Organic LETTERS
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Cu(I)-Catalyzed Enantioselective Friedel–Crafts Alkylation of Indoles with 2-Aryl-*N*-sulfonylaziridines as Alkylating Agents

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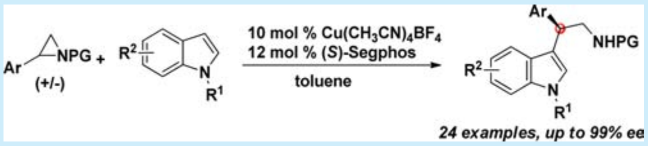
Ⓢ *Supporting Information*

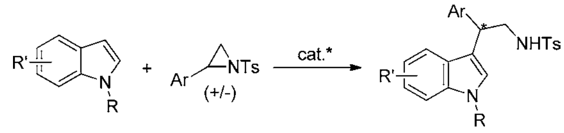
ABSTRACT: A highly enantioselective Friedel–Crafts alkylation of indoles with *N*-sulfonylaziridines as alkylating agents has been developed by utilizing the complex of Cu(CH_3CN)$_4$$BF_4$/(*S*)-Segphos as a catalyst. A range of optically active tryptamine derivatives are obtained in good to excellent yields and enantioselectivities (up to >99% ee) via a kinetic resolution process.



In the past two decades, significant progress has been achieved for catalytic asymmetric Friedel–Crafts alkylation reactions, and numerous efficient approaches have been established toward the synthesis of optically active aromatic compounds.[1] A range of alkylating agents have been studied in this transformation, most of which are C(sp^2)-based alkylating agents that contain polar double bonds, such as olefins, aldehydes, ketones, and imines. The asymmetric 1,2- or 1,4-addition of aromatic systems to the aforementioned alkylating agents is readily catalyzed by chiral Lewis acids or organic molecules through a LUMO activation strategy. In contrast, catalytic asymmetric Friedel–Crafts reactions based on nucleophilic substitution of C(sp^3)-based alkylating agents have remained rarely explored. Recently, phenolyl methanols,[2] *ortho*-aminobenzyl alcohol,[3] and indolyl methanols or methylamines[4] were employed as C(sp^3)-based alkylating agents in the enantioselective indole alkylations, whereas quinone methides and the extended iminium ions are mechanistically proposed as intermediates to which the subsequent addition of indoles is stereoselectively controlled by chiral Brønsted acid catalysts. So far, only a few examples of catalytic asymmetric Friedel–Crafts alkylations via nucleophilic substitution of C(sp^3) carbon atoms were documented, which included enantioselective desymmetrization of *meso*-epoxides[5] and dynamic kinetic resolution of cyclopropanes[6] and α-tosyloxy ketones.[7] Therefore, further exploration of suitable C(sp^3)-based alkylating agents for catalytic asymmetric Friedel–Crafts alkylation is in high demand and of great importance.

As a versatile building block for the synthesis of nitrogen-containing biologically active molecules, aziridine has been employed in a variety of enantioselective nucleophilic ring-opening reactions.[8] Among these, indole has been proven to be a popular nucleophile in the Friedel–Crafts-type ring-opening reactions of aziridine, while most of the reported examples are in their racemic variants or transformations based on chiral aziridines.[9,10] The only example of catalytic asymmetric Friedel–Crafts-type ring opening of aziridines employing indoles as nucleophiles in a magnesium-catalyzed desymmetrization of *meso*-aziridines was reported very recently by Wang and co-workers.[11] Interestingly, when 3-substituted indoles were used as substrates, [3 + 2] cycloaddition reactions with aziridines occurred with excellent enantioselectivities.[12] To the best of our knowledge, the catalytic asymmetric Friedel–Crafts reaction with *rac*-aziridines as alkylating agents has not been reported until now. As a continuous effort in developing catalytic asymmetric Friedel–Crafts reactions,[13] we report here an enantioselective indole alkylation with racemic *N*-sulfonylaziridines via a nucleophilic substitution pathway using a Cu(I)/(*S*)-Segphos complex as a catalyst (Scheme 1). A series of optically active tryptamine derivatives are afforded in good to excellent enantioselectivities, and a kinetic resolution of racemic *N*-sulfonylaziridines is observed in this reaction.

Scheme 1. Enantioselective Friedel–Crafts Alkylation of Indole with Racemic *N*-Sulfonylaziridines



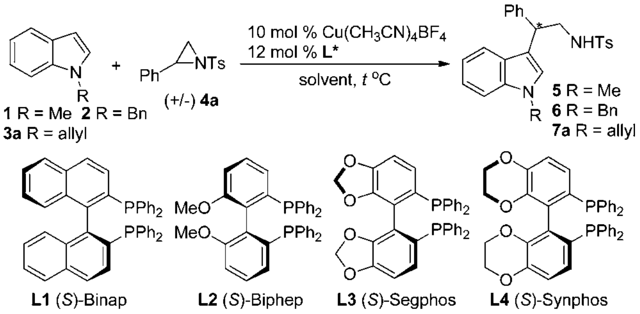
At the outset, 2-phenyl-*N*-tosylaziridine **4a** and 1-methylindole **1** were chosen as the model substrates for condition optimization. As shown in Table 1, an initial test using 2.2 equiv of **4a** led to the desired product **5** in 57% yield and 55% ee under the catalysis of the Cu(CH_3CN)$_4$$BF_4$/(*S*)-BINAP complex in DCM at 50 °C for 40 h (entry 1). Other chiral diphosphine ligands were subsequently tested to improve the ee value. It was found that both (*S*)-Biphep and (*S*)-Synphos delivered product **5** in relatively lower enantioselectivities; however, ligand (*S*)-Segphos led to a higher ee value (Table 1, entries 2–4). Solvent effect was then investigated. The enantioselectivity was remarkably improved to 89% when the reaction was performed in toluene, albeit with a moderate yield (entry 5). Comparable results were obtained in THF, whereas poor enantioselectivity

Received: May 5, 2016
Published: June 16, 2016

ACS Publications

DOI: 10.1021/acs.orglett.6b01317
Org. Lett. 2016, 18, 3122–3125

Table 1. Optimization of the Reaction Conditions[a]



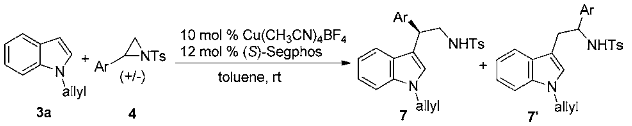
entry	L*	solvent	t (°C)	time (h)	yield (%)	ee (%)[b]
1	**L1**	DCM	50	40	57	55
2	**L2**	DCM	50	40	58	49
3	**L3**	DCM	50	40	58	64
4	**L4**	DCM	50	40	50	42
5	**L3**	toluene	50	40	57	89
6	**L3**	THF	50	40	55	71
7	**L3**	DCE	50	40	57	20
8	**L3**	toluene	rt	60	58	93
9[c]	**L3**	toluene	rt	72	73	94
10[d]	**L3**	toluene	rt	72	47	98
11[c,e]	**L3**	toluene	rt	72	65	87

[a] Reaction conditions: indole (**1**, 0.2 mmol), *N*-tosylaziridine (**4a**, 0.44 mmol), $Cu(CH_3CN)_4BF_6$ (10 mol %), and **L*** (12 mol %) in 4.0 mL solvent; rt = room temperature. [b] Determined by chiral HPLC. [c] *N*-Allylindole **3a** (0.2 mmol) was used. [d] *N*-Benzylindole **2** (0.2 mmol) was used. [e] Using 10 mol % of $Cu(CH_3CN)_4PF_6$.

was detected in DCE (entries 6 and 7). As expected, the ee value was further improved to 93% by decreasing the temperature from 50 °C to room temperature, whereas product yield still remained moderate (entry 8). To enhance the reactivity, the N-protecting group of indole was then modified. Product **7a** was isolated in a higher yield and an excellent enantioselectivity for the reaction of *N*-allylindole **3a** with aziridine **4a** (entry 9). Despite excellent enantioselectivity being detected, the yield of **6** was much lower for the reaction of *N*-benzylindole **2** (entry 10). In addition, relatively lower yield and enantioselectivity were observed for the reaction of *N*-allylindole **3a** with **4a** using $Cu(CH_3CN)_4PF_6$ as a catalyst instead of $Cu(CH_3CN)_4BF_4$ (entry 9 vs 11). To this end, the optimal conditions were established as follows: $Cu(CH_3CN)_4BF_4$ (10 mol %) and (*S*)-Segphos (12 mol %) in toluene at room temperature.

With the optimal conditions in hand, we then examined the substrate scope of this reaction. As shown in Table 2, a range of racemic 2-aryl-*N*-tosylaziridines **4** reacted smoothly with *N*-allylindole **3a** to afford the desired products in moderate to good yields and good to excellent enantioselectivities. A series of functionalities on the benzene ring of *N*-tosylaziridines **4** were well-tolerated, whereas the enantioselectivities were influenced unfavorably by the electron-donating substituents. The ee values for products **7e**−**7h** containing electron-donating groups were slightly lower than those of products **7b**−**7d** and **7i** that bear electron-withdrawing substituents (entries 5–8 vs 2–4 and 9). A lower but good enantioselectivity was also observed for the reaction of 2-naphthyl-substituted *N*-tosylaziridine **4k** (entry 11). Moreover, the reaction of aziridine **4j** bearing an *ortho*-methylphenyl group led to product **7j** in 87% ee, indicating that enantioselectivity was affected by steric hindrance. Note that in most of the reactions excellent regioselectivities were observed

Table 2. Scope of Aziridine 4[a]

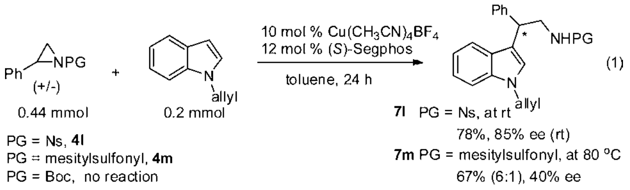


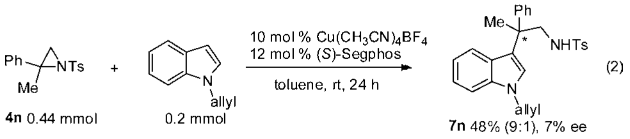
entry	4 (Ar)		yield (%)[b]	ee (%)[c]
1	**4a** (Ph)	**7a**	73	94(*R*)
2[d]	**4b** (4-Br-C_6H_4)	**7b**	65	95
3	**4c** (4-Cl-C_6H_4)	**7c**	73	95
4	**4d** (4-F-C_6H_4)	**7d**	88	91
5	**4e** (4-^{t}Bu-C_6H_4)	**7e**	75	90
6	**4f** (4-AcO-C_6H_4)	**7f**	75 (8:1)	88
7	**4g** (3-Me-C_6H_4)	**7g**	72	92
8[e]	**4h** (3-MeO-C_6H_4)	**7h**	65	86
9[e]	**4i** (3-Cl-C_6H_4)	**7i**	88	93
10[e]	**4j** (2-Me-C_6H_4)	**7j**	77 (5:1)	87
11	**4k** (2-naphthyl)	**7k**	74 (13:1)	80

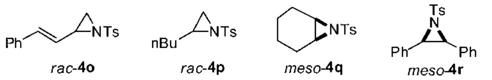
[a] Reaction conditions: **3a** (0.2 mmol), **4** (0.44 mmol), $Cu(CH_3CN)_4BF_4$ (10 mol %), and (*S*)-Segphos (12 mol %) in toluene (4.0 mL) at rt for 72 h. [b] Ratio of **7**/**7′** in parentheses. [c] Determined by chiral HPLC. [d] 80 h. [e] At 50 °C.

and only compound **7** was isolated; however, in the cases of **4f**, **4j**, and **4k**, regioisomers **7′** were detected and the ratios of **7**/**7′** were determined by their ^1H NMR spectra.

Other N-protecting groups of aziridine were examined and had a significant effect on the reactivity. Reaction of *N*-(4-nitrophenyl)sulfonylaziridine (**4l**) with *N*-allylindole at room temperature afforded product **7l** in 78% yield and 85% ee (eq 1), while lower reactivity and poor enantioselectivity were observed for *N*-mesitylsulfonylaziridine (**4m**). Moreover, no reaction occurred for *N*-Boc-aziridine (**4n**). To further extend the scope of *N*-tosylaziridine, 2,2-disubstituted substrate **4n** was synthesized and tested in the reaction with *N*-allylindole. Desired product **7n** bearing a quaternary stereogenic center was obtained in 48% yield but with poor enantioselectivity (eq 2). However, to our disappointment, allylic or alkyl *N*-tosylaziridines (**4o**, **4p**) and *meso*-*N*-tosylaziridines (**4q**, **4r**) were inactive, indicating the limitation of the present reaction.

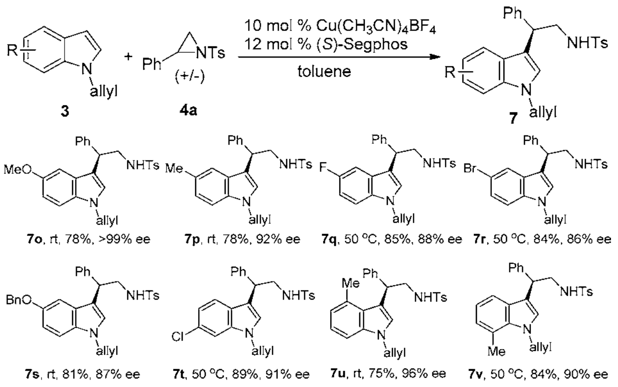






We next investigated the substituent effect of *N*-allylindole, and the results are summarized in Scheme 2. Reactions of aziridine **4a** with *N*-allylindoles bearing alkyl, alkoxyl, and halogen groups at the C5 position proceeded smoothly to afford the corresponding products **7o**−**7s** in good yields and good to excellent enantioselectivities. However, lower reactivities were observed for *N*-allylindoles containing halogen substituents due

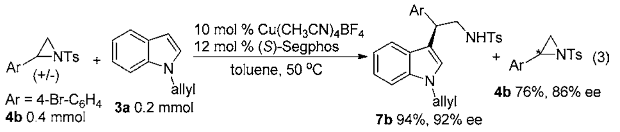
Scheme 2. Substituent Effect of *N*-Allylinodole[a]



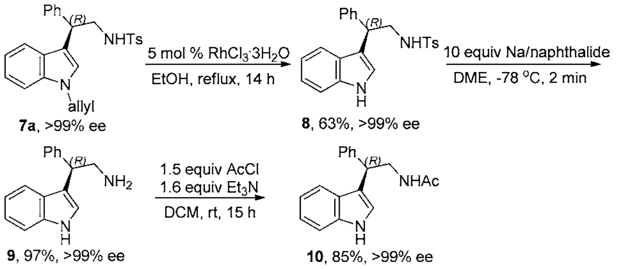
[a]Reaction conditions: **3** (0.2 mmol), **4a** (0.44 mmol), Cu(CH_3CN)$_4$$BF_4$ (10 mol %), and (*S*)-Segphos (12 mol %) in toluene (4.0 mL) for 72 h.

to their lower nucleophilicity, and in these cases, the reactions needed to be performed at a higher temperature. Therefore, by improving the temperature to 50 °C, products **7q**, **7r**, and **7t** were isolated in good yields but with relatively lower ee values (still at a high level). In addition, the methyl group at the C4 position of *N*-allylindole was compatible, and desired product **7u** was isolated in moderate yield and excellent enantioselectivity, which might indicate that the substituted group of indole had no steric effect on the reaction.

As shown in eq 3, a kinetic resolution of *N*-sulfonylaziridine **4b** was verified. The remaining starting material **4b** was isolated in 76% yield and 86% ee in the reaction with 0.4 mmol **4b** with 0.2 mmol *N*-allylindole **3a** at 50 °C, together with the isolation of **7b** in 94% yield and 92% ee. Synthetic transformations of product **7a** were then conducted. As shown in Scheme 3, the allyl group of indole **7a** (>99% ee after recrystallization) was readily removed in the presence of 5 mol % of $RhCl_3 \cdot 3H_2O$ in refluxing EtOH for 14 h, which afforded tryptamine derivative **8** in 63% yield.[14] Deprotection of *N*-sulfonylamide using Na/naphthalide led to a free amine **9** in an excellent yield of 97%, which was subsequently converted to acetylamide **10** in 85% yield. Note that all of these transformations had no erosion in enantiopurities. Moreover, the absolute configuration of **7a** was determined to be *R* by the comparison of its optical rotation value with that reported in ref 15.



Scheme 3. Product Transformations



In conclusion, we have demonstrated an efficient Cu(I)/(*S*)-Segphos-catalyzed enantioselective Friedel–Crafts-type ring-opening reaction of 2-aryl-*N*-sulfonylaziridines with indoles in good yields and good to excellent enantioselectivities, which provides a reliable approach toward chiral tryptamine derivatives. It complements the catalytic asymmetric Friedel–Crafts alkylation reaction based on nucleophilic substitution of C(sp^3)-based alkylating agents. An efficient kinetic resolution of racemic *N*-sulfonylaziridines is observed along with the asymmetric Friedel–Crafts alkylation reaction.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01317.

> Experimental procedure, characterization data, and NMR spectra for the obtained compounds (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We are grateful for the financial support from the National Natural Science Foundation of China (21372202, 21502169, and 21522207), the Program for New Century Excellent Talents in University (NCET-12-1086), and the Natural Science Foundation of Zhejiang Province (LR14B020001 and LQ15B020003).

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Org. Lett. 2016, 18, 3122−3125