OL | Organic Letters

Cite This: Org. Lett. XXXX, XXX, XXX−XXX

Letter

pubs.acs.org/OrgLett

NaClO-Promoted Atroposelective Couplings of 3-Substituted Indoles with Amino Acid Derivatives

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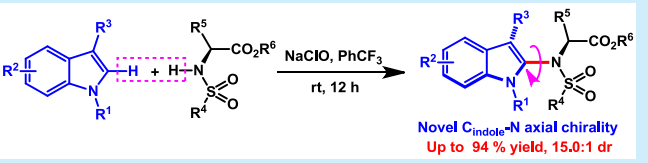
Supporting Information

ABSTRACT: A new class of C−N axial chirality based on *N*-indole sulfonamides has been disclosed. This new axially chiral *N*-indole sulfonamides were constructed by NaClO-promoted couplings of 3-substituted indoles with chiral amino acid-based sulfonamides. A series of structurally diverse *N*-indole sulfonamide-based atropisomers were prepared using this established method. The stability of these structurally interesting atropisomers highly relied on the C3-substituents of indoles and side chains of amino acid derivatives.



Atropisomerism is a property exhibited by molecules where bond rotation is restricted.[1] Progress in this area saw a steep increase after the advent of biaryl-based atropisomeric catalysts and the discovery of natural products with biaryl atropisomeric skeletons.[2] Along with biaryls, several other classes of compounds display atropisomerism.[3] As one of the most important classes of nonbiaryl axially chiral compounds, atropisomers around the C−N chiral axis have received much attention recently as novel chiral molecules.[4] These C−N axially chiral compounds have widespread appearance in naturally occurring compounds[5] and also play a significant role in acting as chiral ligands or organocatalysts.[6] These C−N axially chiral compounds have also been found to be useful in molecular devices.[7] As such, their stereoselective syntheses are the focus of recent studies.[8] After the pioneering works on atropisometric anilides by Curran and co-workers,[9] syntheses of compounds with C−N axial chirality were reported by several other groups[10] (Figure 1a), most of which are amide-type compounds, such as naphthamides, carbamates, imides, oxoamides, and ureas. As pioneered by Uemura[11] and others,[12] aromatic heterocyclic frameworks, such as indoles and pyrroles, could also be involved in axial chirality. The C_{aryl}−N chiral axis of atropisomers aforementioned are all based on *N*-phenyl motifs. *N*-Heteroaryl atropisomers with a C−N chiral axis were rarely reported to date.[13] Herein, we would like to report our efforts on the investigation of atropisomeric phenomenon with an *N*-indole chiral axis (Figure 1b).

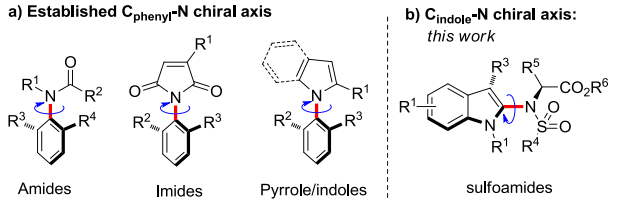


Figure 1. C−N chiral axis.

Indoles are one of the most important heteroarenes, which widely exist in natural products and pharmaceuticals, and they have been of intensive research interest in synthetic and medicinal chemistry.[14] Recently, we are engaged in amidation of indole derivatives with sulfonamides.[15] Inspired by these works, we are interested in couplings of indole derivatives with amino acid derivatives. Our initial investigation started by the coupling of 1,3-dimethylindole (**1a**) with *N*-triflyl-(L)-valine *tert*-butyl ester (**2a**) promoted by NaClO aqueous solution at room temperature (Figure 2). Interestingly, two products **3a** and **3a′** were isolated with a 7.7:1 ratio in 41% combined yield. These two compounds, in which structures and stereochemistry were established unambiguously by single crystal X-ray diffraction analysis,[16] were assigned as two diastereoisomers with an *N*-indole chiral axis. This type of *N*-indole axial chirality has not hitherto been disclosed.

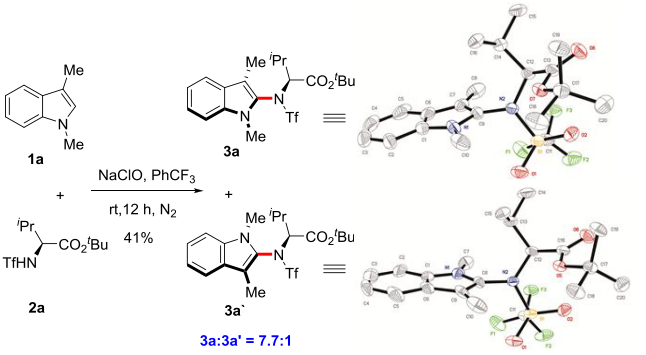


Figure 2. Coupling of 3-methylindole with valine derivative.

Received: May 8, 2019

DOI: 10.1021/acs.orglett.9b01638
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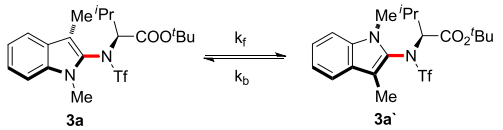
It is known that the indole-based atropisomers are expected to have less steric congestion and relatively lower rotation barriers than the corresponding benzene derivatives.[17] In order to investigate the stereochemical stability of this *N*-indole atropisomer, the half-lives and free energy barriers for racemization of **3a** in toluene at three different temperatures were measured (Table 1, see the Supporting Information for details). It was found that the half-life of **3a** was more than 5 days (122.68 h) at 313.15 K (40 °C), while the half-life was about 1.2 h at 353.15 K (80 °C). The energy barrier for racemization of **3a** was 28.04 kcal/mol ($\Delta G^{\ddagger}k_f$) and 27.07 kcal/mol ($\Delta G^{\ddagger}k_b$) at 353.15 K (80 °C).

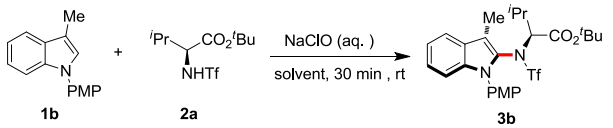
Table 1. Rate, Half-Life, and Free Energy Barrier for the Racemization of 3a in Toluene



T	$\tau_{1/2rac}$ (h)	$\Delta G^{\ddagger}k_f$ (kcal/mol)	$\Delta G^{\ddagger}k_b$ (kcal/mol)	K_{eq}
313.15 K (40 °C)	122.68	27.66	26.80	
333.15 K (60 °C)	9.21	27.75	26.84	0.25
353.15 K (80 °C)	1.22	28.04	27.07	0.25

In order to improve the efficiency and stereoselectivity of this NaClO-promoted atroposelective coupling further, the optimization of the reaction conditions was conducted using indole **1b** and L-valine derivative **2a** as the model coupling partners (Table 2). When a solution of **1b**, **2a**, and NaClO with a ratio of 2:1:3 in toluene for 30 min at room temperature, the coupling product **3b** could be isolated with 51% yield and 13:1 dr (entry 1). It was found that the solvent effect had significant influence on the efficiency of this coupling but did not affect the stereoselectivity (entries 2–6). $PhCF_3$ proved to be the optimal solvent (74% yield, entry 6). The ratio of **1b**/**2a**/NaClO was then tested and no improvement in the results was obtained (entries 7–9). When the reaction time was prolonged from 30 min to 12 h, the isolated yield was improved to 87% without affecting the stereoselectivity (entry 10). Nitrogen protection was not necessary, and when the reaction performed under an air atmosphere, the same reaction outcome was observed (entry 10).

Table 2. Reaction Conditions Optimization[a]



entry	**1b**/**2a**/NaClO	solvent	yield/%[b]	dr[c]
1	2:1:3	$PhCH_3$	51	13:1
2	2:1:3	$PhOCH_3$	15	13:1
3	2:1:3	DMF	trace	13:1
4	2:1:3	1,4-dioxane	12	13:1
5	2:1:3	CH_3CN	12	13:1
6	2:1:3	$PhCF_3$	74	13:1
7	1:2:3	$PhCF_3$	60	13:1
8	1.5:1:3	$PhCF_3$	67	13:1
9	1.5:1:1.5	$PhCF_3$	69	13:1
10[d]	2:1:3	$PhCF_3$	87	13:1

[a]Reaction conditions: a solution of **1b**, **2a** (0.1 mmol), and NaClO in the indicated solvent (2 mL) for 30 min under N_2. [b]Combined yields of two atropisomers. [c]The dr values were determined by ^{19}F NMR. [d]12 h under air. PMP = 4-methoxyphenyl.

After establishing the optimized conditions of this atroposelective coupling, we next diversified this *N*-indole axial chirality. First, a series of structurally diverse substituted indole derivatives coupled with the L-valine derivative **2a** (Figure 3). The substituents at the N1 position were explored.

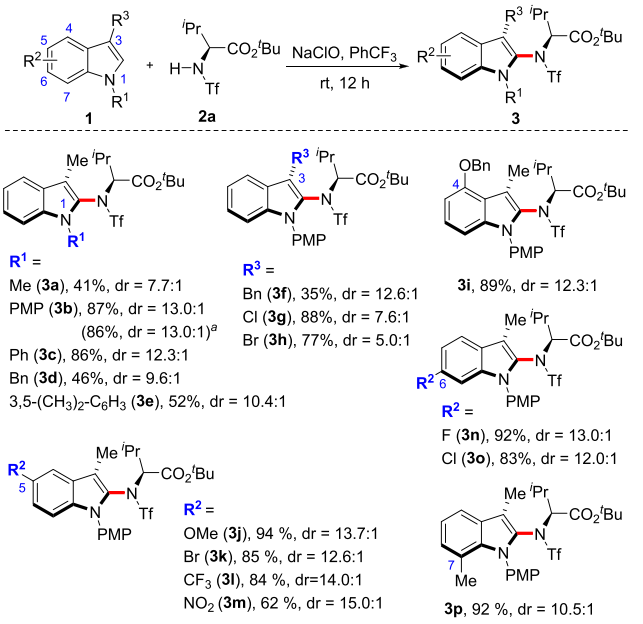


Figure 3. Scope of indole derivatives. Reaction conditions: a solution of **1** (0.2 mmol), **2a** (0.1 mmol), and NaClO (0.3 mmol) in $PhCF_3$ (2 mL) for 12 h under air. The yields were isolated yields, and the dr values were determined by ^{19}F NMR. [a]The reaction was run at the 3 mmol scale (**2a**).

N1 substituents could be aryl groups with different functionalities, and good yields and stereoselectivities could be achieved (**3b**, **3c**, and **3e**, 52–87% yields and >10:1 dr). When the N1 position was alkylated, the coupling was less efficient in terms of yields and dr values (41% yield and 7.7:1 dr for **3a**, 46% yield and 9.6:1 dr for **3d**, respectively). When the substituent at the C3 position was changed from methyl to benzyl group, the coupling product **3f** was delivered with 12.6:1 dr but moderate yield (35%). 3-Chloro and 3-bromoindole derivatives could also go through this reaction with good yields and dr values (88% yield and 7.6:1 dr for **3g** and 77% yield and 5:1 dr for **3h**, respectively). Subsequently, indoles bearing various substituents at the C4–C7 positions were coupled with **2a** to give the corresponding products **3i**–**3p** with satisfactory to excellent yields (62–94%) and good dr values (10.5:1–15.0:1). Not only electron-withdrawing groups, such as 5-CF_3 (**3l**) and 5-NO_2 (**3m**), but also electron-donating groups, such as 4-OBn (**3i**) and 5-OMe (**3j**), tolerated well in this transformation. To demonstrate the practicability of this method, we subsequently conducted this reaction on the gram scale. When 1.42 g of **1b** was subjected to the standard conditions, a comparative isolated yield of **3b**

DOI: 10.1021/acs.orglett.9b01638
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(1.39 g, 86% yield) was achieved with the same stereoselectivity (13.0:1 dr).

We next sought to establish the scope of the amino acid derivatives using indole **1b** as the coupling partner (Figure 4).

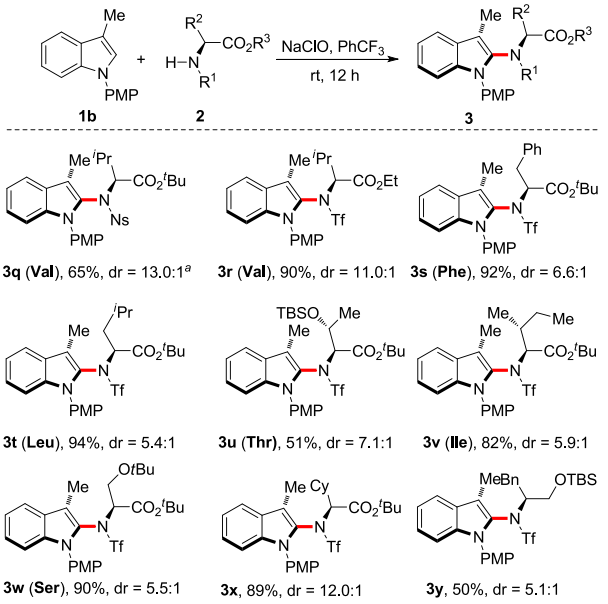

Figure 4. Scope of sulfonamides. Reaction conditions: a solution of **1b** (0.2 mmol), **2** (0.1 mmol), and NaClO (0.3 mmol) in $PhCF_3$ (2 mL) for 12 h under air. The yields were based on two isolated atropisomers. The dr values were determined by ^{19}F NMR. [a]The dr value was determined by ^{1}H NMR.

4-Nitrobenzenesulfonyl (Ns) could be used as the protecting group of amino group instead of triflyl group to give the atropisomer **3q** with the identical stereoselectivity and slightly low yield (65%). When the *t*-butyl ester was changed to ethyl ester, the stereoselectivity of the coupling was affected negatively (**3r**, 11.0:1 dr) but with slightly better yield (90%). A variety of natural amino acid derivatives, such as phenylalanine (Phe, **3s**), leucine (Leu, **3t**), threonine (Thr, **3u**), isoleucine (Ile, **3v**), and serine (Ser, **3w**), were coupled with indole **1b**, and the corresponding products **3s**−**3w** were isolated in 51−94% yields and good dr values (5.4:1−7.1:1). Steric bulky side chains of amino acid derivatives have a positive influence on the stereoselectivity. It is not surprising that alanine derivative could go through this reaction but without stereoselectivity (not shown). The cyclohexyl (Cy)-based non-natural amino acid derivative could also undergo this reaction to give the product **3x** with high yield and dr value (89% yield and 12.0:1 dr). A chiral amino alcohol derivative was also explored, and a moderate yield and stereoselectivity were observed (50% yield and 5.1:1 dr for **3y**).

To better understand the mechanism of this reaction, a series of control experiments were conducted, as show in Figure 5. Treatment of sulfonamide **2a** with NaClO could not give the *N*-chlorosulfonamide **4**, which was the potential chlorinating reagent in our previous work (Figure 5a).[15c] Therefore, it was proposed that NaClO directly served as the chlorinating reagents in this reaction. Indole **1b** reacting with NaClO could give 3-chloroindolinone **5** and indolinone **6** but in low yields (10% and 8%, respectively) (Figure 5b). It is known that chlorine transfer may be assisted by acid when NaClO is the chlorinating reagent.[18] The introduction of

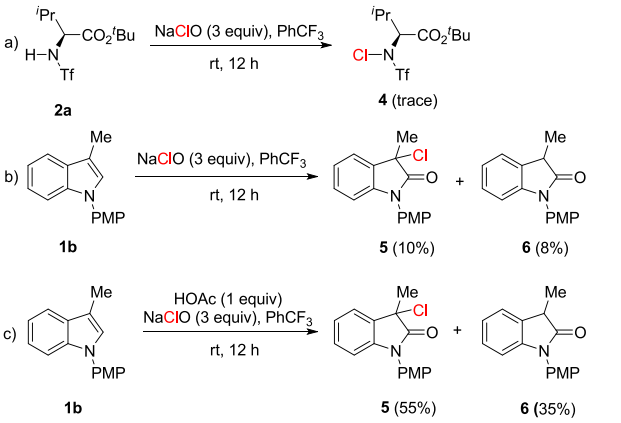

Figure 5. Control experiments.

HOAc into the reaction mixture of **1b** and NaClO gave 3-chloroindolinone **5** and indolinone **6** in significantly improved yields (55% and 35%, respectively, Figure 5c). Given the acidity of sulfonamides,[19] amino acid-derived sulfonamide **2a** acts not only as an amine source but also as an acid to promote the chlorine transfer from NaClO in this reaction.

Based on the aforementioned experimental observations and related literature,[20] a possible reaction pathway is proposed for this transformation (Figure 6). Indole **1b** undergoes electro-

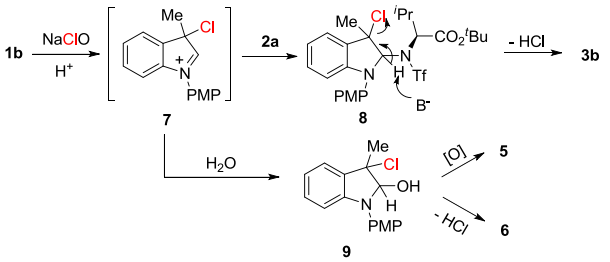

Figure 6. Plausible reaction mechanism.

philic chlorination with NaClO with the help of sulfonamide **2a** to give the iminium ion **7**. Subsequently, the iminium ion **7** is attacked by amino acid-based sulfonamide **2a**. After losing HCl assisted by a base, the desired product **3b** is given. As observed, the iminium ion **7** can also be attacked by water to afford **9**. Intermediate **9** can either be oxidized to furnish the byproduct 3-chloroindolinone **5** or lose HCl to give indolinone **6**.

In summary, we have disclosed a new class of C−N axial chirality based on *N*-indole sulfonamides. This new axially chiral *N*-indole sulfonamides were constructed by NaClO-promoted couplings of 3-substituted indoles with chiral amino acid-based sulfonamides. The stability of these structurally interesting atropisomers highly relied on the C3-substituents of indoles and side chains of amino acid derivatives. Further improvement of the diastereoselectivity and investigation of the application of this novel axially chiral indoles are underway in our laboratory.

DOI: 10.1021/acs.orglett.9b01638
Org. Lett. XXXX, XXX, XXX−XXX

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b01638.

Experimental details, NMR spectra, and details of the experiments (PDF)

Accession Codes

CCDC 1909079−1909080 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Financial support from National Natural Science Foundation of China (Grant 21672098) and National Key Research and Development Program of China (Grant 2018YFC0310900) is acknowledged.

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