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Sulfoximine Directed Intermolecular *o*-C−H Amidation of Arenes with Sulfonyl Azides

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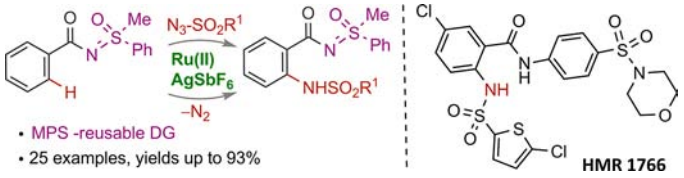
ABSTRACT



The Ru(II)-catalyzed intermolecular *o*-C−H amidation of arenes in N-benzoylated sulfoximine with sulfonyl azides is demonstrated. The reaction proceeds with broad substrate scope and tolerates various functional groups. Base hydrolysis of the amidation product provides the anthranilic acid derivatives and methylphenyl sulfoximine (MPS) directing group. This method is successfully employed for the synthesis of HMR 1766.

Anthranilic acid derivatives are found in numerous natural products and biologically active compounds of pharmaceutical importance (Figure 1).[1] The transition-metal-catalyzed *o*-C−H amination of benzoic acid derivatives enables the synthesis of structurally diverse anthranilic acids in a straightforward manner. Among the strategies developed for C−N bond formations on arenes, the Buchwald−Hartwig amination protocol is highly useful.[2] This process requires the prefunctionalized arenes in general, employs Pd and/or Cu catalysts in combination with appropriate ligands and bases, and generates the salts of HX and base byproducts.

The direct C−N bond formation through amination of C−H bond appears appealing, as this process does not need the prefunctionalized arenes.[3] For example: the C−H bond of azoles, perfluorobenzenes, and other directing groups containing arenes were successfully aminated with the aid of Pd/Cu/Rh catalyst and oxidant.[4,5]

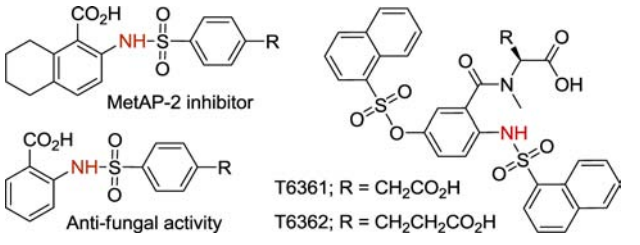


Figure 1. Biologically active molecules containing anthranilic acid derivative.

Recently, the Yu group demonstrated the Pd(II)-catalyzed *o*-C−H amination of benzamides with *O*-benzoyl hydroxyl amines in the presence of AgOAc oxidant.[5e]

(1) (a) Michael, J. P. *Nat. Prod. Rep.* **2008**, *25*, 166. (b) Doungsoongnuen, S.; Worachartcheewan, A.; Pingaew, R.; Suksrichavalit, T.; Prachayasittikul, S.; Ruchirawat, S.; Prachayasittikul, V. *EXCLI J.* **2011**, *10*, 155. (c) Eschenburg, S.; Priestman, M. A.; Abdul Latif, F. A.; Delachaume, C.; Fassy, F.; Schönbrunn, E. *J. Biol. Chem.* **2005**, *280*, 14070.

(2) (a) Hartwig, J. F. *Acc. Chem. Res.* **2008**, *41*, 1534. (b) Guram, A. S.; Buchwald, S. L. *J. Am. Chem. Soc.* **1994**, *116*, 7901. (c) Wolfe, J. P.; Wagaw, S.; Marcoux, J.-F.; Buchwald, S. L. *Acc. Chem. Res.* **1998**, *31*, 805.

(3) (a) Cho, S. H.; Kim, J. Y.; Kwak, J.; Chang, S. *Chem. Soc. Rev.* **2011**, *40*, 5068. (b) Wencel-Delord, J.; Dröge, T.; Liu, F.; Glorius, F. *Chem. Soc. Rev.* **2011**, *40*, 4740. (c) Zhang, M.; Zhang, A. *Synthesis* **2012**, *44*, 1. (d) Matsuda, N.; Hirano, K.; Satoh, T.; Miura, M. *Synthesis* **2012**, *44*, 1792. (e) Stokes, B. J.; Driver, T. G. *Eur. J. Org. Chem.* **2011**, 4071.

(4) (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) Kawano, T.; Hirano, K.; Satoh, T.; Miura, M. *J. Am. Chem. Soc.* **2010**, *132*, 6900. (f) Zhao, H.; Wang, M.; Su, W.; Hong, M. *Adv. Synth. Catal.* **2010**, *352*, 1301. (g) Miyasaka, M.; Hirano, K.; Satoh, T.; Kowalczyk, R.; Bolm, C.; Miura, M. *Org. Lett.* **2011**, *13*, 359. (h) Liu, X.-Y.; Gao, P.; Shen, Y.-W.; Liang, Y.-M. *Org. Lett.* **2011**, *13*, 4196. (i) Li, Y.; Liu, J.; Xie, Y.; Zhang, R.; Jin, K.; Wang, X.; Duan, C. *Org. Biomol. Chem.* **2012**, *10*, 3715.

(5) (a) Thu, H.-Y.; Yu, W.-Y.; Che, C.-M. *J. Am. Chem. Soc.* **2006**, *128*, 9048. (b) Ng, K.-H.; Chan, A. S. C.; Yu, W.-Y. *J. Am. Chem. Soc.* **2010**, *132*, 12862. (c) Xiao, B.; Gong, T.-J.; Xu, J.; Liu, Z.-J.; Liu, L. *J. Am. Chem. Soc.* **2011**, *133*, 1466. (d) Sun, K.; Li, Y.; Xiong, T.; Zhang, J.; Zhang, Q. *J. Am. Chem. Soc.* **2011**, *133*, 1694. (e) Yoo, E. J.; Ma, S.; Mei, T.-S.; Chan, K. S. L.; Yu, J.-Q. *J. Am. Chem. Soc.* **2011**, *133*, 7652. (f) Ng, K.-H.; Zhou, Z.; Yu, W.-Y. *Org. Lett.* **2011**, *14*, 272. (g) Grohmann, C.; Wang, H.; Glorius, F. *Org. Lett.* **2012**, *14*, 656.

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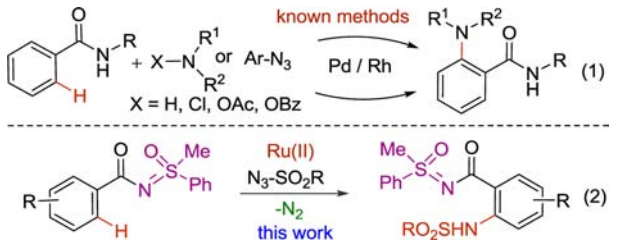
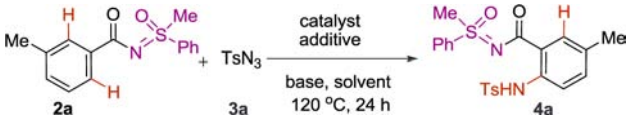
The electrophilic aminating reagents have been used for the C−N bond formation in the absence of external oxidants. The *o*-C−H bonds of benzamides/aryl oximes were aminated at an ambient temperature with the aid of *N*-chloroamines (Scheme 1, eq 1).[5f,g] An elegant approach Rh(III)-catalyzed pyridyl- and/or oxime-directed amidation of arene C−H bonds with sulfonyl azides[6,7] has recently been reported by the Chang group;[7a] this process produces the benign N_2 gas byproduct.

Scheme 1. Amide-Directed *o*-C−N Bond Formation



A survey of these reports reveal that the *o*-C−H amination on arenes has been achieved with the assistance of modifiable directing groups (DGs),[5,7] while the identical reaction with the aid of a reusable DG has yet to be investigated. Furthermore, the Ru-catalyzed intermolecular *o*-C−H amination is rare.[7−9] The use of reusable sulfoximine[10] DGs for the development of novel C−H functionalizations led us to disclose our preliminary studies on the Ru(II)-catalyzed intermolecular direct chemo- and regioselective *o*-C−H amidation of arenes in *N*-benzoylated methylphenyl sulfoximine (MPS) with sulfonyl azide amino source (Scheme 1, eq 2). The MPS-DG can be cleaved from the product and recovered. This method is successfully employed herein, enabling the synthesis of HMR 1766.

Table 1. Screening of *o*-C−H Amidation with Tosyl Azide[a]



entry	additive (40 mol %)	base (0.1 mmol)	solvent (1.0 mL)	yield (%)[b]
1[c]	$AgSbF_6$		$ClCH_2CH_2Cl$	<5
2	$AgSbF_6$		$ClCH_2CH_2Cl$	41
3	$AgBF_4$		$ClCH_2CH_2Cl$	32
4	$AgPF_6$		$ClCH_2CH_2Cl$	<5
5	KPF_6		$ClCH_2CH_2Cl$	<5
6	$AgSbF_6$		CH_2Cl_2	37
7	$AgSbF_6$		$CHCl_3$	38
8	$AgSbF_6$		toluene	9
9[d]	$AgSbF_6$		$ClCH_2CH_2Cl$	56[e]
10[d]	$AgSbF_6$	$Cu(OAc)_2.H_2O$	$ClCH_2CH_2Cl$	60[e]
11[d]	$AgSbF_6$	NaOAc	$ClCH_2CH_2Cl$	76[e]
12[d]	$AgSbF_6$	KOAc	$ClCH_2CH_2Cl$	81[e]
13[d]	$AgSbF_6$	AgOAc	$ClCH_2CH_2Cl$	59[e]
14[d,f]	**$AgSbF_6$**	**KOAc**	**$ClCH_2CH_2Cl$**	**78**[e]
15[b,d]	$AgSbF_6$	KOAc	$ClCH_2CH_2Cl$	56[g]
16[b,d]	$AgSbF_6$	KOAc	$ClCH_2CH_2Cl$	69[h]

[a] Reaction conditions: **2a** (0.1 mmol), **3a** (0.2 mmol), $[RuCl_2(p\text{-cymene})]_2$ (5 mol %). [b] Crude ^1H NMR conversion based on the ratio of starting material to product. [c] $[RhCp^*Cl_2]_2$ (5 mol %). [d] $[RuCl_2(p\text{-cymene})]_2$ (10 mol %). [e] **2a** (0.5 mmol), $ClCH_2CH_2Cl$ (2.0 mL), isolated yields. [f] KOAc (0.25 mmol). [g] 80 °C. [h] 100 °C.

To find the general reaction conditions for the *o*-C−H amidation of arenes, compound *N*-[*m*-methylbenzoyl]-MPS (**2a**) was subjected to the known reaction conditions $(RhCp^*Cl_2)_2$ (5 mol %)/$AgSbF_6$ (0.4 equiv) in $ClCH_2CH_2Cl$ (DCE) with tosyl azide at 120 °C] reported by Chang.[7a] We were pleased to notice a trace amount of the desired product **4a** (entry 1, Table 1). Interestingly, the *o*-C−H amidation product **4a** was observed in 41% yield by NMR, when $[RuCl_2(p\text{-cymene})]_2$ was employed in combination with $AgSbF_6$ (entry 2). Among the two different arenes of **2a**, the less hindered *o*-C−H bonds of the *N*-benzoylated aryl ring has been exclusively functionalized, demonstrating chemo- as well as regioselective C−H amidation of arenes. Screening of other Ag/K salts did not show satisfactory results (entries 3−5). Among various solvents examined, DCE was found to be the best compared with CH_2Cl_2, $CHCl_3$, and toluene (entries 6−8). The enhanced catalyst loading resulted in improved yield of **4a** (entry 9). Base plays an important role in the case of C−H functionalizations;[8,9] thus, exploration of different bases is investigated. Among AgOAc, NaOAc, KOAc, and

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

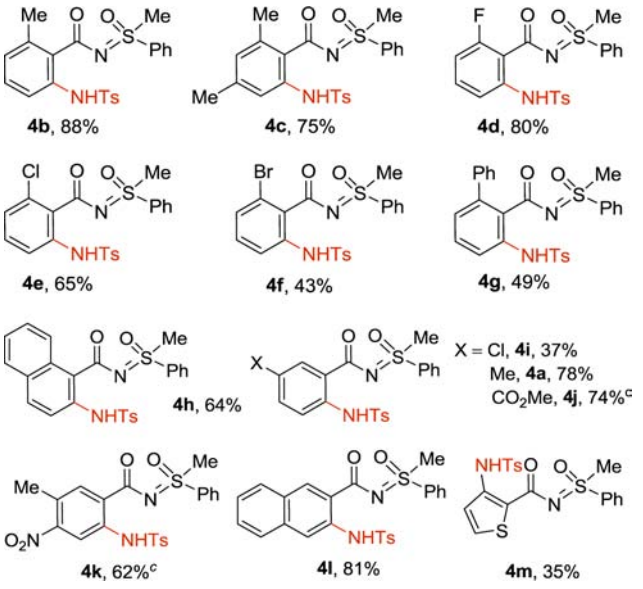
(7) (a) Kim, J. Y.; Park, S. H.; Ryu, J.; Cho, S. H.; Kim, S. H.; Chang, S. *J. Am. Chem. Soc.* **2012**, *134*, 9110. (b) Ryu, J.; Shin, K.; Park, S. H.; Kim, J. Y.; Chang, S. *Angew. Chem., Int. Ed.* **2012**, *51*, 9904. (c) Shi, J.; Zhou, B.; Yang, Y.; Li, Y. *Org. Biomol. Chem.* **2012**, *10*, 8953.

(8) (a) Louillat, M.-L.; Patureau, F. W. *Org. Lett.* **2013**, *15*, 164. (b) Hu, J.; Chen, S.; Sun, Y.; Yang, J.; Rao, Y. *Org. Lett.* **2012**, *14*, 5030. (c) Leung, S. K.-Y.; Tsui, W.-M.; Huang, J.-S.; Che, C.-M.; Liang, J.-L.; Zhu, N. *J. Am. Chem. Soc.* **2005**, *127*, 16629. (d) Liang, J.-L.; Yuan, S.-X.; Huang, J.-S.; Yu, W.-Y.; Che, C.-M. *Angew. Chem., Int. Ed.* **2002**, *41*, 3465. (e) He, L.; Chan, P.W.H.; Tsui, W.-M.; Yu, W.-Y; Che, C.-M. *Org. Lett.* **2004**, *6*, 2405. (f) Harvey, M. E.; Musaev, D. G.; Du Bois, J. *J. Am. Chem. Soc.* **2011**, *133*, 17207. (g) Milczek, E.; Boudet, N.; Blakey, S. *Angew. Chem., Int. Ed.* **2008**, *47*, 6825.

(9) (a) Kozhushkov, S. I.; Ackermann, L. *Chem. Sci.* **2013**, *4*, 886. (b) Arockiam, P. B.; Bruneau, C.; Dixneuf, P. H. *Chem. Rev.* **2012**, *112*, 5879. (c) Ackermann, L. *Chem. Rev.* **2011**, *111*, 1315. (d) Ackermann, L. *Pure Appl. Chem.* **2010**, *82*, 1403. (e) Ackermann, L.; Vicente, R. *Top. Curr. Chem.* **2010**, *292*, 211. (f) Ackermann, L.; Lygin, A. V. *Org. Lett.* **2012**, *14*, 764. (g) Ackermann, L.; Wang, L.; Lygin, A. V. *Chem. Sci.* **2012**, *3*, 177. (h) Padala, K.; Jeganmohan, M. *Org. Lett.* **2012**, *14*, 1134. (i) Hashimoto, Y.; Hirano, K.; Satoh, T.; Kakiuchi, F.; Miura, M. *Org. Lett.* **2012**, *14*, 2058. (j) Kwon, K.-H.; Lee, D. W.; Yi, C. S. *Organometallics* **2012**, *31*, 495. (k) Li, B.; Ma, J.; Wang, N.; Feng, H.; Xu, S.; Wang, B. *Org. Lett.* **2012**, *14*, 736. (l) Li, B.; Feng, H.; Wang, N.; Ma, J.; Song, H.; Xu, S.; Wang, B. *Chem.—Eur. J.* **2012**, *18*, 12873. (m) Flegeau, E. F.; Bruneau, C.; Dixneuf, P. H.; Jutand, A. *J. Am. Chem. Soc.* **2011**, *133*, 10161. (n) Lakshman, M. K.; Deb, A. C.; Chamala, R. R.; Pradhan, P.; Pratap, R. *Angew. Chem., Int. Ed.* **2011**, *50*, 11400. (o) Ackermann, L.; Lygin, A. V.; Hofmann, N. *Angew. Chem., Int. Ed.* **2011**, *50*, 6379.

(10) (a) Yadav, M. R.; Rit, R. K.; Sahoo, A. K. *Chem.—Eur. J.* **2012**, *18*, 5541. (b) Rit, R. K.; Yadav, M. R.; Sahoo, A. K. *Org. Lett.* **2012**, *14*, 3724.

Scheme 2. Scope of *N*-Benzoylated Sulfoximines[a,b]



[a] Reaction conditions: **2** (0.5 mmol), azide (1.0 mmol), $[RuCl_2(p\text{-cymene})]_2$ (10 mol %), $AgSbF_6$ (40 mol %), KOAc (0.25 mmol), $ClCH_2CH_2Cl$ (2.0 mL). [b] Isolated yields. [c] $Cu(OAc)_2 \cdot H_2O$ (1.0 mmol) was used instead of KOAc.

$Cu(OAc)_2 \cdot H_2O$ screened, KOAc was found to be effective and afforded **4a** in 81% yield (entries 10−13). The use of KOAc (0.25 mmol) did not affect the product yield (entry 14). A moderate amount of **4a** was obtained when the reaction conducted at lower temperature (entries 15 and 16). Thus, the optimized conditions in entry 14, Table 1 [$[RuCl_2(p\text{-cymene})]_2$ (10 mol %), $AgSbF_6$ (40 mol %) and KOAc (50 mol %) in DCE at 120 ^oC for 24 h] have been chosen for the *o*-C−H amidation of arenes.

We then studied the scope and generality of the C−H amidation reaction by exposing various *N*-benzoylated-MPS with tosyl azide (**3a**) under the optimized conditions (Scheme 2). The steric and electronic nature of the *ortho*-substituted arenes was probed first. The amidation of *N*-(*o*-methylbenzoyl)-MPS (**2b**) gave the desired **4b** in 88% yield. Similarly, **4c** was obtained in good yield from 2,4-dimethyl-substituted **2c**. Importantly, the halo-substituted arenes successfully underwent the C−H amidation reaction, and the corresponding **4d**−**f** were isolated in 80%, 65%, and 43% yields, respectively. Interestingly, the electron-deficient fluoro group on arene did not affect the reaction efficiency. However, the sterically demanding *o*-phenyl group in **2g** hindered the reaction and afforded **4g** in moderate yield. Reaction of α-naphthyl derivative **2h** with **3a** produced **4h** in good yield. The *meta*-substituted substrates regioselectively underwent amidation in the sterically less hindered position. The chloro- and methyl-substituted products **4i** and **4a** were obtained in moderate to good yields. The electron-withdrawing ester and nitro groups did not affect the efficiency, and the corresponding products **4j** and **4k** were isolated in 74% and 62% yields,

Table 2. Scope of *Para*-Substituted *N*-Benzoylated Sulfoximines[a,b]

entry	R	TsN_3 (equiv)	yield of **4** (%)	yield of **4′** (%)
1	Me (**2n**)		**4n**	**4n′**
		1.0	30[c]	22[c]
		1.5	43[c]	28[c]
		2.0	49	32
		2.5	14	66
		3.0	10	73
		4.0	16[c]	59[c]
2	OMe (**2o**)		**4o**	**4o′**
		2.0	55	28
		3.0	<5	71
3	F (**2p**)		**4p**	**4p′**
		2.0	49	40
		3.0	12	68
4	CF_3 (**2q**)		**4q**	**4q′**
		2.0	50	25
		3.0	48	30
5	H (**2r**)		**4r**	**4r′**
		2.0	37	28
		3.0	20	52

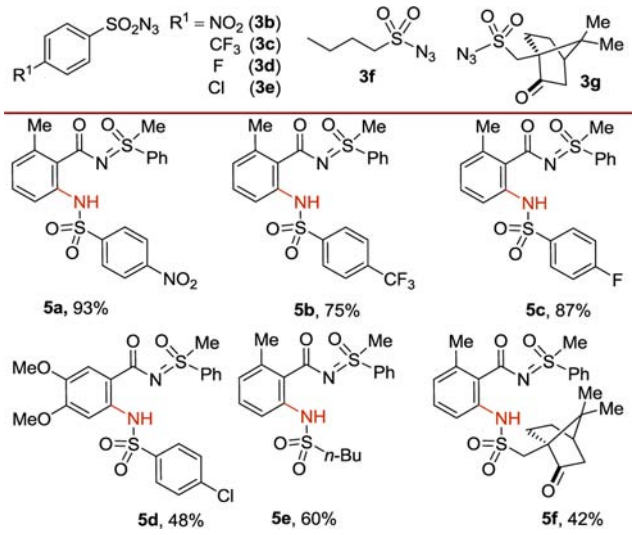
[a] Reaction conditions: **2** (0.5 mmol), $[RuCl_2(p\text{-cymene})]_2$ (10 mol %), $AgSbF_6$ (40 mol %), KOAc (0.25 mmol), $ClCH_2CH_2Cl$ (2.0 mL). [b] Isolated yields. [c] Crude ^1H NMR conversion based on the ratio of starting material to product.

respectively, when the reaction was performed in the presence of $Cu(OAc)_2$. The β-naphthyl derivative **2l** under the catalytic conditions gave **4l** in 81% yield. Gratifyingly, reaction of **2**-thienyl-substituted **2m** with **3a** afforded **4m** albeit in poor yield.

The reaction of *para*-substituted *N*-benzoylated-MPS with TsN_3 (**3a**) provided the mono- and diamidation products (Table 2). At first, the *p*-Me-substituted *N*-benzoylated-MPS (**2n**) was exposed to different amounts of TsN_3 (**3a**) under the optimized conditions.[11] However, the use of **3a** (2.0 equiv) was found to be optimum affording **4n** (major) and **4n′** (minor) in 49% and 32% yields, respectively (entry 1). Interestingly, an excess amount of **3a** (2.5/3.0/4.0 equiv) led to **4n′** as major product; in particular, the reaction of **2n** with 3.0 equiv of **3a** resulted **4n′** in 73% yield (entry 1). These modified conditions were then applied to various *para*-substituted *N*-benzoylated-MPS compounds (**2o**−**r**). The reaction of electron-rich *p*-OMe-substituted **2o** with **3a** (2.0 equiv) gave 55% of **4o** as major product, while diamidation product **4o′** (71%) was isolated when **3a** (3.0 equiv) was employed (entry 2).[11] The mono- and diamidation products **4p** and **4p′** were obtained in 49% and 40% yields, respectively, from the reaction of the F-group bearing electron-deficient **2p** with **3a** (2.0 equiv), whereas 3.0 equiv of TsN_3 yielded **4p′** in 68% yield (entry 3).

(11) For more details, see the Supporting Information.

Scheme 3. Scope of Azides[a,b]

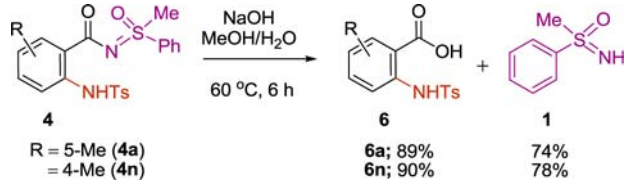


[a] Reaction conditions: **2** (0.5 mmol), azide (1.0 mmol), $[RuCl_2(p\text{-cymene})]_2$ (10 mol %), $AgSbF_6$ (40 mol %), KOAc (0.25 mmol), $ClCH_2CH_2Cl$ (2.0 mL). [b] Isolated yields.

Surprisingly, the use of an enhanced amount of TsN_3 did not affect the reactivity of *p*-CF_3-susbstituted **2q**, producing the monoamidation **4q** as the major product (entry 4). The electron-neutral *N*-benzoylsulfoximine **2r** gave a moderate amount of **4r**/**4r′** in the presence of 2.0/3.0 equiv of **3a**.

We next examined the scope of different sulfonyl azides with **2** (Scheme 3). Electron-withdrawing substituted arylsulfonyl azides **3b**, **3c**, and **3d** effectively participated; the corresponding *o*-C−H amidation products **5a**−**c** were obtained in good yields. Similarly, amidation of *N*-(3,4-dimethoxybenzoyl)-MPS (**2s**) with **3e** yielded 48% of **5d**. Pleasingly, the reaction of aliphatic sulfonyl azides **3f**/**3g** with **2a** produced a moderate amount of the desired amidation products **5e** and **5f**.

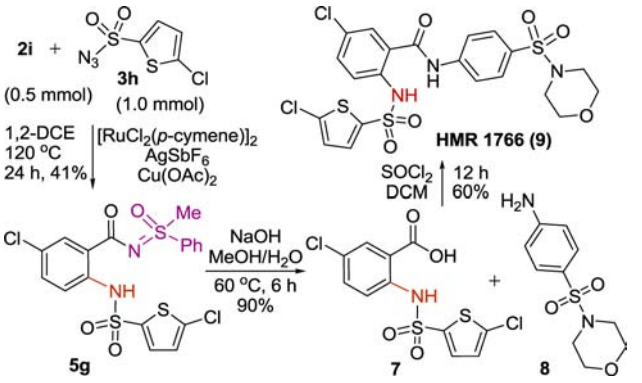
Scheme 4. Recovery of the Sulfoximine Directing Group



Cleavage of the MPS-directing group from the product would broaden the synthetic versatility of the method. To our delight, **4a** was hydrolyzed under the base hydrolysis conditions (NaOH in $MeOH/H_2O$ at 60 °C in 6 h), providing the corresponding anthranilic acid **6a** and MPS in 89% and 74% yield, respectively (Scheme 4).

(12) Schindler, U.; Strobel, H.; Schönafinger, K.; Linz, W.; Löhn, M.; Martorana, P. A.; Rütten, H.; Schindler, P. W.; Busch, A. E.; Sohn, M.; Töpfer, A.; Pistorius, A.; Jannek, C.; Mülsch, A. *Mol. Pharmacol.* **2006**, *69*, 1260.

Scheme 5. Synthesis of HMR 1766



Following the same conditions, **4n** was successfully hydrolyzed and the MPS moiety was recovered in 78% yield.

Next, we envisioned the synthesis of HMR 1766 (**9**) involving the reusable MPS-directed C−H amidation protocol as a key step. HMR 1766, named ataciguat, is a class of sGC activators useful in targeting deficient NO signaling in hypertension, peripheral, and coronary artery disease, heart failure, etc.[12] The campaign for the synthesis of **9** commenced by inserting the Cl-thienyl-sulfonyl amido group at the less hindered *o*-C−H bond on **2i** (Scheme 5); the desired product **5g** was produced in 41% yield. Hydrolysis of **5g** delivered the corresponding acid **7** in 90% yield. Finally, coupling of **7** with amine **8**[11] resulted in HMR 1766 (**9**) in 60% yield. X-ray crystallographic analysis unambiguously confirms the structure of **9**.[11]

In summary, we have developed a Ru-catalyzed, sulfoximine-directed, chemo- and regioselective *o*-C−N bond formation of arenes with broad substrate scope. The reaction of *para*-substituted *N*-benzoylated-MPS with an excess amount of tosyl azide delivered major amount of *ortho*-diamidation product. Anthranilic acid derivatives and recovery of MPS-DG are realized through the base hydrolysis of amidation products. The utility of this method is demonstrated in the synthesis of HMR 1766. Efforts to unravel milder reaction conditions for sp^2 and sp^3 C−H amination and diastereoselective C−H aminations are currently underway.

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Supporting Information Available. Detailed experimental procedures, spectra, and X-ray data (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.