Organic LETTERS

Letter

pubs.acs.org/OrgLett

Rh(III)-Catalyzed Intermolecular C−H Amination of 1-Aryl-1*H*-pyrazol-5(4*H*)-ones with Alkylamines

Kui Wu,[†,‡] Zhoulong Fan,[‡] Yu Xue,[†] Qizheng Yao,*[,†] and Ao Zhang*[,‡]

[†]Department of Medicinal Chemistry, China Pharmaceutical University, Nanjing 210009, China

[‡]CAS Key Laboratory of Receptor Research, and Synthetic Organic & Medicinal Chemistry Laboratory (SOMCL), Shanghai Institute of Materia Medica (SIMM), Chinese Academy of Sciences, Shanghai, China

Supporting Information

ABSTRACT: An intermolecular C−H amination of 1-aryl-1*H*-pyrazol-5(4*H*)-ones was achieved under mild reaction conditions, using a low catalyst loading and with a broad scope of aminating reagents. This protocol not only provides the first example of rhodium(III)-catalyzed intermolecular aromatic C−H amination directed by an intrinsic functionality of the substrate/product but also features aminating an existing drug with either primary or secondary *N*-benzoate alkylamines as the coupling partners.

Aryl amines are essential structural fragments that widely exist in both natural products and synthetic pharmaceuticals.[1] Conventional preparation of functional aryl amines is largely dependent on Pd- or Cu-catalyzed C−N couplings[2a−f] that generally require prefunctionalization of arenes (halides or their equivalents). Recently, advances in the transition-metal-catalyzed C−H activation/amination of inactivated simple arenes have greatly revolutionalized the design concept and disconnection strategy in the synthesis of aryl amines, especially those complexes with multiple functionalities.[3,4] However, compared to the achievements in the intramolecular C−N bond formation,[5] the intermolecular arene C−H activation/amination has received limited success.[6−8] One of the earliest examples of Pd-catalyzed intermolecular C−H activation/amination was reported by Yu[8a] who used *N*-(4-CF_3-C_6F_4)-benzamides as the arene substrates and *O*-benzoyl hydroxylamines as the coupling partners (*N*-source) under the $Pd(OAC)_2$/AgOAc/CsF system. With the assistance of CONH-(4-CF_3)C_6F_4 as the directing group, a series of secondary amino groups were successfully introduced (eq a, Scheme 1). Similarly, with *N*-pivaloyloxy benzamides as the substrates and *N*-chloroamines as the coupling partners, a Rh(III)-catalyzed intermolecular electrophilic C−H amination was also reported recently by Glorius[8b] (eq b, Scheme 1). Meanwhile, with the *O*-methyloxime moiety as the directing group, Rh(III)-catalyzed intermolecular C−H amination of acetophenone *O*-methyloximes with either secondary or primary *N*-chloroalkylamines was achieved by Yu et al. (eq c, Scheme 1).[9] Very recently, $Cu(OAc)_2$-catalyzed[10a] intermolecular C−H amination using benzamides bearing an 8-aminoquinoline moiety as the directing group and Ru(II)-catalyzed[10b] C−H amination of various heterocycles directed by a weakly coordinating amide auxiliary with *O*-benzoyl hydroxylamines were also reported.

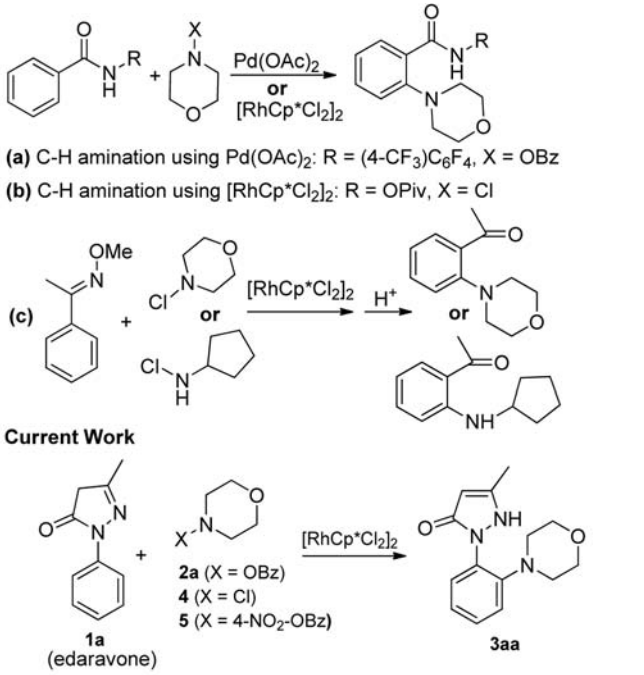
Notably, all the pioneering work was limited to simple benzamides, acetophenone *O*-methyloximes, or their equivalents as the arene substrates, and the directing group needs to be pre-built-in and removed afterward. It would be desirable to develop new intermolecular C−H aminations on arene substrates bearing an intrinsic functionality capable of directing the position selectivity of the C−H amination. To this end, we recently found that 3-methyl-1-phenyl-1*H*-pyrazol-5(4*H*)-one (**1a**) is an optimal arene substrate for Rh(III)-catalyzed intermolecular electrophilic C−H amination (Scheme 1). With the pyrazol-5(4*H*)-one fragment in **1a** as the intrinsic directing group, both secondary and primary alkylamines could be introduced to the $[RhCp^*Cl_2]_2$/CsOAc system. To the best of our knowledge, transition-metal-catalyzed C−H activation/amination directed by a pyrazol-5(4*H*)-one moiety (as in **1a**) has not been reported yet. Meanwhile, compound **1a** itself is a neuroprotective drug marked as Edaravone[11,12] in 2001 in Japan for neurological recovery following acute brain ischemia and subsequent cerebral infarction. Therefore, our current C−H activation/amination study on compound **1a** not only provides a novel example of intermolecular C−H amination on arenes bearing an intrinsic directing group, but also offers a new strategy to generate new analogues of the existing drug **1a** for immediate drug screening.

With 3-methyl-1-phenyl-1*H*-pyrazol-5(4*H*)-one (**1a**) as the arene substrate and $[Cp^*RhCl_2]_2$ as the catalyst, we first

Received: October 14, 2013
Published: December 12, 2013

dx.doi.org/10.1021/ol402965d | *Org. Lett.* 2014, 16, 42−45

Scheme 1. Reported C−H Aminations and Our Proposal

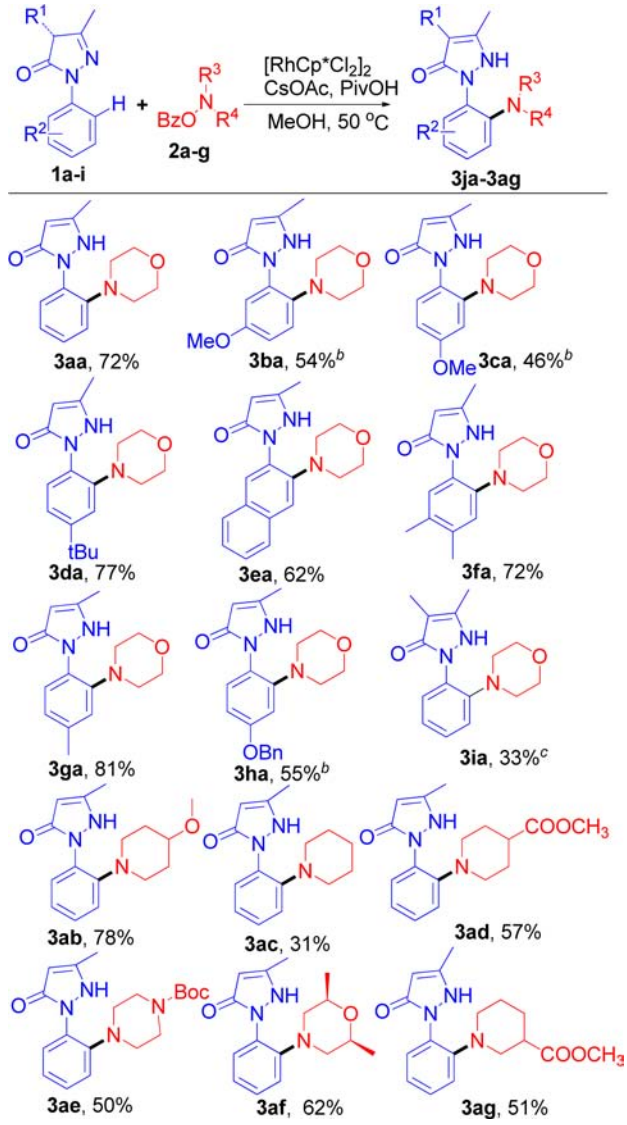


screened various C−H amination conditions using either morpholine benzoate **2a**[13] or *N*-chloromorpholine **4**[14] as the coupling partner. Meanwhile, various silver salts, additives, oxidants, and solvents were also tested (see Supporting Information (SI)).[8,9] It was found that the optimal amination conditions included using $[Cp^*RhCl_2]_2$ (2.5 mol %) as the catalyst, PivOH (0.5 equiv) and CsOAc (2.0 equiv) as the additives, and morpholine *N*-benzoate as the coupling reagent in MeOH at 50 °C, forming product **3aa** in 72% yield.

With the optimized conditions in hand, we then explored the scope and generality of the reaction with a series of *N*-aryl pyrazol-5-one substrates (Scheme 2). It was found that *N*-aryl pyrazol-5-ones (**1a**−**h**), bearing electron-neutral or -donating groups in the phenyl ring, were well tolerated, and products **3aa**−**3ha** were obtained in 46−81% yields with exclusive *ortho*-selectivity. In the cases of **1b**−**f** where two *ortho*-positions were available, the amination occurred only on the less steric site (**3ba**, **3ea**, **3fa**). Similarly, *N*-naphthalenyl pyrazolone was aminated in the less sterically hindered position in good yield (62%, **3ea**). Substrate **1i**[15] bearing a 4-methyl group on the pyrazol-5-one ring also participated in the amination reaction, although product **3ia** was obtained in a relatively lower yield (33%). The result seems reasonable since the 1*H*-pyrazol-5(4*H*)-one in **1i** was tautomerized to 1*H*-pyrazol-3(2*H*)-one in the product during the reaction and the existence of a 4-methyl hampered this conversion.

Meanwhile, a small series of benzoates **2b**−**g** derived from various secondary alkylamines were employed as the coupling partners to react with **1a** under the optimized amination conditions. As shown in Scheme 2, all the tested benzoates derived from piperidine/piperazine/morpholine took part in the amination reaction smoothly and gave corresponding products **3ab**−**3ag** in 31−78% yields. Both electron-donating (−OMe) and electron-withdrawing (−COOMe) substituents

Scheme 2. Scope of the *N*-Aryl Pyrazol-5-ones and *N*-Benzoate Secondary Alkylamines[a]



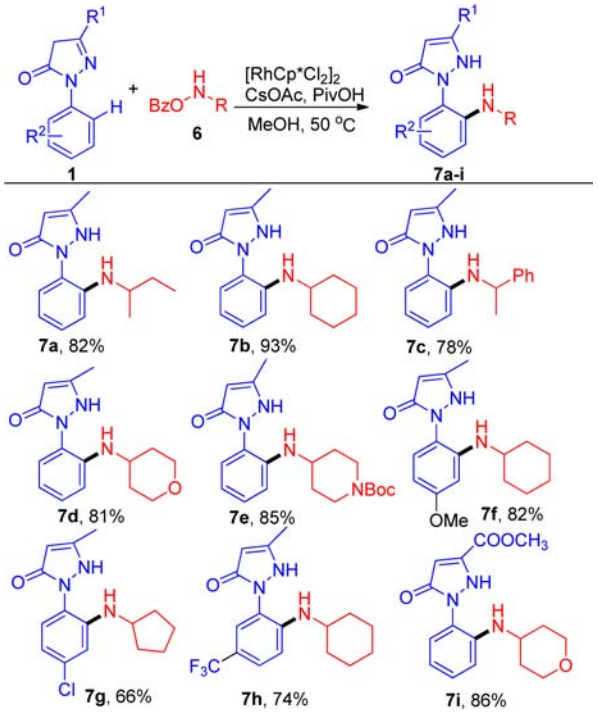
[a]Reaction conditions: **1** (0.5 mmol), **2** (0.75 mmol), $[Cp^*RhCl_2]_2$ (2.5 mol %), CsOAc (2 equiv), PivOH (0.5 equiv), 50 °C, 12 h. [b] Reaction time was 24 h. [c] The reaction was performed at rt for 4 h.

were well tolerated (**3ab**, **3ad**, **3ag**). A bulky amination reagent derived from 2,6-dimethylmorpholine was also tolerated to afford product **3ag** in 62% yield. However, it was not clear why the nonsubstituted piperidine benzoate gave a lower yield (**3ac**, 31%).

Encouraged by the C−H amination with both secondary and primary *N*-chloroalkylamines reported by Yu,[9] we then tested whether this is also the case in our study. Accordingly, a small series of *N*-benzoate primary alkylamines were prepared and subjected to the amination of *N*-aryl pyrazol-5-one substrates under the optimized conditions (Scheme 3). To our delight, all the *N*-benzoate primary amines showed superior activities in terms of both reaction efficiency and yield. With **1a** as the model substrate, amination with benzoate derived from cyclohexanamine proceeded very well leading to corresponding primary amino substituted pyrazol-5-one **7b** in 93% yield. Compounds **7a** and **7c** bearing acyclic primary amino groups were obtained as well in 82% and 78% yields, respectively. High

dx.doi.org/10.1021/ol402965d | *Org. Lett.* 2014, 16, 42−45

Scheme 3. C−H Amination with Primary Amines[a]



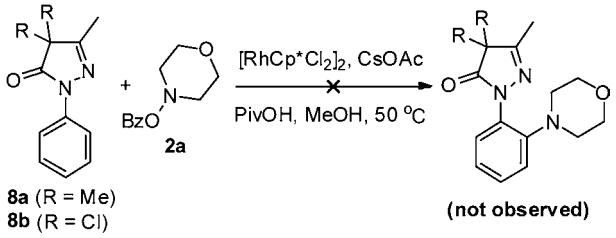
[a]Reaction conditions: **1** (0.5 mmol), **6** (0.75 mmol), $[Cp^*RhCl_2]_2$ (2.5 mol %), CsOAc (2 equiv), PivOH (0.5 equiv), 50 °C, 1 h.

yields (>80%) were obtained from tetrahydro-2*H*-pyran-4-amine and (*N*-Boc-piperidinyl)-4-amine (**7d**, **7e**). Meanwhile, with the *N*-benzoate primary amine as the coupling partner, various *N*-aryl pyrazol-5-ones were also investigated. As shown in Scheme 3, amination reagents with an electron-withdrawing group (Cl or CF_3) or with an electron-donating group (OMe) reacted smoothly giving the corresponding products **7f**–**h** in 66–82% yields. Notably, the substrate bearing an ester group in the pyrazol-5-one ring also participated in the reaction readily and offered product **7i** in 86% yield.

All the structures of the products were fully characterized and secured by the X-ray single crystal analysis of **7d** (see SI). Notably, the structure of 1*H*-pyrazol-5(4*H*)-one as in **1** tautomerizes to 1*H*-pyrazol-3(2*H*)-one as in product **3**. Since it has been reported that 1*H*-pyrazol-5(4*H*)-one **1a** is stable in $CDCl_3$ and readily tautomerizes to 1*H*-pyrazol-3(2*H*)-one **1a′** in DMSO-d_6,[12] we conducted an NMR analysis of substrate **1a** in CD_3OD and found that it was indeed tautomerized completely to **1a′**. Meanwhile, aminations of dimethyl- and dichloro-substituted pyrazol-5(4*H*)-ones **8a** and **8b** were conducted under the same conditions and no reaction was observed (Scheme 4) suggesting that the reactive carbonyl α-H is critical for the amination reactions.

Based on the above results, a tentative mechanism was proposed. As shown in Figure 1, substrate **1a** converts to its tautomer **1a′** in MeOH and then undergoes a C−H activation with the active catalyst $RhCp^*(OAc)_2$ to give a Rh^{III} species **A**. As proposed by Yu[9] and Glorius,[8b] species **A** might go through two possible paths to form aminated product **3aa**. In path a, oxidative addition of benzoate **2a** to rhodacycle **A** leads to a Rh^V species **B**, which then undergoes a reductive elimination followed by acidification to afford final product **3aa**. Alternatively, the rhodacycle **A** can directly react with morpholine benzoate **2a** through an electrophilic amination[8a,13]

Scheme 4. Control Experiments



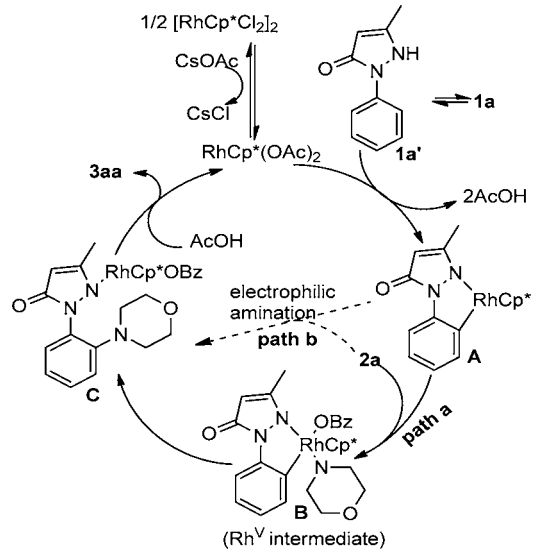


Figure 1. Proposed mechanism.

to give the complexes **C** which then converts to product **3aa** under the acidic conditions (path b).

In summary, a new rhodium(III)-catalyzed intermolecular C−H amination of arenes directed by a pyrazolone moiety was developed. This protocol is characterized by the following features: (1) it is the first example of rhodium(III)-catalyzed intermolecular C−H aromatic amination directed by an intrinsic functionality of the substrate/product; (2) both primary and secondary alkylamines can be introduced; (3) Since substrate **1a** itself is a marketed neuroprotective drug (Edaravone), new amino analogues will directly generate pharmaceutically useful products for biological screening. Besides, the relatively mild reaction conditions, low catalyst loading, and broad scope of aminating reagents make this reaction valuable for practical use.

■ ASSOCIATED CONTENT

Supporting Information

Experimental details and full spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: aozhang@simm.ac.cn.
*E-mail: qz_yao@yahoo.com.cn.

Notes

The authors declare no competing financial interest.

dx.doi.org/10.1021/ol402965d | *Org. Lett.* 2014, 16, 42–45

■ ACKNOWLEDGMENTS

This work was supported by grants from the Chinese NSF (81125021, 81373277) and from the State Key Laboratory of Drug Research (SIMM1302KF-08), Shanghai Institute of Materia Medica.

■ REFERENCES

(1) (a) Hili, R.; Yudin, A. K. *Nat. Chem. Biol.* **2006**, *2*, 284. (b) Ricci, A. *Amino Group Chemistry: From Synthesis to the Life Sciences*; Wiley-VCH: Weinheim, 2008.

(2) For recent reviews, see: (a) Hartwig, J. F. *Acc. Chem. Res.* **2008**, *41*, 1534. (b) Wolfe, J. P.; Wagaw, S.; Marcoux, J.-F.; Buchwald, S. L. *Acc. Chem. Res.* **1998**, *31*, 805. (c) Surry, D. S.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2008**, *47*, 6338. (d) Monnier, F.; Taillefer, M. *Angew. Chem., Int. Ed.* **2009**, *48*, 6954. (e) Evano, G.; Blanchard, N.; Toumi, M. *Chem. Rev.* **2008**, *108*, 3054. (f) Qiao, J. X.; Lam, P. Y. S. *Synthesis* **2011**, 829.

(3) Recent reviews on C−H activation: (a) Giri, R.; Shi, B.-F.; Engle, K. M.; Maugel, N.; Yu, J.-Q. *Chem. Soc. Rev.* **2009**, *38*, 3242. (b) Chen, X.; Engle, K. M.; Wang, D.-H.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2009**, *48*, 5094. (c) Lyons, T. W.; Sanford, M. S. *Chem. Rev.* **2010**, *110*, 1147. (d) Colby, D. A.; Bergman, R. G.; Ellman, J. A. *Chem. Rev.* **2010**, *110*, 624. (e) Xu, L. M.; Yang, Z.; Shi, Z.-J. *Chem. Soc. Rev.* **2010**, *39*, 712. (f) Ackermann, L. *Chem. Rev.* **2011**, *111*, 1315. (g) Wencel-Delord, J.; Dröge, T.; Liu, F.; Glorius, F. *Chem. Soc. Rev.* **2011**, *40*, 4740. (h) Neufeldt, S. R.; Sanford, M. S. *Acc. Chem. Res.* **2012**, *45*, 936. (i) Kuhl, N.; Hopkinson, M. N.; Wencel-Delord, J.; Glorius, F. *Angew. Chem., Int. Ed.* **2012**, *51*, 10236. (j) Yamaguchi, J.; Yamaguchi, A. D.; Itami, K. *Angew. Chem., Int. Ed.* **2012**, *51*, 8960. (k) Wencel-Delord, J.; Glorius, F. *Nat. Chem* **2013**, *5*, 369.

(4) Recent reviews on C-H amination: (a) Müeller, P.; Fruit, C. *Chem. Rev.* **2003**, *103*, 2905. (b) Davies, H. M. L.; Long, M. S. *Angew. Chem., Int. Ed.* **2005**, *44*, 3518. (c) Dick, A. R.; Sanford, M. S. *Tetrahedron* **2006**, *62*, 2439. (d) Beccalli, E. M.; Broggini, G.; Martinelli, M.; Sottocornola, S. *Chem. Rev.* **2007**, *107*, 5318. (e) Davies, H. M. L.; Manning, J. R. *Nature* **2008**, *451*, 417. (f) Collet, F.; Dodd, R. H.; Dauban, P. *Chem. Commun.* **2009**, 5061. (g) Armstrong, A.; Collins, J. C. *Angew. Chem., Int. Ed.* **2010**, *49*, 2282. (h) Cho, S. H.; Kim, J. Y.; Kwak, J.; Chang, S. *Chem. Soc. Rev.* **2011**, *40*, 5068. (i) Stokes, B. J.; Driver, T. G. *Eur. J. Org. Chem.* **2011**, 4071.

(5) Examples of intramolecular C−N bond formation: (a) Tsang, W. C. P.; Zheng, N.; Buchwald, S. L. *J. Am. Chem. Soc.* **2005**, *127*, 14560. (b) Inamoto, K.; Saito, T.; Katsuno, M.; Sakamoto, T.; Hiroya, K. *Org. Lett.* **2007**, *9*, 2931. (c) Wasa, M.; Yu, J.-Q. *J. Am. Chem. Soc.* **2008**, *130*, 14058. (d) Jordan-Hore, J. A.; Johansson, C. C. C.; Gulias, M.; Beck, E. M.; Gaunt, M. J. *J. Am. Chem. Soc.* **2008**, *130*, 16184. (e) Brasche, G.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2008**, *47*, 1932. (f) Mei, T.-S.; Wang, X.; Yu, J.-Q. *J. Am. Chem. Soc.* **2009**, *131*, 10806. (g) Neumann, J.; Rakshit, S.; Dröge, T.; Glorius, F. *Angew. Chem., Int. Ed.* **2009**, *48*, 6892. (h) Tan, Y.; Hartwig, J. F. *J. Am. Chem. Soc.* **2010**, *132*, 3676. (i) Cho, S. H.; Yoon, J.; Chang, S. *J. Am. Chem. Soc.* **2011**, *133*, 5996. (j) Youn, S. W.; Bihn, J. H.; Kim, B. S. *Org. Lett.* **2011**, *13*, 3738. (k) Nadres, E. T.; Daugulis, O. *J. Am. Chem. Soc.* **2012**, *134*, 7. (l) He, G.; Lu, C.; Zhao, Y.; Nack, W. A.; Chen, G. *Org. Lett.* **2012**, *14*, 2944. (m) He, G.; Zhao, Y.; Zhang, S.; Lu, C.; Chen, G. *J. Am. Chem. Soc.* **2012**, *134*, 3.

(6) Selected examples of intermolecular C−H amidation: (a) Yin, G.; Wu, Y.; Liu, G. *J. Am. Chem. Soc.* **2010**, *132*, 11978. (b) Ng, K.-H.; Chan, A. S. C.; Yu, W.-Y. *J. Am. Chem. Soc.* **2010**, *132*, 12862. (c) Xiong, T.; Li, Y.; Lv, Y.; Zhang, Q. *Chem. Commun.* **2010**, *46*, 6831. (d) Xiao, B.; Gong, T.-J.; Xu, J.; Liu, Z.-J.; Liu, L. *J. Am. Chem. Soc.* **2011**, *133*, 1466. (e) Sun, K.; Li, Y.; Xiong, T.; Zhang, J.; Zhang, Q. *J. Am. Chem. Soc.* **2011**, *133*, 1694. (f) Thu, H.-Y.; Yu, W.-Y.; Che, C.-M. *J. Am. Chem. Soc.* **2006**, *128*, 9048. (g) Ng, K.-H.; Ng, F.-N.; Yu, W.-Y. *Chem. Commun.* **2012**, *48*, 11680. (h) Tang, R.-J.; Luo, C.-P.; Yang, L.; Li, C.-J. *Adv. Synth. Catal.* **2013**, *355*, 869. (i) Grohmann, C.; Wang, H.; Glorius, F. *Org. Lett.* **2013**, *15*, 3014. (j) Yu, S.; Wan, B.; Li, X. *Org. Lett.* **2013**, *15*, 3706.

(7) For C−H amination on azoles and polyfluorinated arenes: (a) Monguchi, D.; Fujiwara, T.; Furukawa, H.; Mori, A. *Org. Lett.* **2009**, *11*, 1607. (b) Wang, Q.; Schreiber, S. L. *Org. Lett.* **2009**, *11*, 5178. (c) Cho, S. H.; Kim, J. Y.; Lee, S. Y.; Chang, S. *Angew. Chem., Int. Ed.* **2009**, *48*, 9127. (d) Kim, J. Y.; Cho, S. H.; Joseph, J.; Chang, S. *Angew. Chem., Int. Ed.* **2010**, *49*, 9899. (e) Zhao, H.; Wang, M.; Su, W.; Hong, M. *Adv. Synth. Catal.* **2010**, *352*, 1301. (f) Miyasaka, M.; Hirano, K.; Satoh, T.; Kowalczyk, R.; Bolm, C.; Miura, M. *Org. Lett.* **2011**, *13*, 359. (g) Liu, X.-Y.; Gao, P.; Shen, Y.-W.; Liang, Y.-M. *Org. Lett.* **2011**, *13*, 4196. (h) Kawano, T.; Hirano, K.; Satoh, T.; Miura, M. *J. Am. Chem. Soc.* **2010**, *132*, 6900. (i) Matsuda, N.; Hirano, K.; Satoh, T.; Miura, M. *Org. Lett.* **2011**, *13*, 2860.

(8) (a) Yoo, E. J.; Ma, S.; Mei, T.-S.; Chan, K. S. L.; Yu, J.-Q. *J. Am. Chem. Soc.* **2011**, *133*, 7652. (b) Grohmann, C.; Wang, H.; Glorius, F. *Org. Lett.* **2012**, *14*, 656.

(9) (a) Ng, K.-H.; Zhou, Z.; Yu, W.-Y. *Org. Lett.* **2012**, *14*, 272. (b) Ng, K.-H.; Zhou, Z.; Yu, W.-Y. *Chem. Commun.* **2013**, *49*, 7031.

(10) (a) Tran, L. D.; Roane, J.; Daugulis, O. *Angew. Chem., Int. Ed.* **2013**, *52*, 6043. (b) Shang, M.; Zeng, S.- H.; Sun, S.-Z.; Dai, H.-X.; Yu, J. Q. *Org. Lett.* **2013**, *15*, 5286.

(11) (a) Watanabe, T.; Tahara, M.; Todo, S. *Cardiovasc. Ther.* **2008**, *26*, 101. (b) Abe, K.; Yuki, S.; Kogure, K. *Stroke* **1988**, *19*, 480. (c) Tabrizch, R. *Curr. Opin. Invest. Drugs* **2000**, *1*, 347. (d) Jin, Y.-J.; Mima, T.; Raicu, V.; Park, K. C.; Shimizu, K. *Neurosci. Res.* **2002**, *43*, 75. (e) The Edaravone Acute Brain Infarction Study Group (Chair: Otomo, E., MD *Cerebrovasc. Dis.* **2003**, *15*, 222.

(12) Pal, S.; Mareddy, J.; Devi, N. S. *J. Braz. Chem. Soc.* **2008**, *19*, 1207.

(13) (a) Berman, A. M.; Johnson, J. S. *J. Am. Chem. Soc.* **2004**, *126*, 5680. (b) Berman, A. M.; Johnson, J. S. *Synlett* **2005**, 1799. (c) Berman, A. M.; Johnson, J. S. *J. Org. Chem.* **2006**, *71*, 219. (d) Campbell, M. J.; Johnson, J. S. *Org. Lett.* **2007**, *9*, 1521.

(14) Kovacic, P.; Lowery, M. K.; Field, K. W. *Chem. Rev.* **1970**, *70*, 639.

(15) Substrate **1i** was gradually decomposed under ambient temperature.