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N-Heterocyclic Carbene-Catalyzed Cross-Coupling of Aldehydes with Arylsulfonyl Indoles

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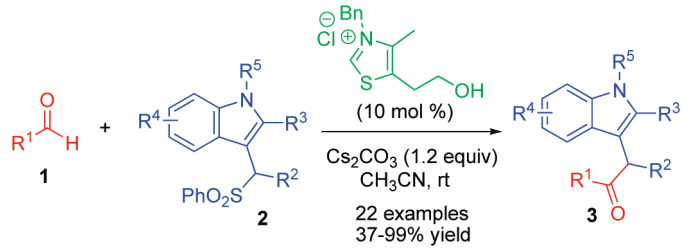
ABSTRACT



3-(1-Arylsulfonylalkyl)indoles as electrophiles in the *N*-heterocyclic carbene-catalyzed umpolung reaction of aldehydes were realized for the first time. This intermolecular Stetter-type reaction features the commercially available catalyst and mild reaction conditions, providing α-(3-indolyl) ketone derivatives in high yields for a wide range of substrates.

The umpolung reactions catalyzed by *N*-heterocyclic carbenes (NHC) provide an unconventional access to various important target molecules.[1,2] It is widely accepted that these umpolung reactions proceed through the addition of "Breslow intermediate" (Figure 1) to some electrophilic reagents, such as aromatic aldehydes, namely the benzoin reaction,[3] and Michael acceptors, namely the Stetter reaction.[4] Recently, several electrophilic reagents such as ketones,[5] aziridines,[6] nitroalkenes,[7] haloheteroarenes,[8] and imines[9] have also been realized as suitable acceptors for the acyl anion during the umpolung reaction, highly broadening the reaction scope. Apparently, novel types of electrophilic receptors suitable for the umpolung reaction are highly desirable and would increase the versatility of this umpolung approach.

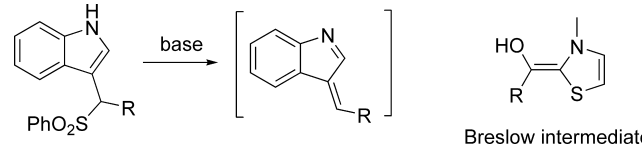


Figure 1. 3-(1-Arylsulfonylalkyl)indole and the Breslow intermediate.

This work was inspired by recent elegant studies of Petrini and co-workers that 3-(1-arylsulfonylalkyl)indoles are demonstrated good electrophilic precursors.[10] The sulfonyl moiety at the benzylic position of 3-substituted indoles serves as a good leaving group, which allows the generation of an electrophilic species under basic conditions (Figure 1). The intermediate generated in situ equals an active α,β-unsaturated imine, and we envision that this electrophilic intermediate might be a suitable acyl receptor in the NHC-catalyzed umpolung reaction. Previously, Stetter utilized gramine as an electrophile in a cyanide-catalyzed umpolung reaction of

(1) For reviews, see: (a) Enders, D.; Balensiefer, T. *Acc. Chem. Res.* **2004**, *37*, 534. (b) Johnson, J. S. *Angew. Chem., Int. Ed.* **2004**, *43*, 1326. (c) Nair, V.; Bindu, S.; Sreekumar, V. *Angew. Chem., Int. Ed.* **2004**, *43*, 5130. (d) Christmann, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 2632. (e) Zeitler, K. *Angew. Chem., Int. Ed.* **2005**, *44*, 7506. (f) Marion, N.; Díez-González, S.; Nolan, S. P. *Angew. Chem., Int. Ed.* **2007**, *46*, 2988. (g) Enders, D.; Niemeier, O.; Henseler, A. *Chem. Rev.* **2007**, *107*, 5606.

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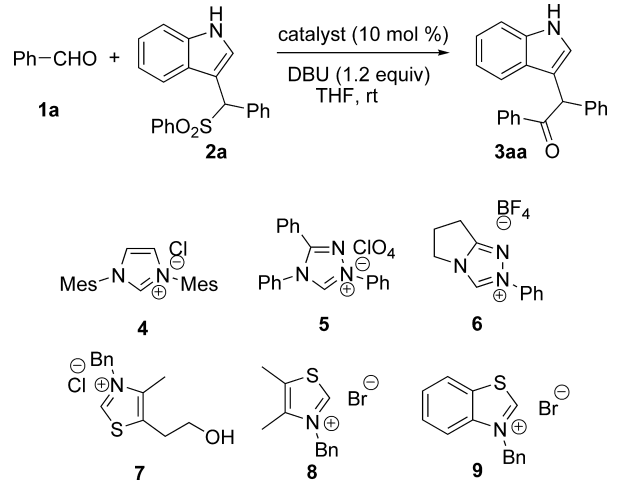
aldehyde, and the desired α-(3-indolyl) ketone was afforded in only moderate yield.[11] Recently, Scheidt reported that the reaction of a stoichiometrically generated acyl anion with a silyl-protected gramine derivative led to the formation of α-(3-indolyl) ketone.[12] To our knowledge, there is no report on NHC-catalyzed reaction with this electrophilic intermediate generated in situ. Given the fact that indoles exist extensively as the structure core of biologically active natural products and pharmaceutical compounds,[13] the significance of developing a new synthetic method for indole derivatives is obvious.[14] Fortunately, after screening the reaction conditions, the cross-coupling reaction of aldehydes with arylsulfonyl indoles has been realized with a readily available thiazolium salt. In this paper, we report the preliminary results.

For the exploratory studies, we selected the reaction between benzaldehyde **1a** and sulfonylindole **2a**, using DBU (1, 8-diazabicyclo[5.4.0]undec-7-ene) as the base. Our studies began with an initial examination of different readily available NHC precursors. The results are summarized in Table 1. Although imidazolium salt **4** and triazolium salts **5** and **6** are reported to be suitable catalysts for the umpolung reactions, none of them displays catalytic activities here (entries 1−3, Table 1). We are delighted to find that the commercially available thiazolium salt **7** is capable of catalyzing the reaction to give the desired product in an 85% yield (entry 4, Table 1). However, the catalyst derived from thiazolium salt **8** gave the product in only 17% yield despite the structural similarity between **8** and **7**. The reaction with the thiazolium salt **9** failed to give any product (entry 6, Table 1).

Table 1. Screening the Catalysts for the Reaction of Benzaldehyde **1a** with Arylsulfonylindole **2a**[a]



entry	catalyst	time (h)	convn (%)[b]
1	**4**	48	N.R.
2	**5**	48	N.R.
3	**6**	48	N.R.
4	**7**	2	85
5	**8**	48	17
6	**9**	48	N.R.

[a] Reaction conditions: **1a**/**2a**/DBU = 1.2/1/1.2, 0.1 M of **2a** in THF at 25 °C. [b] Determined by ^{1}H NMR.

(2) For recent examples on NHC as umpolung catalysts, see: (a) Phillips, E. M.; Wadamoto, M.; Chan, A.; Scheidt, K. A. *Angew. Chem., Int. Ed.* **2007**, *46*, 3107. (b) Bode, J. W.; Sohn, S. S. *J. Am. Chem. Soc.* **2007**, *129*, 13798. (c) Phillips, E. M.; Reynolds, T. E.; Scheidt, K. A. *J. Am. Chem. Soc.* **2008**, *130*, 2416. (d) Seayad, J.; Patra, P. K.; Zhang, Y.-G.; Ying, J. Y. *Org. Lett.* **2008**, *10*, 953. (e) Wong, F. T.; Patra, P. K.; Seayad, J.; Zhang, Y.; Ying, J. Y. *Org. Lett.* **2008**, *10*, 2333. (f) He, M.; Bode, J. W. *J. Am. Chem. Soc.* **2008**, *130*, 418. (g) Rommel, M.; Fukuzumi, T.; Bode, J. W. *J. Am. Chem. Soc.* **2008**, *130*, 17266. (h) He, M.; Beahm, B. J.; Bode, J. W. *Org. Lett.* **2008**, *10*, 3817. (i) Maki, B. E.; Scheidt, K. A. *Org. Lett.* **2008**, *10*, 4313. (j) Chan, A.; Scheidt, K. A. *J. Am. Chem. Soc.* **2008**, *130*, 2740. (k) Phillips, E. M.; Wadamoto, M.; Roth, H. S.; Ott, A. W.; Scheidt, K. A. *Org. Lett.* **2009**, *11*, 105. (l) Wang, L.; Thai, K.; Gravel, M. *Org. Lett.* **2009**, *11*, 891. (m) Yang, L.; Tan, B.; Wang, F.; Zhong, G. *J. Org. Chem.* **2009**, *74*, 1744. For recent examples on NHC as nucleophilic catalysts, see: (n) He, L.; Jian, T.-Y.; Ye, S. *J. Org. Chem.* **2007**, *72*, 7466. (o) Zhang, Y.-R.; He, L.; Wu, X.; Shao, P.-L.; Ye, S. *Org. Lett.* **2008**, *10*, 277. (p) Zhang, Y.-R.; Lv, H.; Zhou, D.; Ye, S. *Chem.—Eur. J.* **2008**, *14*, 8473. (q) Huang, X.-L.; He, L.; Shao, P.-L.; Ye, S. *Angew. Chem., Int. Ed.* **2009**, *48*, 192. (r) Duguet, N.; Campbell, C. D.; Slawin, A. M. Z.; Smith, A. D. *Org. Biomol. Chem.* **2008**, *6*, 1108. (s) Campbell, C. D.; Duguet, N.; Gallagher, K. A.; Thomson, J. E.; Lindsay, A. G.; O'Donoghue, A. C.; Smith, A. D. *Chem. Commun.* **2008**, 3528. (t) Thomson, J. E.; Campbell, C. D.; Concellon, C.; Duguet, N.; Rix, K.; Slawin, A. M. Z.; Smith, A. D. *J. Org. Chem.* **2008**, *73*, 2784. (u) Thomson, J. E.; Kyle, A. F.; Gallagher, K. A.; Lenden, P.; Concellon, C.; Morrill, L. C.; Miller, A. J.; Joannesse, C.; Slawin, A. M. Z.; Smith, A. D. *Synthesis* **2008**, *17*, 2805.

(3) (a) Breslow, R. *J. Am. Chem. Soc.* **1958**, *80*, 3719. (b) Sheehan, J.; Hunneman, D. H. *J. Am. Chem. Soc.* **1966**, *88*, 3666. (c) Enders, D.; Breuer, K.; Teles, J. H. *Synth. Commun.* **1999**, *29*, 1. (d) Enders, D.; Kallfass, U. *Angew. Chem., Int. Ed.* **2002**, *41*, 1743. (e) Enders, D.; Han, J. *Tetrahedron* **2008**, *64*, 1637. (f) Ma, Y.-J.; Wei, S.-P.; Wu, J.; Yang, F.; Liu, B.; Lan, J.-B.; Yang, S.-Y.; You, J.-S. *Adv. Synth. Catal.* **2008**, *350*, 2645. (g) Zhao, H.; Foss, F. W., Jr.; Breslow, R. *J. Am. Chem. Soc.* **2008**, *130*, 12590.

(4) (a) Enders, D.; Breuer, K.; Runsink, J.; Teles, J. H. *Helv. Chim. Acta* **1996**, *79*, 1899. (b) Kerr, M. S.; Read de Alaniz, J.; Rovis, T. *J. Am. Chem. Soc.* **2002**, *124*, 10298. (c) Kerr, M. S.; Rovis, T. *Synlett* **2003**, 1934. (d) Kerr, M. S.; Rovis, T. *J. Am. Chem. Soc.* **2004**, *126*, 8876. (e) Read de Alaniz, J.; Rovis, T. *J. Am. Chem. Soc.* **2005**, *127*, 6284. (f) Enders, D.; Han, J.; Henseler, A. *Chem. Commun.* **2008**, 3989. (g) Liu, Q.; Perreault, S.; Rovis, T. *J. Am. Chem. Soc.* **2008**, *130*, 14066. (h) Alaniz, J. R.; Kerr, M. S.; Moore, J. L.; Rovis, T. *J. Org. Chem.* **2008**, *130*, 2033. (i) Cullen, S. C.; Rovis, T. *Org. Lett.* **2008**, *10*, 3141. (j) Orellana, A.; Rovis, T. *Chem. Commun.* **2008**, 730. (k) Enders, D.; Han, J. *Synthesis* **2008**, *23*, 3864.

(5) (a) Hachisu, Y.; Bode, J. W.; Suzuki, K. *J. Am. Chem. Soc.* **2003**, *125*, 8432. (b) Enders, D.; Niemeier, O.; Balensiefer, T. *Angew. Chem., Int. Ed.* **2006**, *45*, 1463. (c) Takikawa, H.; Hachisu, Y.; Bode, J. W.; Suzuki, K. *Angew. Chem., Int. Ed.* **2006**, *45*, 3492. (d) Li, Y.; Feng, Z.; You, S.-L. *Chem. Commun.* **2008**, 2263.

(6) Liu, Y.-K.; Li, R.; Yue, L.; Li, B.-J.; Chen, Y.-C.; Wu, Y.; Ding, L.-S. *Org. Lett.* **2006**, *8*, 1521.

(7) Mattson, A. E.; Zuhl, A. M.; Reynolds, T. E.; Scheidt, K. A. *J. Am. Chem. Soc.* **2006**, *128*, 4932.

(8) (a) Suzuki, Y.; Ota, S.; Fukuta, Y.; Ueda, Y.; Sato, M. *J. Org. Chem.* **2008**, *73*, 2402. (b) Suzuki, Y.; Toyota, T.; Imada, F.; Sato, M.; Miyashita, A. *Chem. Commun.* **2003**, 1314.

(9) (a) Murry, J. A.; Franz, D. E.; Soheil, A.; Tillyer, R. E.; Grabowski, J. J.; Reider, P. J. *J. Am. Chem. Soc.* **2001**, *123*, 9696. (b) Mennen, S. M.; Gipson, J. D.; Kim, Y. R.; Miller, S. J. *J. Am. Chem. Soc.* **2005**, *127*, 1654. (c) Li, G.-Q.; Dai, L.-X.; You, S.-L. *Chem. Commun.* **2007**, 852.

(10) (a) Ballini, R.; Palmiei, A.; Petrini, M.; Torregiani, E. *Org. Lett.* **2006**, *8*, 4093. (b) Palmiei, A.; Petrini, M. *J. Org. Chem.* **2007**, *72*, 1863. (c) Ballini, R.; Palmiei, A.; Petrini, M.; Shaikh, R. R. *Adv. Synth. Catal.* **2008**, *350*, 129. (d) Shaikh, R. R.; Mazzanti, A.; Petrini, M.; Bartoli, G.; Melchiorre, P. *Angew. Chem., Int. Ed.* **2008**, *47*, 8707.

(11) (a) Stetter, H.; Schmitz, P. H.; Schreckenberg, M. *Chem. Ber.* **1977**, *110*, 1971. (b) Stetter, H.; Kuhlmann, H. *Org. React.* **1991**, *40*, 407.

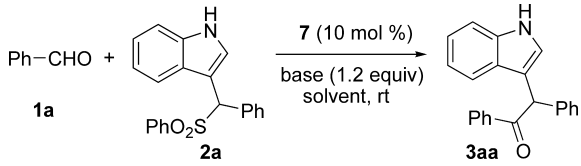
(12) Mattson, A. E.; Scheidt, K. A. *J. Am. Chem. Soc.* **2007**, *129*, 4508.

(13) (a) Bosch, J.; Bennasar, M.-L. *Synlett* **1995**, 587. (b) Faulkner, D. J. *Nat. Prod. Rep.* **2002**, *19*, 1. (c) Agarwal, S.; Caemmerer, S.; Filali, S.; Froehner, W.; Knoell, J.; Krahl, M. P.; Reddy, K. R.; Knoelker, H.-J. *Curr. Org. Chem.* **2005**, *9*, 1601. (d) O'Connor, S. E.; Maresh, J. J. *Nat. Prod. Rep.* **2006**, *23*, 532.

(14) For reviews, see: (a) Bandini, M.; Melloni, A.; Umani-Ronchi, A. *Angew. Chem., Int. Ed.* **2004**, *43*, 550. (b) Bandini, M.; Melloni, A.; Tommasi, S.; Umani-Ronchi, A. *Synlett* **2005**, 1199.

As summarized in Table 2, different solvents and bases have been examined for the reaction. Several common

Table 2. Optimizing the Conditions for the Reaction of Benzaldehyde **1a** with Arylsulfonylindole **2a**[a]



entry	solvent	base	time (h)	convn (%)[b]
1	THF	DBU	2	85
2	CH_2Cl_2	DBU	4	>95
3	toluene	DBU	10	89
4	Et_2O	DBU	48	N.R.
5	DMF	DBU	48	N.R.
6	CH_3CN	DBU	1	93
7	dioxane	DBU	1	69
8	CH_3CN	DABCO	48	20
9	CH_3CN	Et_3N	48	44
10	CH_3CN	DIEA	48	32
11	CH_3CN	K_2CO_3	4	>95
12	CH_3CN	Cs_2CO_3	0.5	>95
13	CH_3CN	KO*t*Bu	48	complex

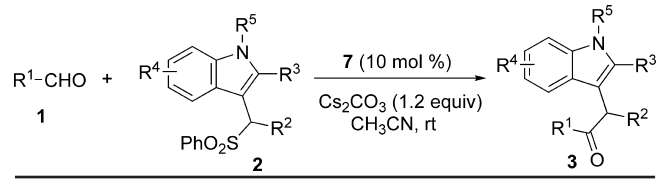
[a] Reaction conditions: **1a/2a**/base = 1.2/1/1.2, 0.1 M of **2a** in solvent at 25 °C. [b] Determined by ^{1}H NMR.

solvents such as THF, CH_2Cl_2, toluene, CH_3CN, and dioxane all led to the formation of the product **3aa** in good to excellent conversions (entries 1−3, 6, and 7, Table 2). No reaction occurs in ether probably due to the poor solubility of **2a** (entry 4, Table 1). CH_3CN was chosen as the optimal solvent since the reaction in CH_3CN proceeded to completion in 1 h with excellent yield (entry 6, Table 1). Among the bases tested, Cs_2CO_3 gave the best result (>95% conversion) in 0.5 h (entries 6 and 8−13, Table 2).

Under the optimized reaction conditions [10 mol % of thiazolium salt **7**, 120 mol % of Cs_2CO_3, in CH_3CN at room temperature], a variety of aromatic or aliphatic aldehydes and substituted 3-(1-arylsulfonylalkyl)indoles have been explored to examine the generality of the reaction. The results are listed in Table 3.

As listed in Table 3, the method proved to be suitable for a wide range of aryl aldehydes (up to 99% yield). It is worth noting that the aromatic aldehydes with substituent on the ortho-position (entry 8, Table 3) or bulky 1-naphthaldehyde (entry 10, Table 3) went well in all cases. Excellent yields were obtained for the heteroaryl aldehydes as well (entries 11 and 12, Table 3). To our delight, the aliphatic aldehydes were also tolerated, and this is not usual for the benzoin-type reaction (entries 13 and 14, Table 3). Using benzaldehyde, structural variation in the 3-(1-arylsulfonylalkyl) indoles was then examined. As to the substituents R^2, aromatic ones with either an electron-withdrawing group or an electron-donating group show much better reactivity than the alkyl substituent (entries 15−18, Table 3). The steric and

Table 3. Substrate Scope for the Reaction of Aldehydes with Arylsulfonylindoles[a]



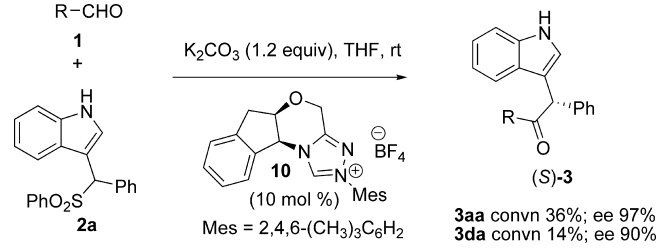
entry	**1**, R^1	**2**, R^2, R^3, R^4, R^5	**3**, yield (%)[b]
1	**1a**, Ph	**2a**, Ph, H, H, H	**3aa**, 99
2	**1b**, 4-MeC_6H_4	**2a**, Ph, H, H, H	**3ba**, 69
3	**1c**, 4-$CF_3C_6H_4$	**2a**, Ph, H, H, H	**3ca**, 99
4	**1d**, 4-BrC_6H_4	**2a**, Ph, H, H, H	**3da**, 99
5	**1e**, 4-FC_6H_4	**2a**, Ph, H, H, H	**3ea**, 99
6	**1f**, 4-ClC_6H_4	**2a**, Ph, H, H, H	**3fa**, 99
7	**1g**, 3-ClC_6H_4	**2a**, Ph, H, H, H	**3ga**, 99
8	**1h**, 2-ClC_6H_4	**2a**, Ph, H, H, H	**3ha**, 99
9	**1i**, 3-MeC_6H_4	**2a**, Ph, H, H, H	**3ia**, 99
10	**1j**, 1-naphthyl	**2a**, Ph, H, H, H	**3ja**, 99
11	**1k**, 2-furyl	**2a**, Ph, H, H, H	**3ka**, 99
12	**1*l***, 2-thienyl	**2a**, Ph, H, H, H	**3la**, 95
13	**1m**, $PhCH_2CH_2$	**2a**, Ph, H, H, H	**3ma**, 62
14	**1n**, *n*-C_3H_7	**2a**, Ph, H, H, H	**3na**, 54
15	**1a**, Ph	**2b**, 4-BrC_6H_4, H, H, H	**3ab**, 87
16	**1a**, Ph	**2c**, 4-ClC_6H_4, H, H, H	**3ac**, 99
17	**1a**, Ph	**2d**, 4-$MeOC_6H_4$, H, H, H	**3ad**, 66
18	**1a**, Ph	**2e**, *n*-C_3H_7, H, H, H	**3ae**, 37
19	**1a**, Ph	**2f**, Ph, Me, H, H	**3af**, 97
20	**1a**, Ph	**2g**, Ph, Ph, H, H	**3ag**, 80
21	**1a**, Ph	**2h**, Ph, H, 4-Me, H	**3ah**, 99
22	**1a**, Ph	**2i**, Ph, H, 6-Br, H	**3ai**, 79
23	**1a**, Ph	**2i**, Ph, H, H, Me	N.R.

[a] Reaction conditions:**1/2/**Cs_2CO_3 = 1.2/1/1.2, 0.1 M of **2** in CH_3CN at 25 °C. [b] Isolated yields.

electronic nature of the indole core had little influence on the outcome of the reaction, and generally high yields were obtained (entries 19−22, Table 3). Notably, *N*-methyl-substituted **2** gives no desired product (entry 23, Table 3).

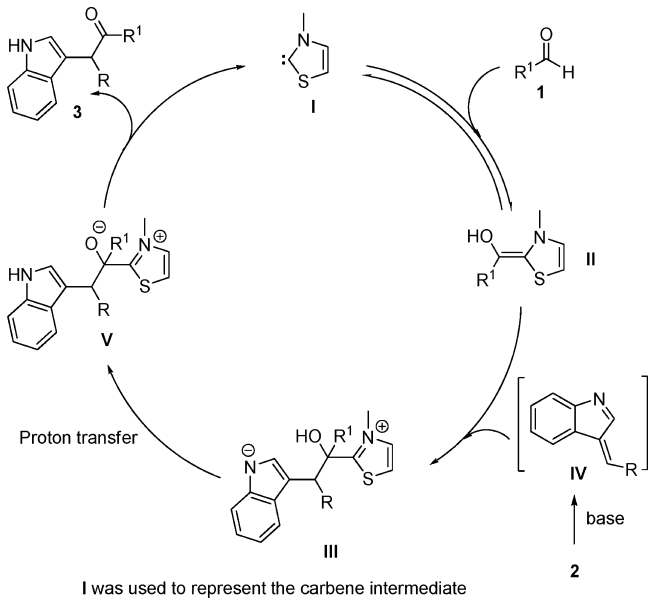
A preliminary study on the enantioselective version of this methodology was carried out (Scheme 1). In the presence

Scheme 1. Enantioselective Reaction of Benzaldehyde **1a** with Phenylsulfonylindole **2a**



of 10 mol % of the chiral NHC catalyst derived from the triazolium salt **10**,[15] the reaction of benzaldehyde **1a** and 3-(1-arylsulfonylalkyl)indole **2a** gave **3aa** in 36% conversion and 97% ee. To determine the absolute configuration of the

Scheme 2. Proposed Catalytic Cycle



product, the crystal structure of enantiopure **3da** was obtained,[16] and a single-crystal X-ray analysis determined its configuration as S.[17] Although more efficient NHC catalysts need to be developed for a better reactivity, these results serve as a proof of concept for developing a highly efficient asymmetric version of the current reaction.

A plausible catalytic cycle was proposed as illustrated in Scheme 2. Carbene **I** is generated by deprotonation of thiazolium salt in the presence of base. **I** reacts with aldehyde **1** to give the Breslow intermediate **II**, which could lead to intermediate **III** by reacting with the electrophilic intermediate **IV** generated from **2** under the basic condition. Upon proton transfer, intermediate **III** will give intermediate **V**, which could further release the carbene catalyst **I** and product **3**.

In summary, we have developed an efficient NHC-catalyzed intermolecular Stetter-type reaction with a novel electrophile generated from 3-(1-arylsulfonylalkyl)indoles, providing a facile access to relevant 3-indolyl derivatives. The reaction features the commercially available catalyst and mild reaction conditions. Further studies on the design of new chiral catalysts for the reaction and application of the methodology in organic synthesis are currently underway.

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Supporting Information Available: Experimental procedures and analysis data for **3**, and the crystallographic data of compound (*S*)-**3da**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(15) Kerr, M. S.; Read de Alaniz, J.; Rovis, T. *J. Org. Chem.* **2005**, *14*, 5725.

(16) The enantiopure **3da** was obtained by semi-preparative HPLC (Chiralpark IC).

(17) CCDC 735894 contains the supplementary crystallographic data for (*S*)-**3da**. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk /data request/cif.