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Rhodium(III)-Catalyzed C(sp^2)–H Activation and Electrophilic Amidation with *N*-Fluorobenzenesulfonimide

Ren-Jin Tang,[a] Cui-Ping Luo,[a] Luo Yang,[a,*] and Chao-Jun Li[b,*]

[a] Key Laboratory for Environmentally Friendly Chemistry and Application of the Ministry of Education, Department of Chemistry, Xiangtan University, Hunan 411105, People's Republic of China
Fax: (+86)-731-5829-2251; phone: (+86)-731-5829-8351; e-mail: yangluo@xtu.edu.cn

[b] Department of Chemistry, McGill University, Montreal, QC, Canada H3A 2K6
Fax: (+1)-514-398-8457; phone: (+1)-514-398-3797; e-mail: cj.li@mcgill.ca

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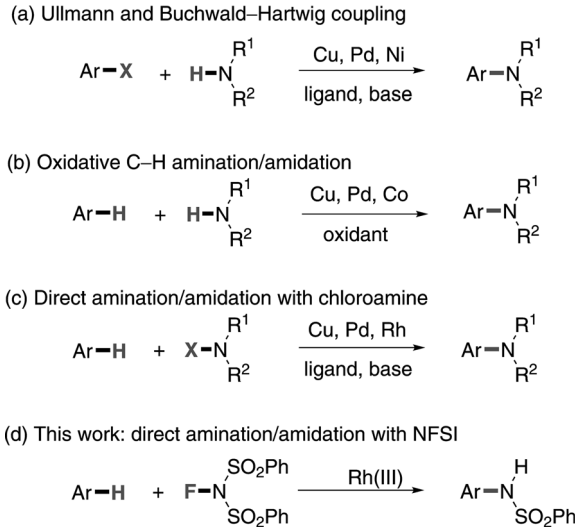
Abstract: An electrophilic amidation *via* a cationic rhodium(III)-catalyzed C(sp^2)–H activation has been developed with the commercially available *N*-fluorobenzenesulfonimide as the amino source under external oxidant-free conditions. This amidation requires only a catalytic amount of base and exhibits excellent functional group tolerance and regioselectivity, providing a new avenue in direct C-(sp^2)–H amidation.

Keywords: amidation; C(sp^2)–H activation; cationic rhodium(III); *N*-fluorobenzenesulfonimide

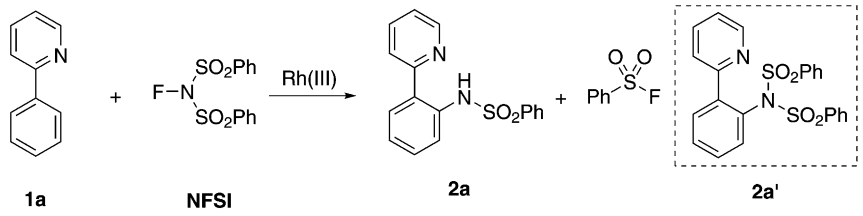
The prevalence of the arylamine motif in natural products, pharmaceuticals, agrochemicals and materials has positioned C(sp^2)–N bond formation high on the agenda of synthetic chemists.[1] The classical synthesis of aromatic amines/amides relies on the cross-coupling of aryl (pseudo)halides with amines/amides as exemplified by the Ullmann–Goldberg[2] and Buchwald–Hartwig couplings[3] [Scheme 1 (a)]. With the rapid advances of transition metal-catalyzed C–H activation, the direct C(sp^2)–H amination/amidation appears to be highly appealing, especially if high regioselectivity can be achieved, which either employs parent amines/amides in the presence of external oxidants[4] [Scheme 1 (b)] or utilizes activated amino precursors[5] such as chloramines or their analogs [Scheme 1 (c)]. While these routes complemented each other to make C(sp^2)–N bond formation available for most substrates, the majority of them were realized under cross-coupling or nitrene insertion[4,6] mechanisms. Herein, we report a new C(sp^2)–N bond formation reaction based on the electrophilic substitution pathway using *N*-fluorobenzenesulfonimide (NFSI) as the amino source [Scheme 1 (d)].



Scheme 1. Various routes for C(sp^2)–N bond formations

N-Fluorobenzenesulfonimide (NFSI) is a well-known fluorination reagent and oxidant in C–H transformation reactions.[7] Recently, it was found to be an efficient amino source in both sp^2 and sp^3 C–H amidations catalyzed by Pd[8a–c] or Cu[8d]. As part of our continuing interest in developing facile and efficient nucleophilic reactions, we recently reported the Rh(III)-catalyzed C(sp^2)–H activation and nucleophilic addition to aldehydes[9] or α,β-unsaturated carbonyl compounds[10] under mild conditions. Other groups[11] also reported similar C(sp^2)–H addition to aldimines. Based on these results and the mechanistic study[11f] by Shi et al., we postulated that C(sp^2)–H activation and nucleophilic substitution should take place when the C=O and C=N unsaturated bonds were replaced by suitable reactive polarized covalent bonds. These considerations led us to envision a Rh(III)-catalyzed C(sp^2)–H activation and electrophilic amidation with NFSI.[12]

Table 1. Optimization of the rhodium-catalyzed C(sp^2)–H amidation.[a]



1a **NFSI** **2a** **2a'**

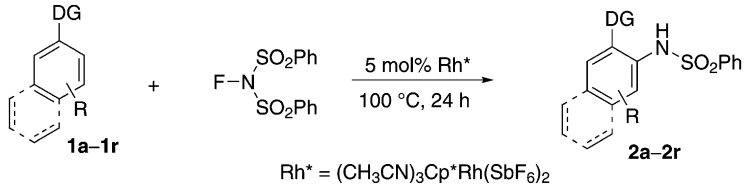
Entry	Catalyst (mol%)	Additive (10 mol%)	Temp. [°C]	Solvent	Yield [%][b]
1	[Cp*$RhCl_2$] (1.25)	Cs_2CO_3	100	DCE	65
2	**Rh* (2.5)**	**Cs_2CO_3**	**100**	**DCE**	**81**
3	Rh* (5.0)	Cs_2CO_3	100	DCE	83
4	Rh* (2.5)	Cs_2CO_3	80	DCE	56
5	Rh* (2.5)	Cs_2CO_3	60	DCE	48
6[c]	Rh* (2.5)	Cs_2CO_3	100	DCE	68
7	$Pd(OAc)_2$ (2.5)	Cs_2CO_3	100	DCE	0
8	$Cu(OAc)_2$ (2.5)	Cs_2CO_3	100	DCE	0
9	Rh* (2.5)	K_2CO_3	100	DCE	55
10	Rh* (2.5)	–	100	DCE	49
11	Rh* (2.5)	CH_3CO_2H	100	DCE	44
12	Rh* (2.5)	Cs_2CO_3	100	THF	62
13	Rh* (2.5)	Cs_2CO_3	100	toluene	55
14	Rh* (2.5)	Cs_2CO_3	100	CH_3CN	39
15	Rh* (2.5)	Cs_2CO_3	100	DMF	<5

[a] *Conditions:* **1a** (0.2 mmol), NFSI (0.4 mmol), additive, solvent (0.2 mL), reacted for 24 h under argon unless otherwise noted; Rh* = $(CH_3CN)_3$Cp*$Rh(SbF_6)_2$.
[b] The yield of isolated product is reported.
[c] NFSI (0.24 mmol) was added.

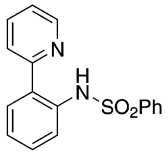
To begin our study, we first examined the reaction of 2-phenylpyridine (**1a**) and NFSI using rhodium catalyst based on our early work. Unexpectedly, product **2a** was isolated instead of the desired *N*-arylbenzenesulfonimide (**2a′**) in moderate yield (Table 1, entry 1), likely because product **2a** was less sterically hindered and stabilized by the intramolecular hydrogen bonding with the nitrogen of the directing pyridine motif. The cationic Rh(III) catalyst, $(CH_3CN)_3$Cp*$Rh(SbF_6)_2$ (Rh*, Cp* = pentamethylcyclopentadienyl) turned out to be more reactive and the yield of **2a** was increased to 81% in 1,2-dichloroethane (DCE) at 100 °C (entry 2). The by-product of NFSI was characterized by GC-MS, ^{1}H NMR and ^{13}C NMR as benzenesulfonyl fluoride ($PhSO_2F$) in 84% isolated yield.[13] While doubling the catalyst loading exerted little improvement on the yield (entry 3), decreasing the reaction temperature gave much inferior yield (entries 4 and 5). An excess of NFSI was required to promote the complete consumption of 2-phenylpyridine; thus the yield diminished considerably when 1.2 equiv. of NFSI were added (entry 6). Surprisingly, other transition metal catalysts such as $Pd(OAc)_2$ and $Cu(OAc)_2$ were completely ineffective in this C(sp^2)–H amidation reaction (entries 7 and 8). A catalytic amount of Cs_2CO_3 was essential for the high yield, and replacing it with K_2CO_3 or acetic acid led to a dramatic decrease of the yields (entries 9–11), which implys that a catalytic amount of base can accelerate the deprotonation step in the rhodium-catalyzed C(sp^2)–H activation. The influence of the solvent on this reaction was studied next and the most satisfactory yield was obtained in low polarity DCE. Other common solvents such as THF, toluene and acetonitrile were also applicable; however displayed lower yields. More polar DMF was ineffective.

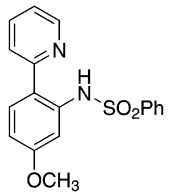
Under the optimized conditions (Table 1, entry 2), the substrate scope of this novel rhodium-catalyzed C(sp^2)–H activation and electrophilic amidation with NFSI was explored. As shown by the results in Table 2, all the 2-phenylpyridine analogs tested (**1a**–**1m**) reacted with NFSI smoothly to produce the corresponding sulfamides efficiently, regardless of whether the phenyl group was substituted by electron-withdrawing or electron-donating groups. We were pleased to observe that functional groups such as alkoxy (**2b**), acetoxy (**2c**), halides (**2i–2k**) and methoxycarbonyl (**2l**) were all tolerated. The influence of substituents at different positions of the phenyl ring was also examined. To our delight, this C–H amidation demonstrated a high regioselectivity. While the less hindered C(sp^2)–H of the *meta*-methyl substrate **1f** reacted with NFSI in good yield, the more sterically hindered *ortho*-methyl substrate **1g**

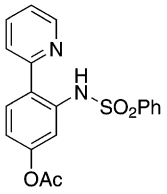
Table 2. The C(sp^2)–H amidation of 2-phenylpyridine analogs with NFSI.[a]

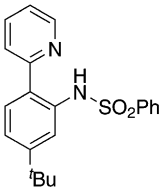


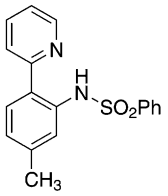
1a: R = H	**1b**: R = *p*-CH_3O	**1c**: R = *p*-AcO
1d: R = *p*-*t*-Bu	**1e**: R = *p*-CH_3	**1f** R = *m*-CH_3
1g: R = *o*-CH_3	**1h**: R = *p*-Ph	**1i**: R = *p*-F
1j: R = *p*-Cl	**1k**: R = *p*-Br	**1l**: R = *p*-CO_2Me
1m: R = *p*-CF_3	**1n**: 2-(β-naphthyl)-pyridine	**1o**: 2-(α-naphthyl)-pyridine
1p: 2-methyl-6-phenylpyridine	**1q**: 2-phenylpyrimidine	**1r**: 1-phenylpyrazole

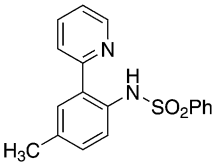

2a, 81 %

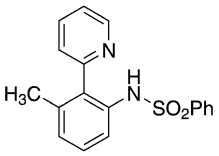

2b, 73 %

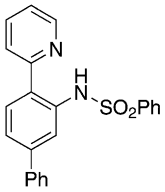

2c, 75 %

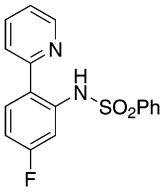

2d, 71 %

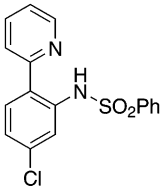

2e, 78 %

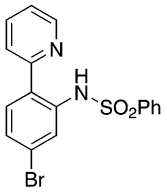

2f, 76 %

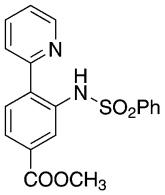

2g, 35 %

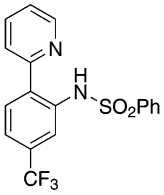

2h, 76 %

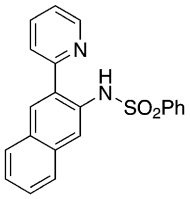

2i, 69 %

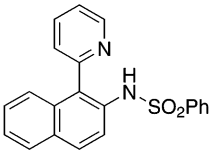

2j, 67 %

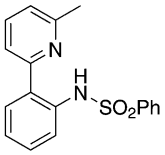

2k, 70 %

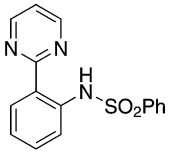

2l, 69 %

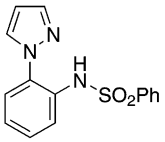

2m, 73 %


2n, 73 %


2o, 66 %


2p, 73 %

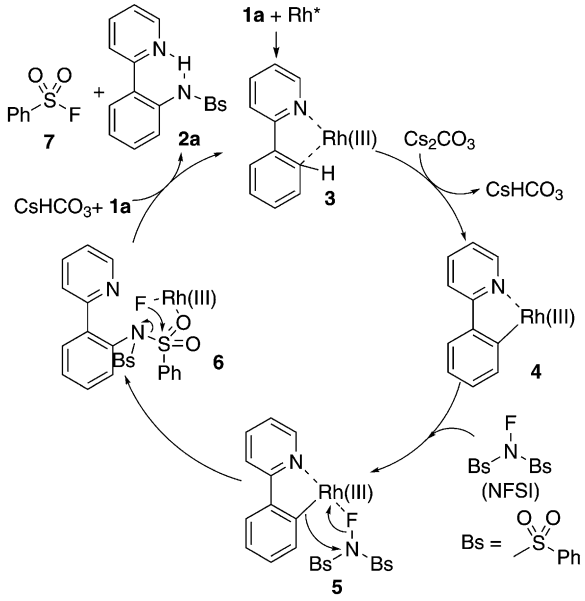

2q, 58 %


2r, 32 %

[a] *Conditions:* $(CH_3CN)_3Cp^*Rh(SbF_6)_2$ (0.005 mmol, 2.5 mol%), **1a**–**1r** (0.2 mmol), NFSI (0.4 mmol), Cs_2CO_3 (0.02 mmol), DCE (0.2 mL), reacted for 24 h under argon unless otherwise noted. The yield of isolated product is reported.

gave a much lower yield. Likewise, 2-β-naphthylpyridine (**1n**) and 2-α-naphthylpyridine (**1o**) were also applicable in this reaction with the former providing only the monoamidation product **2n**. Pyridinyl directing group with a methyl substituent at C-6 (**1p**) also showed good reactivity, giving **2p** in 73% yield. Other nitrogen-containing heterocyclic substituents such as pyrimidinyl and pyrazolyl can also act as the directing group,[13] albeit the corresponding C–H amidation products **2q** and **2r** were obtained in lower yields.

A plausible mechanism to rationalize this novel rhodium-catalyzed C(sp^2)–H activation and electrophilic amidation with NFSI is illustrated in Scheme 2.



Scheme 2. Tentative mechanism for the rhodium-catalyzed C(sp^2)–H activation and electrophilic amidation.

First, the coordination of rhodium catalyst (Rh*) to 2-phenylpyridine and subsequent electrophilic substitution generates the arylrhodium complex **3** and one equivalent of proton,[11f] which is captured by the Cs_2CO_3. Then, the fluorine atom on the NFSI coordinates to the arylrhodium complex **4** to produce arylrhodium complex **5**, which is followed by the substitution of the F in the polarized N–F bond by the nucleophilic C(sp^2)–Rh to yield the *N*-arylbenzenesulfonimide complex **6**.[12] Due to the steric hinderance and instability of this *N*-arylbenzenesulfonimide, the fluoride will further substitute the sulfonyl group to release the benzenesulfonyl fluoride (**7**)[14] and the *N*-arylbenzenesulfonamide anion, to provide the product **2a** and regenerate of the rhodium catalyst (Rh*) after protonation.

In summary, we have developed an efficient C-(sp^2)–H activation–electrophilic amidation strategy with NFSI as the commercially available amino source. This reaction does not require any external oxidant and only a catalytic amount of base was needed. The amidation could tolerate a wide range of functional groups such as alkoxy, acetoxy, halides and methoxycarbonyl and was highly regioselective, occurring exclusively at the less hindered *ortho*-position relative to the 2-pyridyl (even in the presence of other potential chelate groups). The detailed reaction mechanism and applications of this novel amidation are under investigation.

Experimental Section

General Experimental Procedure

An oven-dried reaction vessel was charged with $(CH_3CN)_3Cp^*Rh(SbF_6)_2$ (Rh*, 4.2 mg, 2.5 mol%, 0.005 mmol), DCE (0.2 mL), 2-phenylpyridine (**1a**, 31 mg, 0.2 mmol), Cs_2CO_3 (0.02 mmol), and NFSI (126 mg, 0.4 mmol) under argon. The vessel was sealed and heated at 100 °C (oil bath temperature) for 24 h. The resulting mixture was cooled to room temperature, filtered through a short silica gel pad and transferred to silica gel column directly and eluted with hexanes and ethyl acetate (3:1) to give products **2a** (yield: 50 mg, 81%) and benzenesulfonyl fluoride (yield: 27 mg, 84%).

Acknowledgements

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References

[1] a) *Amino Group Chemistry, From Synthesis to the Life Sciences*, (Ed.: A. Ricci), Wiley-VCH, Weinheim, **2007**; b) R. Hili, A. K. Yudin, *Nat. Chem. Biol.* **2006**, *2*, 284.
[2] a) F. Ullmann, *Ber. Dtsch. Chem. Ges.* **1903**, 36, 2382; b) I. Goldberg, *Ber. Dtsch. Chem. Ges.* **1906**, 39, 1691; c) G. Evano, N. Blanchard, M. Toumi, *Chem. Rev.* **2008**, *108*, 3054; d) F. Monnier, M. Taillefer, *Angew. Chem.* **2009**, *121*, 7088; *Angew. Chem. Int. Ed.* **2009**, *48*, 6954.
[3] a) F. Paul, J. Patt, J. F. Hartwig, *J. Am. Chem. Soc.* **1994**, *116*, 5969; b) A. S. Guram, S. L. Buchwald, *J. Am. Chem. Soc.* **1994**, *116*, 7901; c) J. F. Hartwig, *Acc. Chem. Res.* **2008**, *41*, 1534; d) D. S. Surry, S. L. Buchwald, *Angew. Chem.* **2008**, *120*, 6438; *Angew. Chem. Int. Ed.* **2008**, *47*, 6338; e) J. P. Wolfe, S. Wagaw, J.-F. Marcoux, S. L. Buchwald, *Acc. Chem. Res.* **1998**, *31*, 805.
[4] For selected reviews on C(sp^2)–H amidation: a) T. W. Lyons, M. S. Sanford, *Chem. Rev.* **2010**, *110*, 1147–1169;

b) M. M. Diaz-Requejo, P. J. Pérez, *Chem. Rev.* **2008**, *108*, 3379; c) E. M. Beccalli, G. Broggini, M. Martinelli, S. Sottocornola, *Chem. Rev.* **2007**, *107*, 5318; d) F. Collet, R. H. Dodd, P. Dauban, *Chem. Commun.* **2009**, 5061; e) S. H. Cho, J. Y. Kim, J. Kwak, S. Chang, *Chem. Soc. Rev.* **2011**, *40*, 5068.

[5] For recent amidations with electrophilic nitrogen sources, 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) N. Matsuda, K. Hirano, T. Satoh, M. Miura, *Org. Lett.* **2011**, *13*, 2860; d) K.-H. Ng, Z. Zhou, W. Y. -Yu, *Org. Lett.* **2012**, *14*, 272; e) C. Grohmann, H. Wang, F. Glorius, *Org. Lett.* **2012**, *14*, 656; f) J. Y. Kim, S. H. Park, J. Ryu, S. H. Cho, S. H. Kim, S. Chang, *J. Am. Chem. Soc.* **2012**, *134*, 9100; g) J. Ryu, K. Shin, S. H. Park, J. Y. Kim, S. Chang, *Angew. Chem.* **2012**, *124*, 10042; *Angew. Chem. Int. Ed.* **2012**, *51*, 9904; h) E. J. Yoo, S. Ma, T.-S. Mei, K. S. L. Chan, J.-Q. Yu, *J. Am. Chem. Soc.* **2011**, *133*, 7652; i) Y. Tan, J. F. Hartwig, *J. Am. Chem. Soc.* **2010**, *132*, 3676; j) X.-Y. Liu, P. Gao, Y.-W. Shen, Y.-M. Liang, *Org. Lett.* **2011**, *13*, 4196.

[6] For excellent reviews on C–H activation through nitrenes, see: a) D. N. Zalatan, J. D. Bois, *Top. Curr. Chem.* **2010**, *292*, 347–378; b) G. Dequirez, V. Pons, P. Dauban, *Angew. Chem. Int. Ed.* **2012**, *124*, 7498; *Angew. Chem. Int. Ed.* **2012**, *51*, 7384; c) P. Muller, C. Fruit, *Chem. Rev.* **2003**, *103*, 2905; d) J. L. Roizen, M. E. Harvey, J. Du Bois, *Acc. Chem. Res.* **2012**, *45*, 911; e) H. Lu, X. P. Zhang, *Chem. Soc. Rev.* **2011**, *40*, 1899; f) F. Collet, C. Lescot, P. Dauban *Chem. Soc. Rev.* **2011**, *40*, 1926; g) C. M. Che, V. K.-Y. Lo, C. Y. Zhou, J.-S. Huang, *Chem. Soc. Rev.* **2011**, *40*, 1950.

[7] For recent examples using NFSI as fluorination reagent or oxidant, see: a) P. A. Sibbald, C. F. Rosewall, R. D. Swartz, F. E. Michael, *J. Am. Chem. Soc.* **2009**, *131*, 15945; b) M. Rurda-Becerril, C. C. Sazepin, J. C. T. Leung, T. Okbinoglu, P. Kennepohl, J.-F. Paquin, G. M. Sammis, *J. Am. Chem. Soc.* **2012**, *134*, 4026; c) Y. H. Lim, Q. Ong, H. A. Duong, T. M. Nguyen, C. W. Johannes, *Org. Lett.* **2012**, *14*, 5676; d) S. Qiu, T. Xu, J. Zhou, Y. Guo, G. Liu, *J. Am. Chem. Soc.* **2010**, *132*, 2856; e) D. V. Liskin, P. A. Sibbald, C. F. Rosewall, *J. Org. Chem.* **2010**, *75*, 6294; f) T. Xu, S. Qiu, G. Liu, *J. Organomet. Chem.* **2011**, *696*, 46; g) A. Lozano, G. Blessley, T. M. del Campo, A. L. Thompson, G. T. Giuffredi, M. Bettati, M. Walker, R. Borman, V. Gouverneur, *Angew. Chem.* **2011**, *123*, 8255; *Angew. Chem. Int. Ed.* **2011**, *50*, 8105; h) K. L. Hull, W. Q. Anani, M. S. Sanford, *J. Am. Chem. Soc.* **2006**, *128*, 7134.

[8] For recent amidations with NFSI, see: a) K. Sun, Y. Li, T. Xiong, J. Zhang, Q. Zhang, *J. Am. Chem. Soc.* **2011**, *133*, 1694; b) A. Iglesias, R. Alvarez, A. R. de Lera, K. Muniz, *Angew. Chem.* **2012**, *124*, 2268; *Angew. Chem. Int. Ed.* **2012**, *51*, 2225; c) T. Xiong, Y. Li, Y. Lv, Q. Zhang, *Chem. Commun.* **2010**, *46*, 6831; d) Z. Ni, Q. Zhang, T. Xiong, Y. Zheng, Y. Li, H. Zhang, J. Zhang, Q. Liu, *Angew. Chem.* **2012**, *124*, 1270; *Angew. Chem. Int. Ed.* **2012**, *51*, 1244; e) H. J. Kim, J. Kim, S. H. Cho, S. Chang, *J. Am. Chem. Soc.* **2011**, *133*, 16382; f) K. Muniz, J. Kirsch, P. Chavez, *Adv. Synth. Catal.* **2011**, *353*, 689.

[9] a) L. Yang, C. A. Correia, C.-J. Li, *Adv. Synth. Catal.* **2011**, *353*, 1269; b) F.-F. Wang, C.-P. Luo, Y. Wang, G. Deng, L. Yang, *Org. Biomol. Chem.* **2012**, *10*, 8605.

[10] L. Yang, Q. Shuai, C.-J. Li, *Org. Biomol. Chem.* **2011**, *9*, 7176–7179.

[11] a) Y. Li, W.-H. Wang, W.-P. Huang, X.-S. Zhang, K. Chen, Z.-J. Shi, *Angew. Chem.* **2011**, *123*, 2163; *Angew. Chem. Int. Ed.* **2011**, *50*, 2115; b) A. S. Tsai, M. E. Tauchert, R. G. Bergman, J. A. Ellman, *J. Am. Chem. Soc.* **2011**, *133*, 1248; c) K. D. Hesp, R. G. Bergman, J. A. Ellman, *J. Am. Chem. Soc.* **2011**, *133*, 11430; d) B.-J. Li, Z.-J. Shi, *Chem. Sci.* **2011**, *2*, 488; e) Y. Li, X.-S. Zhang, H. Li, W.-H. Wang, K. Chen, B.-J. Li, Z.-J. Shi, *Chem. Sci.* **2012**, 1634; f) J. Takaya, N. Iwasawa, *J. Am. Chem. Soc.* **2011**, *133*, 1251; g) Y. Li, X.-S. Zhang, K. Chen, K.-H. He, F. Pan, B.-J. Li, Z.-J. Shi, *Org. Lett.* **2012**, *14*, 636.

[12] E. Erdik, *Tetrahedron* **2004**, *60*, 8747.

[13] The nitrogen-containing heterocycles are effective directing group but difficult to remove, so another synthetically more useful substrate such as *N*-(pivaloyloxy)benzamide would be chosen in the further research.

[14] The spectral data of benzenesulfonyl fluoride are also listed in the Supporting Information.

