to **II**. Subsequent formation of a rhodium(III) amido species **IV** from **II** can take place by either a concerted migratory insertion or, alternatively, a stepwise nitrenoid pathway in which a high valent rhodium(V) species **III** is involved.[23,24] Finally, the desired aminated product **3** is delivered by protonolysis of **IV**.

Diarylamines accessible by the present direct C–H amination have high synthetic utility. Since they are known to be redily converted into 9*H*-carbazoles,[25] our method was combined with a Pd-catalyzed oxidative cyclization procedure to afford functonalized carbazoles **6a**–**6c** in respectable yields (Scheme 6).

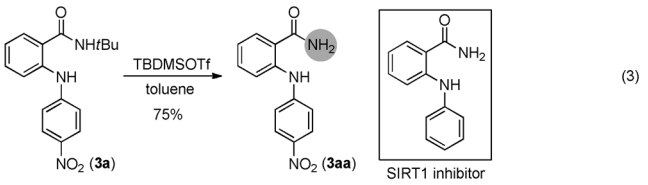


Scheme 6. Synthesis of multi-functionalized carbazoles.

Facile manipulation of the functional groups present in 2-anilinobenzamides offers an additional synthetic opportunity. For example, *N-tert*-butyl-(3-trifluoromethyanilino)-benzamide **3v**, which was produced in 63% yield (Scheme 3), can serve as a precursor to flufenamic acid, a nonsteroidal anti-inflammatory drug (NSAID).[26] Moreover, its analogues, which exhibit diverse bioactivity,[3] can also be envisioned to be obtained by our approach. We were successful in preparing an *N*-nitrosoamino derivative of flufenamic acid, **3vv**, which is also an anti-inflammatory agent[27] and a precursor of 1-aryl indazoles,[4b] from **3v** in acceptable yield from a literature procedure [Eq. (2)] (see the



Supporting Information for details).[28] Furthermore, the *N*-dealkylation of **3a** was readily carried out upon treatment with *tert*-butyldimethylsilyl trifluoromethanesulfonate (TBDMSOTf), giving rise to primary amide **3aa** [Eq. (3)],[29] thus opening a new synthetic route to 2-anilinobenzamides, a pharmacophore exhibiting novel biological activity, such as SIRT1-inhibitory action.[2]



(3)

In summary, we have presented the first example of a rhodium-catalyzed direct C–H amination of benzamides using aryl azides to deliver 2-anilinobenzamides, which have versatile synthetic and medicinal utility. The substrate scope was quite broad with respect to both benzamides and aryl azides, and it was readily extended to the direct aminaton of ketoximes with high functional group tolerance. The reaction does not require any external oxidants and releases only N_2 as a by-product, thus providing an environmentally benign amination process.

Experimental Section

Representative synthetic procedure: *N*-*tert*-butyl benzamide (**1a**, 64 mg, 0.36 mmol), 4-nitirophenyl azide (**2a**, 33 mg, 0.2 mmol), $[RhCp^*Cl_2]_2$ (3.1 mg, 2.5 mol%), $AgSbF_6$ (6.9 mg, 10 mol%) and 1,2-dichloroethane (0.5 mL) were added under atmospheric conditions to a screw cap vial equipped with a spinvane triangular-shaped Teflon stir bar. The reaction mixture was stirred in a pre-heated oil bath at 85°C for 18 h, then cooled to room temperature, filtered through a plug of celite, and washed with CH_2Cl_2 (10 mL × 3). The crude reaction mixture was purified by chromatography on silica gel (*n*-hexane/EtOAc = 10:1) to give the desired product, **3a** (52 mg, 83%).

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[1] a) A. Ricci, *Amino Group Chemistry: From Synthesis to the Life Sciences*, Wiley-VCH, Weinheim, **2008**; b) S. A. Lawrence, *Amines: Synthesis Properties and Applications*, Cambridge University Press, Cambridge, **2004**.

[2] For selected reports related to the bioactivity of 2-anilinobenzamides, see: a) T. Suzuki, K. Imai, H. Nakagawa, N. Miyata, *ChemMedChem* **2006**, *1*, 1059; b) T. Suzuki, K. Imai, E. Imai, S. Iida, R. Ueda, H. Tsumoto, H. Nakagawa, N. Miyata, *Bioorg. Med. Chem.* **2009**, *17*, 5900; c) K. D. Rice et al., *ACS Med. Chem. Lett.* **2012**, *3*, 416.

[3] For selected medicinal and biological reports related to 2-anilinobenzaoic acid (*N*-phenylanthranilates), see: a) P. W. Baures, V. B. Oza, S. A. Peterson, J. W. Kelly, *Bioorg. Med. Chem.* **1999**, *7*, 1339; b) C. Cougiu, M. T. Cocco, V. Lilliiu, V. Onnis, *J. Med. Chem.* **2005**, *48*, 8245; c) A. O. Adeniji, B. M. Twenter, M. C. Byrns, Y. Jin, M. Chen, J. D. Winkler, T. M. Penning, *J. Med. Chem.* **2012**, *55*, 2311.

[4] a) W. E. Coyne, J. W. Cusic, *J. Med. Chem.* **1968**, *11*, 1208; b) L. Baiocchi, G. Corsi, G. Palazzo, *Synthesis* **1978**, 633; c) K. Ozaki, Y. Yamada, T. Oine, *J. Org. Chem.* **1981**, *46*, 1571; d) G. P. Moloney, D. P. Kelly, P. Mack, *Molecules* **2001**, *6*, 230; e) H. Koshima, K. Kutsunai, *Heterocycles* **2002**, *57*, 1299; f) A. W. Schmidt, K. R. Reddy, H.-J. Knölker, *Chem. Rev.* **2012**, *112*, 3193.

[5] G. Evano, N. Blanchard, M. Toumi, *Chem. Rev.* **2008**, *108*, 3054.

[6] M. Kosugi, M. Kameyama, T. Migita, *Chem. Lett.* **1983**, *12*, 927.

[7] a) A. S. Guram, S. L. Buchwald, *J. Am. Chem. Soc.* **1994**, *116*, 7901; b) F. Paul, J. Patt, J. F. Hartwig, *J. Am. Chem. Soc.* **1994**, *116*, 5969.

[8] For selected reviews, see: a) A. Armstrong, J. C. Collins, *Angew. Chem.* **2010**, *122*, 2332; *Angew. Chem. Int. Ed.* **2010**, *49*, 2282; b) J. Wencel-Delord, T. Dröge, F. Liu, F. Glorius, *Chem. Soc. Rev.* **2011**, *40*, 4740; c) S. H. Cho, J. Y. Kim, J. Kwak, S. Chang, *Chem. Soc. Rev.* **2011**, *40*, 5068.

[9] For the oxidative direct amination of activated arenes, see: a) Q. Wang, S. L. Schreiber, *Org. Lett.* **2009**, *11*, 5178; b) D. Monguchi, T. Fujiwara, H. Furukawa, A. Mori, *Org. Lett.* **2009**, *11*, 1607; c) Y. Oda, K. Hirano, T. Satoh, M. Miura, *Org. Lett.* **2012**, *14*, 664. For the oxidative direct amination of arenes containing chelating groups, see: d) X. Chen, X.-S. Hao, C. E. Goodhue, J.-Q. Yu, *J. Am. Chem. Soc.* **2006**, *128*, 6790; e) H.-Y. Thu, W.-Y. Yu, C.-M. Che, *J. Am. Chem. Soc.* **2006**, *128*, 9048; f) B. Xiao, T.-J. Gong, J. Xu, Z.-J. Liu, L. Liu, *J. Am. Chem. Soc.* **2011**, *133*, 1466; g) A. John, K. M. Nicholas, *J. Org. Chem.* **2011**, *76*, 4158; h) B. Haffemayer, M. Gulias, M. J. Gaunt, *Chem. Sci.* **2011**, *2*, 312; i) J. Du Bois, *Org. Process Res. Dev.* **2011**, *15*, 758.

[10] For the direct amination of (hetero)arenes using a pre-activated amino precursor, see: a) T. Kawano, K. Hirano, T. Satoh, M. Miura, *J. Am. Chem. Soc.* **2010**, *132*, 6900; b) K.-H. Ng, A. S. C. Chan, W.-Y. Yu, *J. Am. Chem. Soc.* **2010**, *132*, 12862; c) K. Sun, Y. Li, T. Xiong, J. Zhang, Q. Zhang, *J. Am. Chem. Soc.* **2011**, *133*, 1694; d) E. J. Yoo, S. Ma, T.-S. Mei, K. S. L. Chan, J.-Q. Yu, *J. Am. Chem. Soc.* **2011**, *133*, 7652; e) K.-H. Ng, Z. Zhou, W.-Y. Yu, *Org. Lett.* **2012**, *14*, 272; f) C. Grohmann, H. Wang, F. Glorius, *Org. Lett.* **2012**, *14*, 656.

[11] a) J. Y. Kim, S. H. Cho, J. Joseph, S. Chang, *Angew. Chem.* **2010**, *122*, 10095; *Angew. Chem. Int. Ed.* **2010**, *49*, 9899; b) M. Kim, S. Chang, *Org. Lett.* **2010**, *12*, 1640; c) H. J. Kim, J. Kim, S. H. Cho, S. Chang, *J. Am. Chem. Soc.* **2011**, *133*, 16382; d) S. H. Cho, J. Yoon, S. Chang, *J. Am. Chem. Soc.* **2011**, *133*, 5996.

[12] J. Y. Kim, S. H. Park, J. Ryu, S. H. Cho, S. H. Kim, S. Chang, *J. Am. Chem. Soc.* **2012**, *134*, 9110.

[13] S. Bräse, C. Gil, K. Knepper, V. Zimmermann, *Angew. Chem.* **2005**, *117*, 5320; *Angew. Chem. Int. Ed.* **2005**, *44*, 5188.

[14] For reviews, see: a) T. Katsuki, *Chem. Lett.* **2005**, *34*, 1304; b) S. Cenini, E. Gallo, A. Caselli, F. Ragaini, S. Fantauzzi, C. Piangiolino, *Coord. Chem. Rev.* **2006**, *250*, 1234; c) T. G. Driver, *Org. Biomol. Chem.* **2010**, *8*, 3831.

[15] a) B. J. Stokes, H. Dong, B. E. Leslie, A. L. Pumphrey, T. G. Driver, *J. Am. Chem. Soc.* **2007**, *129*, 7500; b) W. G. Shou, J. Li, T. Guo, Z. Lin, G. Jia, *Organometallics* **2009**, *28*, 6847; c) J. Bonnamour, C. Bolm, *Org. Lett.* **2011**, *13*, 2012; d) Q. Nguyen, K. Sun, T. G. Driver, *J. Am. Chem. Soc.* **2012**, *134*, 7262.

[16] a) S. Cenini, E. Gallo, A. Penoni, F. Ragaini, S. Tollari, *Chem. Commun.* **2000**, 2265; b) Y. M. Badiei, A. Dinescu, X. Dai, R. M. Palomino, F. W. Heinemann, T. R. Cundari, T. H. Warren, *Angew. Chem.* **2008**, *120*, 10109; *Angew. Chem. Int. Ed.* **2008**, *47*, 9961.

[17] For selected additional examples of C–H functionalization using organic azides, see: a) Y.-F. Wang, K. K. Toh, E. P. J. Ng, S. Chiba, *J. Am. Chem. Soc.* **2011**, *133*, 6411; b) Y.-F. Wang, K. K.

Toh, J.-Y. Lee, S. Chiba, *Angew. Chem.* **2011**, *123*, 6049; *Angew. Chem. Int. Ed.* **2011**, *50*, 5927.
[18] Although the exact reason for this difference is not clear at present, the degree of coordination of the rhodium center to the benzamido nitrogen atom is assumed to vary depending on substrates.
[19] For the metal-catalyzed direct C2 amination of indoles, see: a) Q. Shuai, G. Deng, Z. Chua, D. S. Bohle, C.-J. Li, *Adv. Synth. Catal.* **2010**, *352*, 632; b) X.-Y. Liu, P. Gao, Y.-W. Shen, Y.-M. Liang, *Org. Lett.* **2011**, *13*, 4196.
[20] L. Ackermann, A. V. Lygin, *Org. Lett.* **2011**, *13*, 3332.
[21] E. M. Simmons, J. F. Hartwig, *Angew. Chem.* **2012**, *124*, 3120; *Angew. Chem. Int. Ed.* **2012**, *51*, 3066.
[22] L. Li, W. W. Brennessel, W. D. Jones, *J. Am. Chem. Soc.* **2008**, *130*, 12414.
[23] For Rh-nitrenoid species, see: a) I. Nägeli, C. Baud, G. Bernardinelli, Y. Jacquier, M. Moran, P. Müller, *Helv. Chim. Acta* **1997**, *80*, 1087; b) H. M. L. Davies, J. R. Manning, *Nature* **2008**, *451*, 417; c) N. Jung, S. Bräse, *Angew. Chem.* **2012**, *124*, 5632; *Angew. Chem. Int. Ed.* **2012**, *51*, 5538.
[24] A Rh^{V} species has been proposed as an intermediate in other reactions; see: a) N. Schröder, J. Wencel-Delord, F. Glorius, *J. Am. Chem. Soc.* **2012**, *134*, 8298; b) J. Wencel-Delord, C. Nimphius, F. W. Patureau, F. Glorius, *Angew. Chem.* **2012**, *124*, 2290; *Angew. Chem. Int. Ed.* **2012**, *51*, 2247.
[25] B. Liégault, D. Lee, M. P. Huestis, D. R. Stuart, K. Fagnou, *J. Org. Chem.* **2008**, *73*, 5022.
[26] For the hydrolysis of secondary amides, see: a) G. G. Tokmadzhyan, *Russ. J. Org. Chem.* **2011**, *47*, 1708; see also, ref [10d].
[27] a) G. Zoni, G. Picciola, *Boll. Chim. Farm.* **1968**, *107*, 598; b) G. Zoni, M. L. Molinari, *Boll. Chim. Farm.* **1971**, *110*, 105.
[28] H. V. Le, L. Fan, B. Ganem, *Tetrahedron Lett.* **2011**, *52*, 2209.
[29] E. Takács, C. Varga, R. Skoda-Földes, L. Kollár, *Tetrahedron Lett.* **2007**, *48*, 2453.

