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Highly Enantioselective Direct Michael Addition of 1*H*-Benzotriazole to Chalcones Catalyzed by Sc(OTf)$_3$/*N*,*N*′-Dioxide Complex

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Keywords: Asymmetric synthesis / Michael addition / Nitrogen heterocycles / Chalcones

The *N*,*N*′-dioxide–Sc(OTf)$_3$ complex was applied in the asymmetric Michael reaction of 1*H*-benzotriazole with chalcones to give the corresponding N-1 products in excellent yields (up to 99 %) with excellent enantioselectivities (up to 99 % *ee*). Further transformation into other optically active derivatives such as β-benzotriazolyl ester, alcohol, and amide were also realized with excellent results.

Introduction

Nitrogen-containing heterocycles and their derivatives have been widely applied in organic and medicinal chemistry as well as material science.[1] Catalytic asymmetric addition of azoles to electron-deficient olefins (e.g., aza-Michael reaction) provided a protocol for the introduction of optically active azole moieties that can be found in many drugs.[2,3] However, to date only a few examples can be identified. For example, Jacobsen described the chiral Al-salen catalyzed asymmetric addition reaction of a range of different aromatic N-heterocycles to α,β-unsaturated ketones and imides bearing aliphatic β-substituents with high enantioselectivities.[4] More recently, organocatalytic nitro-Michael reactions have received considerable attention. Jørgensen and co-workers reported the conjugate addition of azoles to aliphatic α,β-unsaturated aldehydes using a chiral secondary amine.[5] Vicario and co-workers succeeded in the asymmetric addition of 5-phenyltetrazole to α,β-unsaturated aldehydes with high enantioselectivity by using a chiral imidazolidinone as the catalyst.[6] Wang and co-workers accomplished the addition of azoles to nitroalkenes and α,β-unsaturated ketones with moderate to good enantioselectivities.[7,8] Despite these important contributions, searching for a highly effective catalyst system with high chemoselectivity and enantioselectivity is still challenging and interesting. As an excellent chiral scaffold, *N*,*N*′-dioxides could coordinate with many metals and exhibited great potential in many asymmetric reactions.[9] Herein, we describe a direct asymmetric Michael addition of 1*H*-benzotriazole to chalcones by using the Sc(OTf)$_3$/*N*,*N*′-dioxide complex.[10] Excellent results (up to 99% yield and 99% *ee*) were obtained for a broad range of substrates. The reaction also featured N-1 adducts as the final products compared with chiral Al-salen system and chiral primary amines, which usually afforded a mixture of N-1 and N-2 addition products.[4]

Results and Discussion

Initial attempts were made by treating chalcone **2a** with 1*H*-benzotriazole (**1a**) under Sc(OTf)$_3$/*N*,*N*′-dioxide (1:1, 2.5 mol-%) catalysis in $CHCl_3$ at –20 °C (Table 1). It was revealed that the Sc(OTf)$_3$/*N*,*N*′-dioxide complex indeed catalyzed this transformation to give desired N-1 addition product **3a** after 24 h. With regard to the chiral backbone moiety, *N*,*N*′-dioxide **L3** (derived from L-pipecolic acid) exhibited superior results to **L1** (derived from L-proline, Figure 1) and **L2** (derived from L-ramipril acid) in terms of both yield and enantioselectivity (Table 1, Entry 3 vs. Entries 1 and 2). As indicated in Table 1, we found that the amide moiety in the *N*,*N*′-dioxide ligand had a significant effect on the yield of the reaction. Ligand **L6** with an electron-withdrawing group in the *para* position of aniline provided a higher yield, whereas **L4** with an electron-donating group and **L5** with bulky isopropyl groups led to a significant decrease in the yield (Table 1, Entry 6 vs. Entries 4 and 5). Further screening of the reaction conditions identified that the solvent obviously influenced the formation of adduct **3a** (Table 1, Entries 6–8), and the best result (>99% yield, 83% *ee*) was obtained with $CHCl_3$. To improve the efficiency of the reaction, other reaction conditions such as the molar ratio of metal to ligand and reaction temperature were investigated (Table 1, Entries 10–13). Excitingly, a remarkable improvement was achieved when the molar ratio

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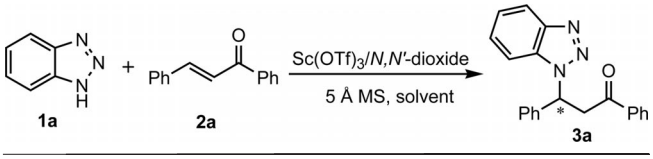
$Sc(OTf)_3$/**L6** was 1.3:1. Lowering the reaction temperature to –20 °C resulted in an improved enantioselectivity (up to 96%*ee*; Table 1, Entry 13). Moreover, reducing the catalyst loading to 1 mol-% produced no decrease in *ee* the value (Table 1, Entry 14).

Table 1. Optimization of the reaction conditions.[a]



Entry	Ligand	Solvent	Metal/Ligand	Yield [%][b]	*ee* [%][c]
1	**L1**	$CHCl_3$	1:1	71	31
2	**L2**	$CHCl_3$	1:1	79	52
3	**L3**	$CHCl_3$	1:1	86	83
4	**L4**	$CHCl_3$	1:1	12	89
5	**L5**	$CHCl_3$	1:1	<5	ND
6	**L6**	$CHCl_3$	1:1	>99	83
7	**L6**	$PhCH_3$	1:1	9	69
8	**L6**	Et_2O	1:1	50	62
9	**L6**	CH_2Cl_2	1:1	85	84
10	**L6**	$CHCl_3$	1.3:1	>99	88
11	**L6**	$CHCl_3$	1.5:1	98	88
12	**L6**	$CHCl_3$	2:1	95	89
13[d]	**L6**	$CHCl_3$	1.3:1	>99	96
14[d,e]	**L6**	$CHCl_3$	1.3:1	80	96

[a] Unless noted otherwise, reactions were carried out with 1*H*-benzotriazole (**1a**, 0.12 mmol), **2a** (0.1 mmol), ligand/$Sc(OTf)_3$ (2.5 mol-%), and 5 Å MS (10 mg) in $CHCl_3$ (1.0 mL) under a nitrogen atmosphere at 0 °C for 24 h. [b] Yield of isolated product. [c] Determined by HPLC analysis. [d] The reaction was performed at –20 °C for 48 h. [e] 1 mol-% of the catalyst was used.

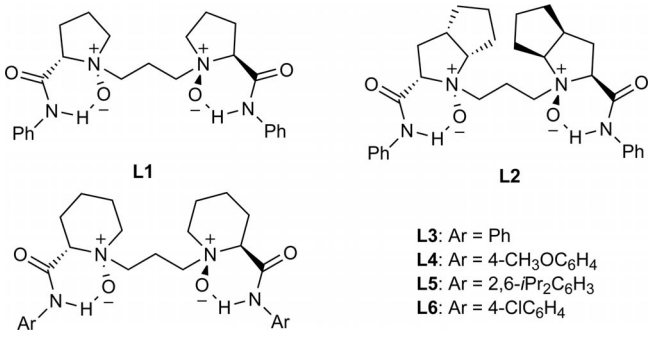
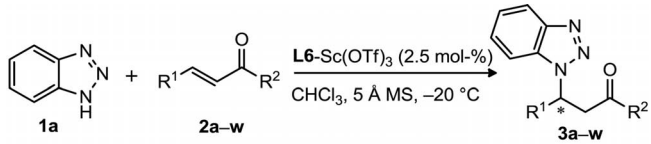
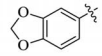
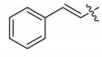


Figure 1. Chiral ligands used in the study.

Under the optimized conditions, a series of chalcone derivatives was examined in the asymmetric Michael reaction with 1*H*-benzotriazole,[11] and the corresponding N-1 adducts were isolated in moderate to excellent yields with excellent *ee* values in the range 80–99% (Table 2). It was noteworthy that this catalyst system exhibited a broad substrate scope. As shown in Table 2, the electronic nature and the position of the substituents at the aromatic ring of R^1 or R^2 had little influence on the enantioselectivity (Table 2, Entries 1–14, 17–20). The electronic and stereochemical effects of the β-aromatic substituents are greater than those of the aromatic substituents of the carbonyl moiety (Table 2, Entries 8, 12, and 14 vs. 18, 19, and 20, respectively). Notably, when the β-substituent R^1 was an unsaturated cinnamyl group or aliphatic cyclohexyl group, Michael adducts **3o** and **3p** could also be obtained in moderate yields with 82 and 88%*ee*, respectively (Table 2, Entries 15 and 16). Significantly, substrates bearing heteroaromatic substituents, either in R^1 or R^2, were also suitable acceptors for the conjugate addition reaction and afforded corresponding products **3u**–**w** with good enantioselectivities (Table 2, Entries 21–23).

Table 2. Catalytic asymmetric Michael Addition of 1*H*-benzotriazole to chalcones promoted by the $Sc(OTf)_3$/*N*,*N*′-dioxide complex.[a]

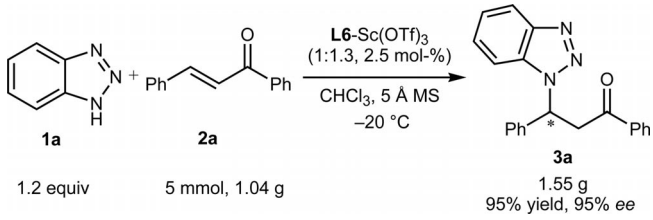


Entry	R^1	R^2	Product	Yield [%][b]	*ee* [%][c]
1	Ph	Ph	**3a**	99	96[e]
2	2-ClC_6H_4	Ph	**3b**	65	88
3	3-ClC_6H_4	Ph	**3c**	99	97[e]
4	4-ClC_6H_4	Ph	**3d**	99	97
5	4-FC_6H_4	Ph	**3e**	88	97[e]
6	4-BrC_6H_4	Ph	**3f**	98	96
7	3-$NO_2C_6H_4$	Ph	**3g**	87	98
8	4-$NO_2C_6H_4$	Ph	**3h**	80	99
9	4-CNC_6H_4	Ph	**3i**	60	98
10	3-MeC_6H_4	Ph	**3j**	99	95
11	4-MeC_6H_4	Ph	**3k**	98	93
12	4-$MeOC_6H_4$	Ph	**3l**	90	85
13		Ph	**3m**	95	90
14	2-naphthyl	Ph	**3n**	65	96[e]
15		Ph	**3o**	45	82
16	*c*-hexyl	Ph	**3p**	60	88
17	Ph	4-ClC_6H_4	**3q**	99	97[d]
18	Ph	4-$NO_2C_6H_4$	**3r**	99	95[e]
19	Ph	4-$MeOC_6H_4$	**3s**	99	95[e]
20	Ph	2-naphthyl	**3t**	96	96[e]
21	2-thienyl	Ph	**3u**	50	80
22	Ph	2-thienyl	**3v**	35	95
23	Ph	2-furyl	**3w**	98	92

[a] Unless noted otherwise, reactions were carried out with 1*H*-benzotriazole (**1a**, 0.12 mmol), **2** (0.1 mmol), **L6**/$Sc(OTf)_3$ (1:1.3, 2.5 mol-%), and 5 Å MS (10 mg) in $CHCl_3$ (1.0 mL) under a nitrogen atmosphere at –20 °C. [b] Yield of isolated product. [c] Determined by HPLC analysis. [d] The absolute configuration was determined to be *R* by comparison to literature data.[7b] [e] The absolute configuration was determined to be *R* by CD spectra.

To show the synthetic utility of the catalyst system, a gram-scale synthesis of **3a** by using the chiral $Sc(OTf)_3$/*N*,*N*′-dioxide complex was performed. As shown in Scheme 1, by treatment of the starting materials (5 mmol) under the optimized conditions, excellent results (95% yield and 95%*ee*) were still obtained. Further transformation into other derivatives was also realized (Scheme 2). Baeyer–

Villiger oxidation of **3s** proceeded with *m*-CPBA to afford β-benzotriazolyl ester **4** in 80% yield without any racemization. Benzotriazolyl alcohol **5** was then obtained by treatment of **4** with $NaBH_4$ in THF in 78% yield. Additionally, exposure of **3s** (95%*ee*) to hydroxylamine hydrochloride in pyridine and ethanol for 12 h and subsequent one-pot treatment with TsCl afforded β-benzotriazolyl amide **6** in 77% yield with complete preservation of the enantiopurity (95%*ee*).



Scheme 1. Catalytic asymmetric Michael addition of **1a** to **2a** on a gram scale.

To gain insight into the reaction mechanism, C_2-symmetric amide **L7**[13] was synthesized, which was the precursor of chiral *N*,*N*′-dioxide **L6**. As expected, only a trace amount of adduct was obtained, and with almost all the starting materials was left unconverted when **L7**/$Sc(OTf)_3$ was used. This fact illuminated that the *N*-oxide and the central metal played a key role for this reaction. In light of the X-ray structure of the *N*,*N*′-dioxide/Sc^{III} complex[10b] and the experimental results, a proposed transition state rationalizing the observed sense of asymmetric induction was proposed. As shown in Figure 2, the *N*-oxides and the amide oxygen atoms of **L6** are coordinated to Sc^{3+} in a tetradentate manner to form two six-membered chelate rings. Meanwhile, the chalcone is attached to Sc^{3+} from the favorable side. The incoming 1*H*-benzotriazole prefers to attack the *Re* face rather than the *Si* face, as the latter is strongly shielded by the nearby 4-chorlophenyl group, giving the *R* configured product.

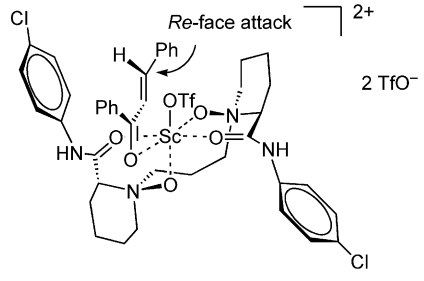


Figure 2. Proposed transition state.

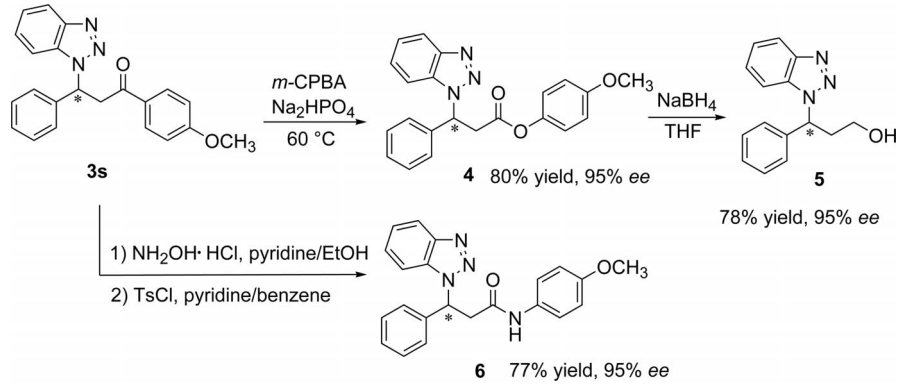
Conclusions

In conclusion, we have developed an efficient $Sc(OTf)_3$/*N*,*N*′-dioxide complex for the asymmetric Michael reaction of chalcone derivatives and 1*H*-benzotriazole. Significant progress has been obtained with a broad substrate scope, giving chiral N-1 addition compounds in moderate to excellent yields (up to 99%) with excellent enantioselectivities (up to 99%*ee*). The reaction could be amplified to gram scales at 2.5 mol-% catalyst loading without loss of enantioselectivity. Further transformation into other derivatives was also realized with excellent results. Future work will be directed to the extension of mechanistic studies and synthetic application.

Experimental Section

Typical Experimental Procedure for the Enantioselective aza-Michael Reaction: The complex **L6/**$Sc(OTf)_3$ (1:1.3, 2.5 mol-%), 1*H*-benzotriazole (**1a**, 0.12 mmol), and 5 Å molecular sieves (10 mg) in $CHCl_3$ (1 mL) was stirred in a test tube under a N_2 atmosphere at room temperature for 1 h. After the mixture was cooled to –20 °C, **2a** (0.1 mmol) was then added sequentially, and the reaction mixture was stirred at this temperature. The process was monitored by TLC. The reaction mixture was purified by column chromatography on silica gel (ethyl acetate/petroleum ether, 1:4 to 1:6) to give product **3a**: 99% yield, 96%*ee*. HPLC (Chiralpak AS-H, *i*PrOH/*n*-hexane = 30:70, flow rate = 0.8 mL/min, λ = 254 nm): t_R = 15.6 (minor), 19.3 (major) min. $[\alpha]_D^{28}$ = –15.7 (*c* = 0.21, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 8.01 (d, *J* = 8.5 Hz, 1 H), 7.93 (d, *J* = 8.5 Hz, 2 H), 7.55–7.27 (m, 10 H), 6.54 (dd, *J* = 9.0, 5.0 Hz, 1 H), 4.84 (dd, *J* = 18.0, 9.0 Hz, 1 H), 3.81 (dd, *J* = 18.0, 5.0 Hz, 1 H) ppm.

Supporting Information (see footnote on the first page of this article): Characterization data, copies of the NMR spectra, HPLC traces, and ellipticity vs. wavelength graphs.



Scheme 2. Synthesis of chiral β-benzotriazolyl ester, β-benzotriazolyl alcohol, and β-benzotriazolyl amide.[12]

Acknowledgments

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[11] For more details see the Supporting Information.

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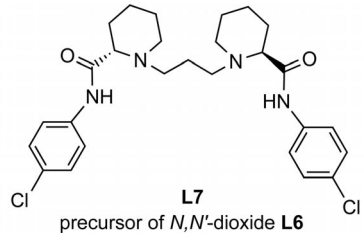
[13] When using **L7**/$Sc(OTf)_3$ as the catalyst under the standard conditions, no adduct was obtained.



L7
precursor of *N,N'*-dioxide **L6**

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