

# Iridium-Catalyzed Direct ortho-C–H Amidation of Benzaldehydes through *N*-Sulfonyl Imines as Mask

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**Supporting Information** 

**ABSTRACT:** Ir-catalyzed direct C–H sulfamidation of benzaldehydes has been achieved. A series of *ortho*-amided benzaldehydes were obtained in up to 95% yields for 21 examples with excellent regioselectivity and broad functional group tolerance. This transformation could proceed smoothly with low catalyst loading under external-oxidant-, acid-, or base-free conditions. Molecular nitrogen was released as the sole byproduct, providing an environmentally benign sulfamidation process.



irect functionalization of C–H bonds has emerged as a powerful tool in organic synthesis to provide complex molecules from easily available starting materials and improve the overall efficiency of the desired transformation. In the past decade, great progress has been achieved in transition-metalcatalyzed C-H bond functionalizations.<sup>1</sup> Controlling site selectivity is one of the challenges. In this regard, the strategy involving regioselective C-H activation assisted by various directing groups shows high potential. Various directing groups have successfully been utilized for regioselective C-H functionalization. So far, directing groups containing oxygen or nitrogen atoms, such as carboxylic acid,<sup>2</sup> ketone carbonyl,<sup>3</sup> phenolic hydroxyl,<sup>4</sup> imine,<sup>5</sup> oxime,<sup>6</sup> benzamide,<sup>7</sup> benzhydroxamic acid,<sup>8</sup> hydroxamic acid,<sup>9</sup> amide,<sup>10</sup> acetanilide,<sup>11</sup> acrylamide,<sup>12</sup> enamine,<sup>13</sup> urea,<sup>14</sup> azide,<sup>15</sup> and some heterocycles<sup>16</sup> including azole, imidazole, benzimidazole, benzoxazole, indole, and pyridine have been developed. However, aldehyde as a directing group remains challenging<sup>17</sup> because of the low ligating ability of the aldehyde oxygen and related competitive side reactions. In addition, aldimine offers stronger chelation assistance for C-H activation and acts as a surrogate of aldehydes.<sup>18</sup> On the other hand, organic azide, as an internal oxidant and environmentally benign reagent, is widely developed by Sukbok Chang and other groups because nontoxic nitrogen gas is released as the only byproduct.<sup>19</sup> Herein, we disclose an Ir-catalyzed amidation of benzaldehydes with sulfonyl azides as amino sources and N-Ts imines as a removable directing group (Scheme 1b). This procedure could proceeded smoothly with a low catalyst loading and tolerate various substituent groups. The products are an important building block in organic synthesis and can be easily converted into various highly valuable molecules via diverse transformations.  $^{\rm 20}$ 

At the outset of our studies, the reaction of N-Ts benzaldehyde imine (1a) and *para*-toluenesulfonyl azide (2a) was chosen as a model reaction to screen various reaction parameters (Table 1). To our great delight, the desired product 3aa was isolated in 68% yield in the presence of  $[IrCp*Cl_2]_2$  (1 mol %) in

Scheme 1. Transition-Metal-Catalyzed C–H Amination from Organic Azides



1,2-DCE using AgSbF<sub>6</sub> as an additive after 12 h at 100 °C (entry 1). The reaction did not work well in the absence of a AgSbF<sub>6</sub> or an Ir(III) catalyst (entries 2–3). Various additives, such as AgOAc, AgBF<sub>4</sub>, AgNTf<sub>2</sub>, were further screened, and it was found that AgNTf<sub>2</sub> could evidently promote this amidation and give the desired product **3aa** in 89% yield (entries 4–6). With such an exciting preliminary result in hand, a systematic screening solvent was carried out (entries 6–9). 1,2-DCE proved to be optimal. In view of the fact that high temperature might lead to decomposition of the product, the reaction temperature was decreased from 100 to 40 °C. A similar result could be maintained at 60 °C (entry 11). When loading of the catalyst was reduced to 0.5 mol %, a slightly lower yield was obtained (entry 13). While, no conversion was observed using [RhCp\*Cl<sub>2</sub>]<sub>2</sub>, [Ru(*p*-cymene)Cl<sub>2</sub>]<sub>2</sub>, or Pd(OAc)<sub>2</sub> as a catalyst (entries 14–16).

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	1a	2a	3aa		
entry	catalyst	silver salt	solvent	<i>t</i> (°C)	3aa (%)
1	$[IrCp*Cl_2]_2$	AgSbF <sub>6</sub>	DCE	100	68
2	none	AgSbF <sub>6</sub>	DCE	100	N.R.
3	[IrCp*Cl <sub>2</sub> ] <sub>2</sub>	none	DCE	100	N.R.
4	[IrCp*Cl <sub>2</sub> ] <sub>2</sub>	AgOAc	DCE	100	50
5	$[IrCp*Cl_2]_2$	AgBF <sub>4</sub>	DCE	100	43
6	$[IrCp*Cl_2]_2$	AgNTf <sub>2</sub>	DCE	100	89
7	$[IrCp*Cl_2]_2$	AgNTf <sub>2</sub>	DMF	100	N.R.
8	$[IrCp*Cl_2]_2$	AgNTf <sub>2</sub>	DMSO	100	N.R.
9	$[IrCp*Cl_2]_2$	AgNTf <sub>2</sub>	1,4-dioxane	100	40
10	$[IrCp*Cl_2]_2$	AgNTf <sub>2</sub>	DCE	80	89
11	[IrCp*Cl <sub>2</sub> ] <sub>2</sub>	AgNTf <sub>2</sub>	DCE	60	89
12	$[IrCp*Cl_2]_2$	AgNTf <sub>2</sub>	DCE	4	73
13 <sup>b</sup>	$[IrCp*Cl_2]_2$	AgNTf <sub>2</sub>	DCE	60	76
14	$[RhCp*Cl_2]_2$	AgNTf <sub>2</sub>	DCE	60	N.R.
15	Pd(OAc) <sub>2</sub>	AgNTf <sub>2</sub>	DCE	60	N.R.
16	$[\operatorname{Ru}(p\text{-cymene})\operatorname{Cl}_2]_2$	AgNTf <sub>2</sub>	DCE	60	N.R.

<sup>a</sup> 1a (0.2 mmol), 2a (0.24 mmol),  $[IrCp*Cl_2]_2$  (1 mol %), AgNTf<sub>2</sub> (8 mol %), solvent (2 mL), 12 h, isolated yields, under air. <sup>b</sup> $[IrCp*Cl_2]_2$  (0.5 mol %), AgNTf<sub>2</sub> (4 mol %). DMF = N<sub>j</sub>N-dimethylformamide. DMSO = dimethyl sulfoxide.

With the optimal reaction conditions in hand, the scope of sulfonyl azides 2 was then examined in the amidation of 4-methyl-*N*-[(2-methylphenyl)methylene]benzenesulfonamide (Scheme 2). Aromatic rings substituted with electron-donating and -withdrawing groups were readily sulfamidated at the orthoposition and provided the desired products in good to excellent yields (3aa-3af). The electron density of arensulfonyl azides has a slight influence on this transformation. In addition broad functional groups were also tolerated. For instance, arensulfonyl azides bearing fluoro (3ae), chloro (3ac) groups were smoothly sulfamidated in excellent yields. A 72% yield was obtained for 4-nitrobenzenesulfonylazide (3ad). Arylsulfonyl azide bearing a chloro group at the meta-position could readily participate in this sulfamidation reaction, providing product (3ah) in 75% yield. A substituent at the ortho-position of the benzene ring (3ag) led to a lower yield than the *para*-methylbenzenesulfonyl azide (3aa) perhaps due to the steric hindrance. Moreover, aliphatic sulfonyl azides also worked well. Ethylsulfonyl azide afforded the corresponding product (3ai) in 95% yield.

Next, we investigated various N-Ts benzaldehyde imines 1 with para-methyl henylsulfonyl azide under the optimized conditions (Scheme 2). Ortho-sulfamidated products with electrondonating substituents, such as methyl (3aa) or methoxyl (3da), were obtained in 89% and 82% yields, respectively. In addition, substrates bearing electron-withdrawing groups, such as fluoro (3ba), bromo (3ca), or trifluoromethyl (3ea) groups, were applied to this reaction system and gave the corresponding products in good yields. For para-substituted imines, two C-H bonds possibly could be aminated. Both mono- and diamidated products could be afforded. In view of the steric effect of the N-TS group, the hydroamidated products (3fa-3ia) could be afforded in moderate yields after slightly modifying the reaction conditions. In the case of meta-substituted imines, the C-H activation occurred selectively and consistently at the less hindered site (3ja). 2-Thienylaldehyde was successfully converted to the corresponding product (3la) in 50% yield. Moreover, 4-methyl-N-(naphthalen-1-ylmethylene)-benzenesulfonyl amide

#### Scheme 2. Substrate Scope<sup>a</sup>

CUC



<sup>*a*</sup>Reaction conditions: **1** (0.2 mmol), **2** (0.24 mmol),  $[IrCp^*Cl_2]_2$  (1 mol %), AgNTf<sub>2</sub> (8 mol %) in DCE (1.0 mL) at 60 °C for 12 h under air. <sup>*b*</sup>**1** (0.24 mmol), **2** (0.2 mmol),  $[IrCp^*Cl_2]_2$  (1.5. mol %), AgNTf<sub>2</sub> (12 mol %).

also proceeded well and provided the targeted compound in 85% yield (3ma). The amidated aldehydes are known as

important precursors for the synthesis of a variety of complex structures. The preinstalled halogen, methoxy, and trifluoromethyl groups in the coupled products are typically encountered in organic synthesis and should allow further chemical transformations.

We conducted parallel reactions of substrates 1k or [D5]-1k with *para*-methyl phenylsulfonyl azide (2a) under the standard reaction conditions. A significant kinetic isotope effect ( $k_{\rm H}/k_{\rm D}$  = 2.7) was found, suggesting the irreversible C–H cleavage to be the rate-determining step (Scheme 3).<sup>21</sup>

# Scheme 3. Kinetic Isotope Effect Studies with Labeled Compound $[D_5]$ -1k



According to the literature,<sup>19</sup> a plausible reaction pathway for this Ir(III)-catalyzed amidation reaction was proposed and is shown in Scheme 4. Initially, the dimeric precursor [IrCp\*Cl<sub>2</sub>]<sub>2</sub>





was converted into a cationic species **A** by the aid of silver salt. The five-membered iridacycle **B** with one vacant accessible site was formed by the coordination of the iridium atom with the N atom, and subsequently an electrophilic attack at the *ortho*-position C atom. Then, intermediate **C** was formed through interaction of azide with the cationic metal center. It was proposed that an iridium N-Ts imines species **D** from complex **C** occurred in an oxidative manner to release the N<sub>2</sub> molecule. A new C–N bond in **E** was formed by insertion of the N-Ts imines species into an iridacycle. The compound **E** was protodemetalated to deliver the sulfamidated product **F**. Finally, the desired product **G** was generated via hydrolysis with HCl solution.<sup>22</sup>

In summary, we have developed an iridium-catalyzed direct C-H amidation of N-Ts imines as a removable directing group with sulfonyl azides, in which C-H amidation and hydrolysis were involved in a one-pot manner. This protocol proceeded smoothly with a low catalyst loading under mild conditions with good functional group tolerance. The products obtained

are important building blocks in organic synthesis and could be easily converted into various highly valuable molecules via diverse transformations.

### ASSOCIATED CONTENT

#### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02406.

Experimental procedures, compound characterization (PDF)

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#### Notes

The authors declare no competing financial interest.

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### REFERENCES

(1) Selected reviews: (a) Seregin, I. V.; Gevorgyan, V. *Chem. Soc. Rev.* 2007, 36, 1173. (b) Daugulis, O.; Do, H. Q.; Shabashov, D. *Acc. Chem. Res.* 2009, 42, 1074. (c) Chen, X.; Engle, K. M.; Wang, D.; Yu, J. Q. *Angew. Chem., Int. Ed.* 2009, 48, 5094. (d) Engle, K. M.; Mei, T.; Wasa, M.; Yu. *Acc. Chem. Res.* 2012, 45, 788.

(2) (a) Ackermann, L.; Pospech, J. Org. Lett. 2011, 13, 4153. (b) Dai,
H.; Li, G.; Zhang, X.; Stepan, A. F.; Yu, J. Q. J. Am. Chem. Soc. 2013,
135, 7567. (c) Lee, D.; Chang, S. Chem. - Eur. J. 2015, 21, 5364.
(d) Wei, M.; Wang, L.; Li, Y.; Cui, X. Chin. Chem. Lett. 2015, 26, 1336.
(3) (a) Zheng, Q.; Liang, Y.; Qin, C.; Jiao, N. Chem. Commun. 2013,
49, 5654.

(4) (a) Chidipudi, S. R.; Wieczysty, M. D.; Khan, I.; Lam, H. W. Org. Lett. 2013, 15, 570. (b) Thirunavukkarasu, V. S.; Donati, M.; Ackermann, L. Org. Lett. 2012, 14, 3416. (c) Xiao, B.; Gong, T.; Liu, Z.; Liu, J.; Luo, D.; Xu, J.; Liu, L. J. Am. Chem. Soc. 2011, 133, 9250.

(5) (a) Gao, K.; Yoshikai, N. J. Am. Chem. Soc. 2013, 135, 9279.
(b) Tredwell, M. J.; Gulias, M.; Bremeyer, N. G.; Johansson, C. C. C.; Collins, B. S. L.; Gaunt, M. J. Angew. Chem., Int. Ed. 2011, 50, 1076.
(6) (a) Parthasarathy, K.; Jeganmohan, M.; Cheng, C. Org. Lett. 2008, 10, 325. (b) Hyster, T. K.; Rovis, T. Chem. Commun. 2011, 47, 11846. (c) Chuang, S.; Gandeepan, P.; Cheng, C. Org. Lett. 2013, 15, 5750.

(7) (a) Hyster, T. K.; Rovis, T. J. Am. Chem. Soc. 2010, 132, 10565.
(b) Shiota, H.; Ano, Y.; Aihara, Y.; Fukumoto, Y.; Chatani, N. J. Am. Chem. Soc. 2011, 133, 14952.

(8) (a) Guimond, N.; Gouliaras, C.; Fagnou, K. J. Am. Chem. Soc. **2010**, 132, 6908. (b) Guimond, N.; Gorelsky, S. I.; Fagnou, K. J. Am. Chem. Soc. **2011**, 133, 6449.

(9) Too, P. C.; Wang, Y.; Chiba, S. Org. Lett. 2010, 12, 5688.

(10) (a) Grohmann, C.; Wang, H.; Glorius, F. Org. Lett. 2012, 14, 656. (b) Ryu, J.; Kwak, J.; Shin, K.; Lee, D.; Chang, S. J. Am. Chem. Soc. 2013, 135, 12861. (c) Kim, H.; Shin, K.; Chang, S. J. Am. Chem. Soc. 2014, 136, 5904.

(11) Stuart, D. R.; Alsabeh, P.; Kuhn, M.; Fagnou, K. J. Am. Chem. Soc. 2010, 132, 18326.

(12) (a) Su, Y.; Zhao, M.; Han, K.; Song, G.; Li, X. Org. Lett. 2010, 12, 5462. (b) Hyster, T. K.; Rovis, T. Chem. Sci. 2011, 2, 1606.

(13) Rakshit, S.; Patureau, F. W.; Glorius, F. J. Am. Chem. Soc. 2010, 132, 9585.

# **Organic Letters**

(14) Huestis, M. P.; Chan, L.; Stuart, D. R.; Fagnou, K. Angew. Chem., Int. Ed. 2011, 50, 1338.

(15) (a) Wang, Y.; Toh, K. K.; Lee, J.; Chiba, S. Angew. Chem., Int. Ed. 2011, 50, 5927. (b) Miura, T.; Yamauchi, M.; Murakami, M. Org. Lett. 2008, 10, 3085.

(16) (a) Umeda, N.; Tsurugi, H.; Satoh, T.; Miura, M. Angew. Chem., Int. Ed. 2008, 47, 4019. (b) Morimoto, K.; Hirano, K.; Satoh, T.; Miura, M. Org. Lett. 2010, 12, 2068. (c) Zhang, G.; Yang, L.; Wang, Y.; Xie, Y.; Huang, H. J. Am. Chem. Soc. 2013, 135, 8850.
(d) Thirunavukkarasu, V. S.; Raghuvanshi, K.; Ackermann, L. Org. Lett. 2013, 15, 3286. (e) Shin, K.; Chang, S. J. Org. Chem. 2014, 79, 12197. (f) Ali, M. A.; Yao, X.; Li, G.; Lu, H. Org. Lett. 2016, 18, 1386. (17) (a) Gandeepan, P.; Parthasarathy, K.; Cheng, C. H. J. Am. Chem.

Soc. **2010**, *132*, 8569. (b) Zhang, T.; Wu, L.; Li, X. Org. Lett. **2013**, *15*, 6294.

(18) (a) Jun, C.; Lee, H.; Park, J.; Lee, D. Org. Lett. 1999, 1, 2161.
(b) Jun, C.; Chung, K.; Hong, J. Org. Lett. 2001, 3, 785. (c) Lim, S.; Lee, J. H.; Moon, C. W.; Hong, J.; Jun, C. Org. Lett. 2003, 5, 2759.
(d) Chen, S.; Yu, J.; Jiang, Y.; Chen, F.; Cheng, J. Org. Lett. 2013, 15, 4754. (e) Tan, P. W.; Juwaini, N. A. B.; Seayad. Org. Lett. 2013, 15, 5166. (f) Lian, Y.; Hummel, J. R.; Bergman, R. G.; Ellman, J. A. J. Am. Chem. Soc. 2013, 135, 12548.

(19) (a) Kim, J.; Chang, S. Angew. Chem., Int. Ed. 2014, 53, 2203.
(b) Kim, J.; Chang, S. Chem. - Eur. J. 2013, 19, 7328. (c) Ryu, J.; Shin, K.; Park, S. H.; Kim, J. Y.; Chang, S. Angew. Chem., Int. Ed. 2012, 51, 9904. (d) Kang, T.; Kim, Y.; Lee, D.; Wang, Z.; Chang, S. J. Am. Chem. Soc. 2014, 136, 4141. (e) Hwang, H.; Kim, J.; Jeong, J.; Chang, S. J. Am. Chem. Soc. 2014, 136, 10770. (f) Pi, C.; Cui, X.; Wu, Y. J. Org. Chem. 2015, 80, 7333. (g) Shin, K.; Kim, H.; Chang, S. Acc. Chem. Res. 2015, 48, 1040. (h) Park, Y.; Park, K. T.; Kim, J. G.; Chang, S. J. Am. Chem. Soc. 2015, 137, 4534. (i) Shin, K.; Baek, Y.; Chang, S. Angew. Chem., Int. Ed. 2013, 52, 8031. (j) Kim, J. Y.; Park, S. H.; Ryu, J.; Cho, S. H.; Kim, S. H.; Chang, S. J. Am. Chem. Soc. 2012, 134, 9110. (k) Zhu, B.; Cui, X.; Pi, C.; Chen, D.; Wu, Y. Adv. Synth. Catal. 2016, 358, 326. (l) Wei, M.; Wang, L.; Cui, X. Chin. Chem. Lett. 2015, 26, 1336.

(20) (a) Doi, R.; Kikushima, K.; Ohashi, M.; Sensuke, O. J. Am. Chem. Soc. 2015, 137, 3276. (b) Kashyap, R.; Talukdar, D. J.; Pratihar, S. New J. Chem. 2015, 39, 1430. (c) Barman, M. K.; Baishya, A.; Nembenna, S. B. J. Organomet. Chem. 2015, 785, 52. (d) Ledoux, A.; Larini, P.; Boisson, C.; Monteil, V.; Raynaud, J.; Lacote, E. Angew. Chem., Int. Ed. 2015, 54, 15744.

(21) (a) Simmons, E. M.; Hartwig, J. F. Angew. Chem., Int. Ed. 2012, 51, 3066. (b) Gomez-Gallego, M.; Sierra, M. Á. Chem. Rev. 2011, 111, 4857.

(22) Cong, X.; Tang, H.; Zeng, X. J. Am. Chem. Soc. 2015, 137, 14367.