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Highly Enantioselective Synthesis of β-Heteroaryl-Substituted Dihydrochalcones Through Friedel–Crafts Alkylation of Indoles and Pyrrole

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Abstract: A highly enantioselective Friedel–Crafts (F–C) alkylation of indoles and pyrrole with chalcone derivatives catalyzed by a chiral *N,N*′-dioxide–Sc(OTf)$_3$ complex has been developed that tolerates a wide range of substrates. The reaction proceeds in moderate to excellent yields and high enantioselectivities (85–92 % enantiomeric excess) using 2 mol % (for indole) or 0.5 mol % (for pyrrole) catalyst loading, which showed the potential value of the catalyst system. Meanwhile, a strong positive nonlinear effect was observed. On the basis of the experimental results and previous reports, a possible working model is proposed to explain the origin of the activation and asymmetric induction.

Keywords: alkylation · asymmetric catalysis · dioxides · chalcones · scandium

Introduction

The catalytic asymmetric Friedel–Crafts (F–C) alkylation is one of the most powerful tools for C−C bond formation; this enables access to a variety of optically active building blocks for organic transformations.[1] Since the pioneering work of Paras and MacMillan,[2a] and Bandini and co-workers,[3a] there have been several reports of highly enantioselective asymmetric F–C alkylation of indole/pyrrole with simple α,β-unsaturated aldehydes[2] and ketones.[3–4] However, when chalcone derivatives were used, few examples were documented and only moderate enantioselectivities (8–58 % enantiomeric excess (*ee*))[5] were achieved, probably owing to the low reactivity of chalcone derivatives and the difficulty in enantiofacial differentiation. In addition, the asymmetric F–C alkylation of pyrrole using chalcones has not been developed. Because β-heteroaryl-substituted dihydrochalcones (DHCs) exhibit biological activities, such as antimycotic and antibacterial properties,[6] it would be highly desirable to develop effective protocols for the enantioselective synthesis of these optically pure compounds.

On the other hand, with a tunable electronic and steric chiral environment, *N,N*′-dioxides have been applied to many asymmetric procedures.[7–8] Herein, we describe a readily available chiral *N,N*′-dioxide–scandium(III) trifluoromethanesulfonate complex system for the enantioselective conjugate addition of indoles and pyrrole to a broad range of chalcones, giving a series of β-heteroaryl-substituted DHCs in moderate to excellent yields (up to 99 %) and high enantioselectivities (up to 92 % *ee*) using 0.5–10 mol % catalyst loading under mild conditions.

Results and Discussion

Our initial investigation began with screening several chiral Lewis acid catalysts that were generated in situ from metal salts and *N,N*′-dioxide **L1** to evaluate their ability to promote the addition of indole **1a** to chalcone **2a**. As shown in Table 1, Sc(OTf)$_3$ gave the best results (Table 1, entries 1–5). As for the chiral backbone moiety, when *N,N*′-dioxide **L3** (derived from L-pipecolic acid) was used instead of the L-proline- and L-ramipril-derived ligands, the enantioselectivity increased to 87 % ee (Table 1, entry 7 compared with entries 1 and 6). Further optimization of the reaction conditions was then aimed at exploring the effectiveness of Sc(OTf)$_3$ with other *N,N*′-dioxide ligands. We found that the amide moiety in the *N,N*′-dioxide ligands had a significant effect on the enantioselectivity (Table 1, entries 8–15). When R was replaced by an aromatic ring, the enantioselectivity as well as the yield decreased dramatically (Table 1, entries 8–9). Pleasingly, when *N,N*′-dioxide **L10** (derived from 9-anthracenylmethylamine) was used, the desired product **3aa** was obtained in 92 % *ee* and 78 % yield

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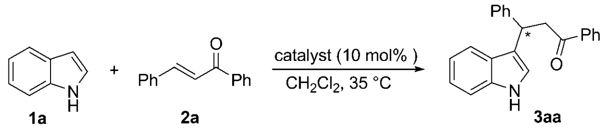
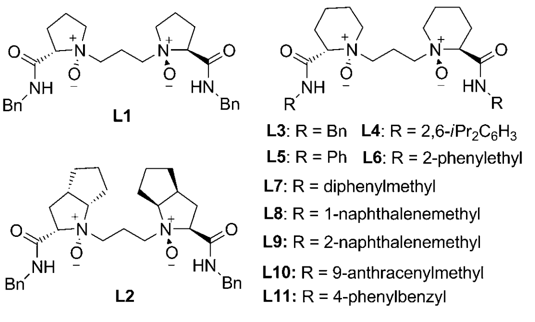
Table 1. Central metal and ligand effects on catalytic asymmetric F–C reaction of indole **1a** and chalcone **2a** under indicated conditions.[a]



Entry	Ligand	Metal	*t* [h]	Yield [%][b]	*ee* [%][c]
1	**L1**	$Sc(OTf)_3$	48	48	45
2	**L1**	$Y(OTf)_3$	40	n.r.[d]	–
3	**L1**	$La(OTf)_3$	36	n.r.[d]	–
4	**L1**	$In(OTf)_3$	24	7	0
5	**L1**	$ZrCl_4$	24	18	0
6	**L2**	$Sc(OTf)_3$	48	54	82
7	**L3**	$Sc(OTf)_3$	40	65	87
8	**L4**	$Sc(OTf)_3$	50	26	21[e]
9	**L5**	$Sc(OTf)_3$	72	17	19
10	**L6**	$Sc(OTf)_3$	36	83	86
11	**L7**	$Sc(OTf)_3$	24	19	70
12	**L8**	$Sc(OTf)_3$	40	47	88
13	**L9**	$Sc(OTf)_3$	40	49	85
14	**L10**	$Sc(OTf)_3$	40	78	92
15	**L11**	$Sc(OTf)_3$	44	77	86

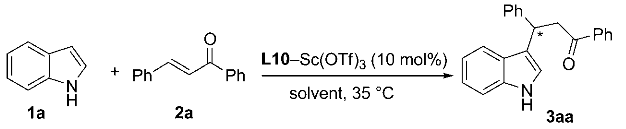
[a] Unless otherwise noted, reactions were carried out with **1a** (0.12 mmol) and **2a** (0.1 mmol) in CH_2Cl_2 (0.5 mL) with **L**/metal complex (10 mol%; 1/1) catalyst under Ar atmosphere at 35 °C. [b] Isolated yield. [c] Determined by HPLC analysis. Unless noted, the absolute configuration was *R* by comparison with the reported optical rotation.[3c] [d] No reaction. [e] The absolute configuration of the major isomer was *S*.

(Table 1, entry 14). Therefore, the **L10**–$Sc(OTf)_3$ system was chosen to assess other reaction parameters.



Encouraged by the initial results, various solvents were tested in the presence of **L10**–$Sc(OTf)_3$ (10 mol%). The results indicated that the reaction solvent plays an important role in governing the rate and enantioselectivity of the reaction. Coordinating and highly polar solvents such as THF, EtOH, and CH_3CN shut down the catalytic activity of the **L10**–$Sc(OTf)_3$ complex, presumably because of coordination to the central metal (Table 2, entries 1–3). No reaction took place in toluene (Table 2, entry 4). Because CH_2Cl_2 was initially found to be the optimal solvent, other chlorinated alkanes were then investigated, but no superior result was obtained (Table 2, entry 5 compared with entries 6–8). The substrate concentration was also a key factor. To our delight, when the concentration of chalcone **2a** was increased to 0.5 M, the product was obtained in excellent yield (99%) and the enantioselectivity was maintained (Table 2, entry 9). Further increases in concentration led to a slight decrease in enantioselectivity although the reaction time was shortened to 17 h (Table 2, entry 10).

Table 2. Solvent and concentration effects on catalytic asymmetric F–C reaction of indole **1a** and chalcone **2a**.[a]

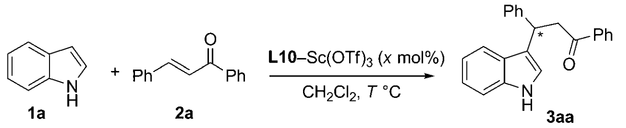


Entry	Solvent	*t* [h]	Yield [%][b]	*ee* [%][c]
1	THF	24	n.r.[d]	–
2	EtOH	36	n.r.[d]	–
3	CH_3CN	24	trace	60
4	toluene	24	n.r.[d]	–
5	CH_2Cl_2	40	78	92
6	$CHCl_3$	32	26	72
7	$Cl_2CHCHCl_2$	36	40	90
8	$ClCH_2CH_2Cl$	72	53	83
9[e]	CH_2Cl_2	28	99	92
10[f]	CH_2Cl_2	17	>99	89

[a] Unless otherwise noted, reactions were carried out with **1a** (0.12 mmol) and **2a** (0.1 mmol) in solvent (0.5 mL) with **L10**–$Sc(OTf)_3$ complex (10 mol%; 1/1) catalyst under Ar atmosphere at 35 °C. [b] Isolated yield. [c] Determined by HPLC analysis. Unless noted, the absolute configuration was *R* by comparison with the reported optical rotation.[3c] [d] No reaction. [e] CH_2Cl_2 (0.2 mL). [f] CH_2Cl_2 (0.1 mL).

Subsequently, the reaction temperature and catalyst loading were examined and the results are presented in Table 3. Decreasing the reaction temperature led to lower reactivity although the enantioselectivity was maintained (Table 3, entries 1–3). When the temperature was increased from 35 to 45 °C, the enantioselectivity was somewhat reduced (Table 3,

Table 3. Effect of temperature and catalyst loading on the catalytic asymmetric F–C reaction of indole **1a** and chalcone **2a**.[a]



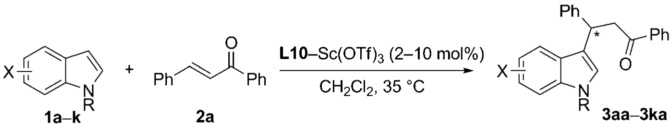
Entry	*T* [°C]	Catalyst loading [*x* mol%]	*t* [h]	Yield [%][b]	*ee* [%][c]
1	−20	10	72	9	92
2	0	10	36	24	92
3	25	10	36	99	92
4	35	10	28	99	92
5	45	10	16	92	89
6	35	15	22	91	92
7	35	5	28	79	89
8[d]	35	1	28	11	90

[a] Unless otherwise noted, reactions were carried out with **1a** (0.12 mmol) and **2a** (0.1 mmol) in CH_2Cl_2 (0.2 mL) with **L10**–$Sc(OTf)_3$ (10 mol%; 1/1) under Ar atmosphere at 35 °C. [b] Isolated yield. [c] Determined by HPLC analysis. Unless noted, the absolute configuration was *R* by comparison with the reported optical rotation.[3c] [d] The reaction was carried out with **L10**–$Sc(OTf)_3$ (1 mol%; 1/1), **1a** (0.24 mmol), and **2a** (0.2 mmol) in CH_2Cl_2 (0.4 mL) under Ar atmosphere at 35 °C.

entry 5). The catalyst loading was then evaluated. Upon increasing the catalyst loading from 10 to 15 mol %, neither the yield nor the enantioselectivity were changed (Table 3, entry 6). Reducing the catalyst loading caused a notable drop in reactivity (Table 3, entry 7 and 8). Some additives (for details see the Supporting Information) were also screened, but no better results were obtained. Extensive screening showed that the optimal conditions were as follows: **L10**–Sc(OTf)$_3$ complex (10 mol %; molar ratio **L10**/Sc(OTf)$_3$ 1/1), chalcone (0.1 mmol), and indole (0.12 mmol) in CH_2Cl_2 (0.2 mL) at 35 °C.

To investigate the scope of the reaction, we examined the reactions of a range of indoles with chalcone **2a** under the optimized conditions and the results are listed in Table 4. Indoles with an electron-donating group could be converted into the desired products in high yields and *ee* values (Table 4, entries 2–7). In the case of halogen-substituted indoles, the catalyst was also efficient (Table 4, entries 8–10). Notably, for some indoles, good results were still maintained using as low as 2 mol % catalyst loading (Table 4, entries 4, 6, and 7). When 1-methylindole (**1k**) was used, a moderate result was obtained (Table 4, entry 11).

Table 4. Catalytic asymmetric F–C reaction of indole derivatives and chalcone **2a** under the optimal conditions.[a]

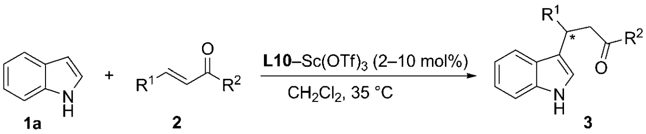


Entry	Indole	Product	*t* [h]	Yield [%][b]	*ee* [%][c]
1	**1a**, X: H, R: H	**3aa**	28	99	92[d]
2	**1b**, X: 7-Me, R: H	**3ba**	40	99	90
3	**1c**, X: 7-Et, R: H	**3ca**	44	92	92
4	**1d**, X: 5-Me, R: H	**3da**	44 (60)	99 (89)	89 (88)[e]
5	**1e**, X: 5-MeO, R: H	**3ea**	44	94	90
6	**1f**, X: 6-MeO, R: H	**3fa**	40 (53)	99 (81)	85 (85)[f]
7	**1g**, X: 2-Me, R: H	**3ga**	44 (48)	99 (80)	81 (81)[e]
8	**1h**, X: 5-Br, R: H	**3ha**	40	50	90
9	**1i**, X: 5-Cl, R: H	**3ia**	40	78	90
10	**1j**, X: 5-F, R: H	**3ja**	44	79	86
11	**1k**, X: H, R: Me	**3ka**	44	74	74

[a] Unless noted, reactions were carried out with **2a** (0.1 mmol) and **1** (0.12 mmol) in CH_2Cl_2 (0.2 mL) with **L10**–Sc(OTf)$_3$ complex (10 mol %) under Ar atmosphere at 35 °C. [b] Isolated yield. [c] Determined by HPLC analysis. [d] The absolute configuration was *R* by comparison with the reported optical rotation.[3c] [e] The results in parentheses were obtained with 2 mol % **L10**–Sc(OTf)$_3$. [f] The results in parentheses were obtained with 5 mol % **L10**–Sc(OTf)$_3$.

With these results in hand, various α,β-unsaturated ketones were then examined (Table 5).[9] Good to excellent yields and high enantioselectivities were obtained, regardless of the electronic nature or positions of the substituents on the phenyl ring (Table 5, entries 1–23). A condensed-ring chalcone reacted smoothly with indole, giving the product **3ap** with 90 % *ee* (Table 5, entry 16). When dibenzalacetone was used, the single F–C alkylation product **3as** was observed, which can thus be further functionalized at the remaining double bond (Table 5, entry 19). Importantly, the catalyst loading could be decreased to 5 or 2 mol % without affecting the efficiency of the catalyst (Table 5, entries 9–12, 18, and 20). In addition, substrates bearing heteroaryl units also proved to be competent candidates for the alkylation of indole (Table 5, entries 24–26). For *trans*-1-phenylbut-2-en-1-one, the desired product **3aaa** was obtained with a moderate *ee* value (Table 5, entry 27). It is noteworthy that some β-indole-substituted DHCs could act as promising antimycotic and antibacterial agents.[6a]

Table 5. Catalytic asymmetric F–C reaction of indole **1a** and enone derivatives **2** under the optimal conditions.[a]

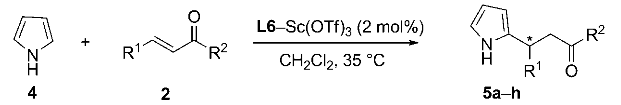


Entry	R^1	R^2	Adduct	Yield [%][b]	*ee* [%][c]
1	Ph	Ph	**3aa**	99	92[d]
2	3-MeC_6H_4	Ph	**3ab**	84	91
3	4-MeC_6H_4	Ph	**3ac**	87	91
4	Ph	4-MeC_6H_4	**3ad**	77	91
5	3-$MeOC_6H_4$	Ph	**3ae**	91	90
6	4-$MeOC_6H_4$	Ph	**3af**	68	92
7	Ph	4-$MeOC_6H_4$	**3ag**	57	92
8	4-ClC_6H_4	Ph	**3ah**	99	92
9	Ph	4-ClC_6H_4	**3ai**	99 (88)	90 (90)[e]
10	3-$CF_3C_6H_4$	Ph	**3aj**	99 (85)	92 (92)[f]
11	3-$NO_2C_6H_4$	Ph	**3ak**	99 (75)	92 (92)[f]
12	4-CNC_6H_4	Ph	**3al**	95 (88)	89 (89)[e]
13	4-PhC_6H_4	Ph	**3am**	95	92
14	3-$PhOC_6H_4$	Ph	**3an**	91	90
15	3,4-$OCH_2OC_6H_3$	Ph	**3ao**	75	92
16	Ph	2-naphthyl	**3ap**	99	90
17	4-FC_6H_4	Ph	**3aq**	99	92
18	4-BrC_6H_4	Ph	**3ar**	99 (95)	90 (91)[f]
19	Ph	$-CH{=}CHC_6H_5$	**3as**	77	90
20	3-ClC_6H_4	Ph	**3at**	99 (82)	89 (89)[e]
21	Ph	4-FC_6H_4	**3au**	71	88
22	Ph	3-ClC_6H_4	**3av**	99	87
23	2-$MeOC_6H_4$	Ph	**3aw**	74	83
24	2-furyl	Ph	**3ax**	43	90
25	2-thienyl	Ph	**3ay**	66	91
26	Ph	2-furyl	**3az**	75	88
27	Me	Ph	**3aaa**	46	58[g]

[a] Unless noted, reactions were carried out with **1a** (0.12 mmol) and **2** (0.1 mmol) in CH_2Cl_2 (0.2 mL) with **L10**–Sc(OTf)$_3$ complex (10 mol %) under Ar atmosphere at 35 °C for 20–60 h (for details see the Supporting Information). [b] Isolated yield. [c] Determined by HPLC analysis. [d] The absolute configuration was *R* by comparison with the reported optical rotation.[3c] [e] The results in parentheses were obtained with 5 mol % **L10**–Sc(OTf)$_3$. [f] The results in parentheses were obtained with 2 mol % **L10**–Sc(OTf)$_3$. [g] The absolute configuration was *S* by comparison with the reported optical rotation.[3e]

Encouraged by the success of the F–C reactions of indoles with chalcones, we also investigated pyrrole as a nucleophile.[10] Under the same reaction conditions, the desired product **5a** was obtained in 45 % yield and 90 % *ee* after 7 h. To our delight, after a slight modification of the catalyst system, by altering the ligand **L10** to **L6**, the *ee* value of **5a** increased to 92% using 2 mol% **L6**–Sc(OTf)$_3$ (Table 6, entry 1). The substrate scope was then surveyed. Various chalcones with electron-withdrawing or -donating groups on the phenyl ring reacted with pyrrole smoothly using 2 mol% **L6**–Sc(OTf)$_3$ under mild conditions, giving the corresponding products in good yields and high enantioselectivities (90–92% *ee*) (Table 6, entries 2–7). When *trans*-1-phenylbut-2-en-1-one was employed, the corresponding 2-alkylated pyrrole **5h** was obtained with 74% *ee* (Table 6, entry 8).

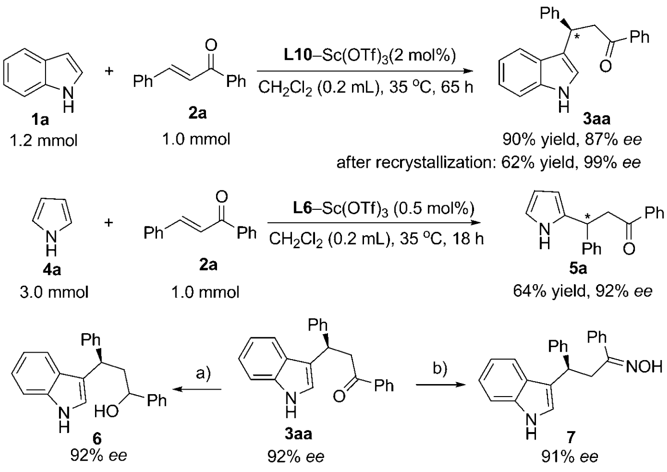
Table 6. Catalytic asymmetric F–C reaction of pyrrole **4** and enones **2** under the indicated conditions.[a]



Entry	R^1	R^2	Adduct	Yield [%][b]	*ee*[%][c]
1	Ph	Ph	**5a**	73	92
2	4-BrC$_6$H$_4$	Ph	**5b**	78	92
3	4-MeC$_6$H$_4$	Ph	**5c**	55	92
4	4-Cl	Ph	**5d**	48	92
5	3-ClC$_6$H$_4$	Ph	**5e**	80	90
6	Ph	4-FC$_6$H$_4$	**5f**	75	92
7	Ph	4-MeC$_6$H$_4$	**5g**	46	92
8	Me	Ph	**5h**	46	74[d]

[a] Unless otherwise noted, reactions were carried out with **4** (0.6 mmol) and **2** (0.2 mmol) in CH$_2$Cl$_2$ (0.4 mL) with **L6**–Sc(OTf)$_3$ (2 mol%; 1/1) complex under Ar atmosphere at 35 °C for 15 h. [b] Isolated yield. [c] Determined by HPLC analysis. [d] When using 5 mol% **L6**–Sc(OTf)$_3$ (1/1) complex for 20 h, the absolute configuration was *S* by comparison with the reported optical rotation.[3e]

To show the synthetic application of the current system, a large-scale synthesis of **3aa**/**5a** was tested. As shown in Scheme 1, catalytic asymmetric F–C reaction of indole with chalcone **2a** was accomplished with good results (90% yield, 87% *ee*) by using only 2 mol% of **L10**–Sc(OTf)$_3$. Optically pure **3aa** was obtained after a single recrystallization. Most notably, the reaction could be performed with pyrrole in the presence of 0.5 mol% of **L6**–Sc(OTf)$_3$, giving the desired product **5a** with 92% *ee*. In addition, reduction of the adduct **3aa** gave a diastereomeric mixture of alcohol **6** (diastereomeric ratio (dr) 53:47). The product **3aa** can also be easily transformed into oxime **7** (92% yield, 91% *ee*), which is a versatile building block.



Scheme 1. Catalytic asymmetric F–C reaction of indole and pyrrole to chalcone **2a** on a 1.0 mmol scale and the transformations of **3aa** to **6** and to **7**. Conditions: a) NaBH$_4$, CH$_3$OH, 0 °C, 1 h, 91% yield, dr 53:47, 92% *ee*; b) pyridine, NH$_2$OH·HCl, EtOH, 35 °C, 2 h, 85% yield, 91% *ee*.

To gain insight into the reaction mechanism, a C_2-symmetric amide, compound **8** (Figure 1), which was the precursor of the chiral *N,N'*-dioxide **L10**, was synthesized. Several experiments were carried out and the results are summarized in Table 7. No adducts were obtained by employing **8** or **L10** as an organocatalyst (Table 7, entries 1 and 2). When **8**–Sc(OTf)$_3$ was employed as the catalyst, the reaction did not take place (Table 7, entry 3), which confirmed that the *N*-oxide and the central metal play a key role in this reaction. In addition, the ratio of ligand **L10** to Sc(OTf)$_3$ was also crucial. The reaction did not occur when the ratio of **L10**/Sc(OTf)$_3$ was 1.5/1 or 2/1 (Table 7, entries 4 and 5), which suggested that the catalyst was poisoned by excess *N,N'*-dioxide **L10**. The enantioselectivity decreased remarkably when a 2/1 molar ratio of Sc(OTf)$_3$/**L10** was used because of the strong background reaction of Sc(OTf)$_3$ (Table 7, entry 8).

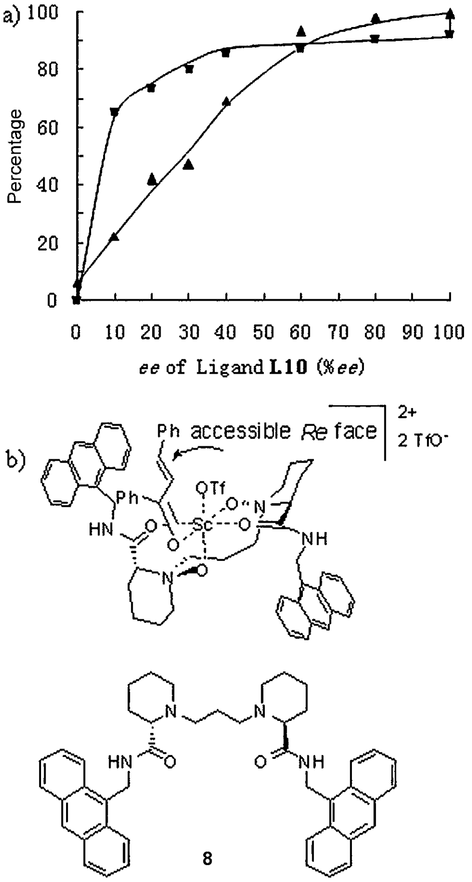
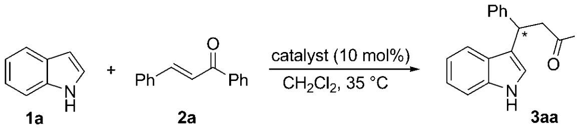


Figure 1. a) Chiral amplification in the F–C alkylation of **1a** with **2a** catalyzed by **L10**–Sc(OTf)$_3$ complex (■: *ee* value of **3aa**, ▲: yield of **3aa**); b) Proposed transition-state model.

Table 7. Control experiments for mechanistic studies.[a]



Entry	Ligand [mol %]	$Sc(OTf)_3$ [mol %]	t [h]	Yield [%][b]	*ee* [%][c]
1	**8** (10)	–	40	n.r.[d]	–
2	**L10** (10)	–	48	n.r.[d]	–
3	**8** (10)	10	24	n.r.[d]	–
4	**L10** (20)	10	28	trace	–
5	**L10** (15)	10	28	trace	–
6	**L10** (11)	10	28	92	92
7	**L10** (10)	10	28	99	92
8	**L10** (5)	10	24	99	57

[a] Unless noted, reactions were carried out with **1a** (0.12 mmol) and **2** (0.1 mmol) in CH_2Cl_2 (0.2 mL) under Ar atmosphere at 35 °C . [b] Isolated yield. [c] Determined by HPLC analysis. Unless noted, the absolute configuration was *R* by comparison with the reported optical rotation.[3c] [d] No reaction.

Next, the relationship between the *ee* value of ligand **L10** and the product **3aa** was investigated under the optimal conditions shown in Table 4. A strong positive nonlinear effect[11] was observed (Figure 1 a), suggesting that two or more monomeric catalyst species form catalytically inactive oligomeric aggregates, thereby enhancing the proportion of one catalytically active scandium *N,N'*-dioxide enantiomer.[12] In the light of the X-ray structure of the *N,N'*-dioxide–Sc^{III} complex recently reported by us,[8h] and the above experimental results, a proposed transition state that rationalizes the observed sense of asymmetric induction is provided in Figure 1 b. In this transition state, the *N*-oxides and amide oxygen atoms of **L10** coordinate to scandium in a tetradentate manner to form two six-membered chelate rings, and the chalcone can coordinate to scandium from the more accessible side. The incoming indole prefers to attack the *Re* face rather than *Si* face of the chalcone because the latter is strongly shielded by the nearby anthracenyl ring, which results in the *R*-configured product.

Conclusion

We have developed a catalytic asymmetric Friedel–Crafts alkylation of indoles and pyrrole with a number of chalcones promoted by a *N,N'*-dioxide–$Sc(OTf)_3$ complex. This type of electrophilic compound is challenging for F–C reactions on account of the nonchelating character of chalcones. A series of β-heteroaryl-substituted dihydrochalcones was obtained with high enantioselectivities (up to 92 % *ee*) and moderate to excellent yields (up to 99 %) under mild conditions. This method also expanded considerably the range of optically active indole/pyrrole derivatives that can be directly generated from readily available prochiral precursors. Good results were still maintained when using 2 (for indole) or 0.5 mol % (for pyrrole) catalyst loading, which showed the potential value of the catalyst system. Meanwhile, a proposed transition-state model was put forward to explain the origin of the asymmetric induction. Further application of the current method is currently underway.

Experimental Section

Typical experimental procedure for indole: A solution of *N,N'*-dioxide **L10** (7.1 mg, 0.01 mmol), scandium triflate (4.9 mg, 0.01 mmol), and chalcone **2a** (0.10 mmol) in CH_2Cl_2 (0.2 mL) was stirred under argon atmosphere at 35 °C for 0.5 h, then indole **1a** (50 µL, 2.4 M in CH_2Cl_2) was added. The reaction mixture was stirred at 35 °C for 28 h and then purified by flash chromatography (petroleum ether/ethyl acetate/CH_2Cl_2 = 5:1:0.1) on silica gel to afford the desired product **3aa** as a white solid (99 % yield, 92 % *ee*). M.p. 139–140 °C; $[\alpha]_D^{26} = -49.2$ ($c = 0.39$ in $CHCl_3$) (99 % *ee*); ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.98$ (br s, 1 H), 7.97–7.94 (m, 2 H), 7.58–7.54 (m, 1 H), 7.47–7.43 (m, 3 H), 7.39–7.34 (m, 3 H), 7.30–7.26 (m, 2 H), 7.20–7.15 (m, 2 H), 7.06–7.02 (m, 2 H), 5.09 (t, $J = 7.2$ Hz, 1 H), 3.84 (dd, $J = 6.8$, 16.8 Hz, 1 H), 3.75 ppm (dd, $J = 7.6$, 16.8 Hz, 1 H); HPLC analysis using a chiral AD-H column (*i*PrOH/hexane = 20/80, 1.0 mL min^{-1}, 254 nm), t_r (major) = 13.267 min, t_r (minor) = 15.368 min, 92 % *ee*.

Typical experimental procedure for pyrrole: A solution of *N,N'*-dioxide **L6** (2.2 mg, 0.004 mmol), scandium triflate (2.0 mg, 0.004 mmol), and chalcone **2a** (0.2 mmol) in CH_2Cl_2 (0.4 mL) was stirred under argon atmosphere at 35 °C for 0.5 h, then pyrrole **4** (42.0 µL, 0.6 mmol) was added. The reaction mixture was stirred at 35 °C for 15 h and then purified by flash chromatography (petroleum ether/ethyl acetate = 10:1) on silica gel to afford the desired product **5aa** as a colorless oil (73 %, 92 % *ee*). $[\alpha]_D^{27} = -3.5$ ($c = 0.80$ in $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): $\delta = 8.31$ (s, 1 H), 7.98–7.95 (m, 2 H), 7.59–7.55 (m, 1 H), 7.48–7.44 (m, 2 H), 7.36–7.26 (m, 4 H), 7.25–7.23 (m, 1 H), 6.67–6.66 (m, 1 H), 6.11–6.09 (m, 1 H), 5.87–5.85 (m, 1 H), 4.81–4.78 (m, 1 H), 3.86–3.79 (dd, $J = 8.0$, 17.2 Hz, 1 H), 3.64–3.58 ppm (dd, $J = 6.8$, 17.6 Hz, 1 H); HPLC analysis using a chiral OD-H column (*i*PrOH/hexane = 10/90, 1.0 mL min^{-1}, 254 nm), t_r (minor) = 10.949 min, t_r (major) = 11.757 min, 92 % *ee*.

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