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Manganese-Catalyzed C–H Amidation of Heteroarenes in Water

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Abstract: We have developed an efficient manganesecatalyzed amidation of various heteroarenes *via* C–H bond activation using readily available sulfonyl azides. The key step is heteroarene directed electrophilic aromatic metalation using $MnBr(CO)_5$ as catalyst. This method offers excellent chemical yields and regioselectivity with good functional group tolerance. This base metal catalyzed reaction proceeds efficiently using water as the only solvent and nitrogen is the only byproduct.

Keywords: C-H activations, manganese, directing group, amidation

C-H activation has evolved as an atom- and stepeconomic tool for synthesis of complex organic molecular. Transition metals such as Rh,^[1] Pd,^[2] Ir^[3] and Ru^[4] based catalysts have played a leading role in C-H activation. However, from the viewpoint of green chemistry, it is desirable to develop more economic alternatives to these precious metals. Also most C-H activation protocols are conducted in organic solvents, especially halogenated solvents such as dichloroethane and dichlorobenzene are commonly used. It is also highly desirable to replace the conventional solvents with greener solvent such as water.

Along this line, first-row transition metals such as iron,^[5] cobalt,^[6] copper,^[2e, 7] and manganese^[8] are naturally abundant and inexpensive and could be promising candidates for catalyst development in C-H activation. More specifically, manganese is of low cost and low toxicity. Manganese based catalysts have unique been shown reactivity for C-H functionalization.^[8] Aromatic amine is a key component in numerous natural products and synthetic compounds displaying important chemical and biological properties.^[9] And the direct C-H amidation of aromatic compounds is one of the most straightforward method to make them and this method does not generate hazardous byproducts. In the context of environmentally benign synthesis, among many amidation reagents, organo azide is an ideal amino source which releasing N₂ as the single byproduct without using of external oxidants.



Scheme 1. Selected examples of Mn-catalyzed C–H activations using organo azide as amidation reagent.

Indeed, the groups of Chang, Ackermann and Zhu have significantly advanced the field of organo azides based amidation process (Scheme 1). For examples, Chang and coworkers have reported Ir-catalyzed,^[10] Rh-catalyzed^[11] and Ru-catalyzed^[12] direct arene C-H bond amidation using organo azides as amino sources respectively (Scheme 1, a-c). Ackermann and coworkers also have reported C-H amidations of heteroaryl arenes catalyzed by versatile Ru (II) catalysts.^[13] Along this line, Zhu and coworkers have reported a Cu-catalyzed amidation with azides as amino sources^[7a] and Kanai, Matsunaga and coworkers reported a cationic cobalt catalyzed C-H amidation of indoles.^[14] However, most of these protocol were based on the precious transitional metal catalysts. What is more, all these syntheses used

chlorinated solvent systems. Herein, we are glad to report a highly efficient base metal (Mn) catalyzed C-H amidation process using water as the only solvent.

Table 1. Optimization of conditions.^a

	$\searrow^{\mathbb{N}}$	MnBr(CO) ₅ (10%), additive		
		solvent, 16 h	· · · · · · · · · · · · · · · · · · ·	
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	1a 2a		3a	~ ~
Entry	Additive	Solvent	Тетр	Yield ^g
	(mol%)		(°C)	(%)
1	-	DCE	80	32
2	-	Dioxane	80	19
3	-	THF	80	Trace
4	-	Toulene	80	Trace
5	-	DMF	80	Trace
6	-	DMSO	80	Trace
7	-	DMA	80	Trace
8	-	CH ₃ CN	80	Trace
9	-	H_2O	80	35
10	$TMAB^{b}$ (10)	H_2O	80	42
11	$TPAB^{c}$ (10)	H_2O	80	75
12	$TBAB^{d}$ (10)	H_2O	80	73
13	TBAI ^e (10)	H_2O	80	13
14	$TBAC^{f}$ (10)	H_2O	80	19
15	TPAB (10)	H_2O	90	80
16	TPAB (10)	H_2O	100	84
17	TPAB (10)	H_2O	110	87
18	TPAB (10)	H ₂ O	120	93
19	TPAB (10)	H_2O	130	92
20	TPAB (5)	H_2O	120	83
21	TPAB (15)	H_2O	120	92
G 11	1 10 1 10		10 1 1	

Conditions: **1a** (0.2 mmol), sulfonyl azide **2a** (0.4 mmol), MnBr(CO)₅ (10 mol%), additive (10 mol%) and solvent (1 mL), 120 °C for 16 h. ^bTMAB: (CH₃)₄NBr. ^cTPAB: (n-C₃H₇)₄NBr. ^dTBAB: (n-C₄H₉)₄NBr. ^cTBAI: (n-C₄H₉)₄NBr. ^fTBAC: (n-C₄H₉)₄NCl. ^gDetermined by GC-MS analysis.

We used the amidation of **1a** as our model reaction (Table 1). Using MnBr(CO)₅ as catalyst, first we investigated the solvent effect (Table 1, entries 1-9). The solvent has a big influence on the reaction: most solvents only give trace amount of product 3a, only DCE, dioxane and water offer moderate conversion and water appeared to be the best solvent (Table 1, entry 9). Szostak and coworker have reported a Ru(II)-catalyzed C-H arylation of indoles with arylsilanes in water.^[4a] Our result indicated that water, as a sustainable solvent, may also have great potential in Mn-catalyzed C-H functionalizations. Because both starting material and product are not very solvable in water, use of surfactant may enhance the mass transfer.^[15] So we screened several common surfactants (Table 1, entries 10-14). To our delight, surfactants such as TBAB ((n-C₄H₉)₄NBr) did significantly increase the chemical yield of **3a** (75%, Table 1, entry 11). And screening of reaction temperature (Table 1, entries 15-19) indicated that 120 °C was the optimal temperature (Table 1, entry 18). We also investigated the effect of surfactant loading (Table 1, entries 20-21). Reduction of surfactant loading from 10% to 5% leaded to poorer yields. However, increase of surfactant loading from 10% to 15% did not improve the reaction, so we used 10% loading as our optimal conditions.

With the optimized conditions in hand, first we explored the substrate scope and functional group

tolerance of the manganese-catalyzed amidation of pyridinyl benzene **1a** with different aromatic and aliphatic sulfonyl azides **2** (Table 2). The substitution pattern (*meta*, *para*) and electronic properties of substitution (electron deficient or rich) on the aromatic ring of sulfonyl azides played a small role; good yields were obtained regardless (Table 2, **3a-3f**). And various functional groups such as amine (Table 2, **3b**), nitrile (Table 2, **3e**), ether (Table 2, **3h**), halides (Table 2, **3d**, **3q**, **3r**), ester (Table 2, **3s**) were well tolerated. This reaction also worked equally well for aliphatic sulfonyl azides **2** (Table 2, **3f**, **3t**, **3m**, **3v**). It should be noted that no reaction took place when a highly bulky sulfonyl azides **2** was used (Table 2, **3x**).

Table 2. Scope for manganese-catalyzed amidation of 1a.^a



^a Conditions: **1** (0.2 mmol), sulfonyl azide **2** (0.4 mmol), $MnBr(CO)_5$ (10 mol %), TPAB (10 mol%) and water (1 mL), 120 °C for 16 h. All yields are isolated yields.

We then evaluated reaction of various pyridinyl/ quinolinyl/benzoquinolinyl heteroarenes with tosyl azide 2a (Table 3). The substitution pattern (*meta*, *para*) and electronic properties of substitution (electron deficient or rich) on the aromatic rings of pyridinyl benzene played a small role; good yields were obtained regardless.

 Table 3. Scope for manganese-catalyzed amidation of heteroarenes with tosyl azide 2a.^a



^a Conditions: **1** (0.2 mmol), sulfonyl azide **2** (0.4 mmol), MnBr(CO)₅ (10 mol %), TPAB (10 mol%) and water (1 mL), 120 °C for 16 h. All yields are isolated yields.

Our reaction conditions also worked well for the amidation of indoles using pyrimidine as the directing group (Table 4). Similarly, this reaction also worked very well with both aromatic and aliphatic sulfonvl azides **2**. And the structure assignment of our obtained product was confirmed by the single-crystal X-ray diffraction of a typical product (see the ORTEP drawing of **3av**^[16] in Table 4).

Also, our methodology can be used in larger scale synthesis without complications (eq 1).

Table 4. Scope for manganese-catalyzed amidation of indoles.^a



^a Conditions: **1** (0.2 mmol), sulfonyl azide **2** (0.4 mmol), $MnBr(CO)_5$ (10 mol %), TPAB (10 mol%) and water (1 mL), 120 °C for 16 h. All yields are isolated yields.



The proposed mechanism is illustrated in Scheme 2 based on precedent reports.^[8] The catalytic cycle starts with the generation of manganese specie A from 1a and catalyst MnBr(CO)₅ via an electrophilic pathway. aromatic metalation Α reversible coordination of tosylazide to the cationic Mn center in A gives Mn-intermediate **B**, then an amido insertion gives Mn-intermediate C by releasing a nitrogen molecule. In the last, the protodemetalation of C of affords the final amidated product 3a and regenerates the Mn catalyst. The water solvent may play an import role in mediating the protodemetalation process.



Semakul, T. D. Taggart, B. S. Newell, C. D. Rithner, R. S. Paton, T. Rovis, J. Am. Chem. Soc. 2017, 139, 1296-1310; h) Z.-J. Jia, C. Merten, R. Gontla, C. G. Daniliuc, A. P. Antonchick, H. Waldmann, Angew. Chem., Int. Ed. 2017, 56, 2429-2434; i) S. Y. Hong, J. Jeong, S. Chang, Angew. Chem., Int. Ed. 2017, 56, 2408-2412; j) H. Deng, H. Li, W. Zhang, L. Wang, Chem. Commun. 2017, 53, 10322-10325; k) T. Piou, T. Rovis, Nature 2015, 527, 86-90.

153; g) T. Piou, F. Romanov-Michailidis, M. Romanova-Michaelides, K. E. Jackson,

- [2] a) J. He, M. Wasa, K. S. L. Chan, Q. Shao, J.-Q. Yu, Chem. Rev. 2017, 117, 8754-8786; b) S. P. Cooper, K. I. Booker-Milburn, Angew. Chem. Int. Ed. 2015, 54, 6496-6500; c) J. Zhang, A. Bellomo, A. D. Creamer, S. D. Dreher, P. J. Walsh, J. Am. Chem. Soc. 2012, 134, 13765-13772; d) T. W. Lyons, M. S. Sanford, Chem. Rev. 2010, 110, 1147-1169; e) O. Daugulis, H.-Q. Do, D. Shabashov, Acc. Chem. Res. 2009, 42, 1074-1086.
- [3] a) J. Kim, S.-W. Park, M.-H. Baik, S. Chang, J. Am. Chem. Soc. 2015, 137, 13448-13451; b) B.-J. Li, Z.-J. Shi, Chem. Sci. 2011, 2, 488-493; c) J. Kim, S. Chang, Angew. Chem., Int. Ed. 2014, 53, 2203-2207; d) G. E. M. Crisenza, N. G. McCreanor, J. F. Bower, J. Am. Chem. Soc. 2014, 136, 10258-10261; e) J. Choi, A. H. R. MacArthur, M. Brookhart, A. S. Goldman, Chem. Rev. 2011, 111, 1761-1779; f) G. Bhalla, S. M. Bischof, S. K. Ganesh, X. Y. Liu, C. J. Jones, A. Borzenko, W. J. Tenn, III, D. H. Ess, B. G. Hashiguchi, K. S. Lokare, C. H. Leung, J. Oxgaard, W. A. Goddard, III, R. A. Periana, Green Chem. 2011, 13, 69-81; 51 D. Balcells, A. Nova, E. Clot, D. Gnanamgari, R. H. Crabtree, O. Eisenstein, Organometallics 2008, 27, 2529-2535; h) G. Bhalla, J. Oxgaard, W. A. Goddard, III, R. A. Periana, Organometallics 2005, 24, 3229-3232.
- a) P. Nareddy, F. Jordan, M. Szostak, Org. Lett. [4] 2018, 20, 341-344; b) M. D. L. Tonin, D. Zell, V. Mueller, L. Ackermann, Synthesis 2017, 49, 127-134; c) P. Nareddy, F. Jordan, M. Szostak, Chem. Sci. 2017, 8, 3204-3210; d) P. Nareddy, F. Jordan, M. Szostak, ACS Catal. 2017, 7, 5721-5745; e) P. Nareddy, F. Jordan, S. E. Brenner-Moyer, M. Szostak, ACS Catal. 2016, 6, 4755-4759; f) G. S. Kumar, M. Kapur, Org. Lett. 2016, 18, 1112-1115; g) C. Bruneau, P. H. Dixneuf, Top. Organomet. Chem. 2016, 55, 137-188.
- [5] a) R. Shang, L. Ilies, E. Nakamura, Chem. Rev. 2017, 117, 9086-9139; b) G. Cera, L. Ackermann, Top. Curr. Chem. 2016, 374, 1-34; c) C.-L. Sun, B.-J. Li, Z.-J. Shi, Chem. Rev. 2011, 111, 1293-1314.
 - a) X. Chen, J. Ren, H. Xie, W. Sun, M. Sun, B. Wu, Org. Chem. Front. 2018, 5, 184-188; b) Z. Zhang, S. Han, M. Tang, L. Ackermann, J. Li, Org. Lett. 2017, 19, 3315-3318; c) D. Zell, M. Bursch, V. Mueller, S. Grimme, L. Ackermann, Angew. Chem., Int. Ed. 2017, 56, 10378-10382; d) T. Yoshino, S. Matsunaga, Adv. Synth. Catal.

Scheme 2. Proposed mechanism for C-H activation of 1a.

In summary, we have developed an efficient amidation of various heteroarenes via C-H bond activation using readily available sulfonyl azides catalyzed by base metal catalyst - MnBr(CO)₅. Other manganese-catalyzed C-H activation systems are currently being investigated in our laboratories.

Experimental Section

General procedure for admidation of 1

1 (0.2 mmol), sulfonyl azide 2 (0.4 mmol), MnBr(CO)₅ (10 mol %), TPAB (10 mol%) and water (1 mL) were added to an oven-dried 25 mL glass reactor equipped with a stir bar. The reaction mixture was stirred in a pre-heated oil bath at 120 °C for 16 h with vigorous stirring. Upon completion, the mixture was diluted with CH_2Cl_2 . The reaction mixture was extracted with CH_2Cl_2 (10 mL × 3). The combined organic layers were dried over MgSO₄. The solvents were removed under reduced pressure and the crude mixture was purified by chromatography on silica gel (hexanes/EtOAc) to give the desired product 3.

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References

[1] a) T. Piou, T. Rovis, Acc. Chem. Res. 2018, 51, 170-180; b) S.-S. Zhang, J. Xia, J.-Q. Wu, X.-G. Liu, C.-J. Zhou, E. Lin, Q. Li, S.-L. Huang, H. Wang, Org. Lett. 2017, 19, 5868-5871; c) J. Wen, H. Cheng, G. Raabe, C. Bolm, Org. Lett. 2017, 19, 6020-6023; d) N. Semakul, K. E. Jackson, R. S. Paton, T. Rovis, Chem. Sci. 2017, 8, 1015-1020; e) S. Qu, C. J. Cramer, J. Org. Chem. 2017, 82, 1195-1204; f) T. J. Potter, D. N. Kamber, B. Q. Mercado, J. A. Ellman, ACS Catal. 2017, 7, 150N.

[6]

2017, *359*, 1245-1262; e) S. Wang, S.-Y. Chen, X.-Q. Yu, *Chem. Commun.* **2017**, *53*, 3165-3180; f) J. Li, Z. Zhang, W. Ma, M. Tang, D. Wang, L.-H. Zou, *Adv. Synth. Catal.* **2017**, *359*, 1717-1724; g) P. G. Chirila, C. J. Whiteoak, *Dalton Trans.* **2017**, *46*, 9721-9739; h) D. Wei, X. Zhu, J.-L. Niu, M.-P. Song, *ChemCatChem* **2016**, *8*, 1242-1263; i) G. Tan, S. He, X. Huang, X. Liao, Y. Cheng, J. You, *Angew. Chem. Int. Ed.* **2016**, *55*, 10414-10418; j) M. Moselage, J. Li, L. Ackermann, *ACS Catal.* **2016**, *6*, 498-525.

- [7] a) J. Peng, Z. Xie, M. Chen, J. Wang, Q. Zhu, Org. Lett. 2014, 16, 4702-4705; b) M. Nishino, K. Hirano, T. Satoh, M. Miura, Angew. Chem. Int. Ed. 2012, 51, 6993-6997; c) P. Subramanian, G. C. Rudolf, K. P. Kaliappan, Chem. - Asian J. 2016, 11, 168-192; d) W.-H. Rao, B.-F. Shi, Org. Chem. Front. 2016, 3, 1028-1047; e) J. Peng, M. Chen, Z. Xie, S. Luo, Q. Zhu, Org. Chem. Front. 2014, 1, 777-781.
- [8] a) R. Cano, K. Mackey, G. P. McGlacken, Catal. Sci. Technol. 2018, Ahead of Print; b) B. Zhou, Y. Hu, T. Liu, C. Wang, Nature Communications 2017, 8, 1169; c) D. Zell, U. Dhawa, V. Mueller, M. Bursch, S. Grimme, L. Ackermann, ACS Catal. 2017, 7, 4209-4213; d) H. Wang, F. Pesciaioli, J. C. A. Oliveira, S. Warratz, L. Ackermann, Angew. Chem. Int. Ed. 2017, 56, 15063-15067; e) H. Wang, M. M. Lorion, L. Ackermann, Angew. Chem. Int. Ed. 2017, 56, 6339-6342; f) C. Wang, A. Wang, M. Rueping, Angew. Chem. Int. Ed. 2017, 56, 9935-9938; g) Z. Ruan, N. Sauermann, E. Manoni, L. Ackermann, Angew. Chem. Int. Ed. 2017, 56, 3172-3176; h) J. Ni, H. Zhao, A. Zhang, Org. Lett. 2017, 19, 3159-3162; i) T. H. Meyer, W. Liu, M. Feldt, A. Wuttke, R. A. Mata, L. Ackermann, Chem. Eur. J. 2017, 23, 5443-5447; j) Q. Lu, F. J. R. Klauck, F. Glorius, Chem. Sci. 2017, 8, 3379-3383; k) O. Lu, S. Gressies, F. J. R. Klauck, F. Glorius, Angew. Chem. Int. Ed. 2017, 56, 6660-6664; 1) Q. Lu, S. Gressies, S. Cembellin, F. J. R. Klauck, C. G. Daniliuc, F. Glorius, Angew. Chem. Int. Ed. 2017, 56, 12778-12782; m) Y.-F. Liang, V. Mueller, W. Liu, A. Muench, D. Stalke,

L. Ackermann, Angew. Chem. Int. Ed. 2017, 56, 9415-9419; n) S.-Y. Chen, Q. Li, X.-G. Liu, J.-Q. Wu, S.-S. Zhang, H. Wang, Chemsuschem 2017, 10, 2360-2364; o) S.-Y. Chen, X.-L. Han, J.-Q. Wu, Q. Li, Y. Chen, H. Wang, Angew. Chem. Int. Ed. 2017, 56, 9939-9943; p) S.-H. Cai, L. Ye, D.-X. Wang, Y.-Q. Wang, L.-J. Lai, C. Zhu, C. Feng, T.-P. Loh, Chem. Commun. 2017, 53, 8731-8734; q) S. Sueki, Z. Wang, Y. Kuninobu, Org. Lett. 2016, 18, 304-307; r) W. Liu, S. C. Richter, Y. Zhang, L. Ackermann, Angew. Chem. Int. Ed. 2016, 55, 7747-7750; s) W. Liu, L. Ackermann, ACS Catal. 2016, 6, 3743-3752; t) Y. Hu, C. Wang, Science China-Chemistry 2016, 59, 1301-1305; u) B. Zhou, Y. Hu, C. Wang, Angew. Chem. Int. Ed. 2015, 54, 13659-13663; v) W. Liu, D. Zell, M. John, L. Ackermann, Angew. Chem. Int. Ed. 2015, 54, 4092-4096; w) B. Zhou, P. Ma, H. Chen, C. Wang, Chem. Commun. 2014, 50, 14558-14561; x) R. He, Z.-T. Huang, Q.-Y. Zheng, C. Wang, Angew. Chem. Int. Ed. 2014, 53, 4950-4953; y) C. Wang, Synlett 2013, 24, 1606-1613; z) Y. Hu, B. Zhou, C. Wang, Acc. Chem. Res. 2018, 51, 816-827.

- [9] A. Ricci, Amino group chemistry : from synthesis to the life sciences, John Wiley & Sons, Inc., Weinheim, 2008.
- [10] J. Y. Kim, S. H. Park, J. Ryu, S. H. Cho, S. H. Kim, S. Chang, J. Am. Chem. Soc. 2012, 134, 9110-9113.
- [11] D. Lee, Y. Kim, S. Chang, J. Org. Chem. 2013, 78, 11102-11109.
- [12] J. Kim, J. Kim, S. Chang, Chem. Eur. J. 2013, 19, 7328-7333.
- [13] V. S. Thirunavukkarasu, K. Raghuvanshi, L. Ackermann, *Org. Lett.* **2013**, *15*, 3286-3289.
- [14] B. Sun, T. Yoshino, S. Matsunaga, M. Kanai, *Adv. Synth. Catal.* 2014, *356*, 1491-1495.
- [15] U. M. Lindström, Chem. Rev. 2002, 102, 2751-2772.
- [16] The crystallographic data of **3av** has been deposited to Cambridge Crystallographic Data Centre (CCDC 1844816).

COMMUNICATION

Manganese-Catalyzed C–H Amidation of Heteroarenes in Water

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