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$AgAsF_6/Sm(OTf)_3$ Promoted Reversal of Enantioselectivity for the Asymmetric Friedel−Crafts Alkylations of Indoles with β,γ-Unsaturated α-Ketoesters

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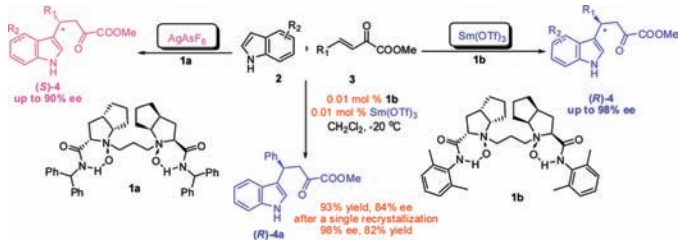
ABSTRACT



The first example of central metal controlled reversal of enantioselectivity in asymmetric Friedel−Crafts alkylation of indoles and β,γ-unsaturated α-ketoesters has been developed. Using the same chiral starting material derived *N,N′*-dioxides 1a and 1b as ligands, various indole esters 4 were obtained in good to excellent yields and enantioselectivities. The reaction also featured mild reaction conditions and remarkably low catalyst loading (down to 0.01 mol %).

The indole framework represents a privileged structural motif of particular value in medicinal chemistry and complex target synthesis.[1] The asymmetric Friedel−Crafts alkylation of indole provides a direct access to the enantiomerically enriched indole derivatives.[2] Although the application of Lewis acids as catalysts is one of the most powerful strategies in organic chemistry,[3] only a few highly enantioselective processes based on chiral metal complexes have been reported for the asymmetric Friedel−Crafts alkylation of indoles with β,γ-unsaturated α-ketoesters,[4] the products of which could be functionalized readily to the corresponding amino acids or α-hydroxy acids.[5] Previous reports by Jørgensen or Desimoni mainly focused on chiral oxazoline complexes as catalysts, in which only one enantiomeric ligand could be achieved easily or in low cost.[6] Therefore,

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(6) For the availability of both (*R*)- and (*S*)-*tert*-leucine, see: Bélanger, É.; Pouliot, M.-F.; Paquin, J.-F *Org. Lett.* **2009**, *11*, 2201.

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the development of an efficient catalytic system to synthesize both enantiomers in high optical purity, especially using a single enantiomeric ligand available, is very challenging, interesting, as well as demanding for this reaction.

Meanwhile, the remarkably different biological property makes it rather essential for simultaneous preparation of both enantiomers in catalytic asymmetric synthesis. Generally, turning of enantioselectivity is most obviously occurred through the use of enantiomeric ligands. However, some chiral ligands or starting materials of chiral ligands are not always readily or economically available in both enantiomers. Therefore, other compensated methods such as alteration of the reaction conditions (solvent, pressure, and additive) and the adjustment of ligand structure with no change of the chiral source have also been developed.[7] Among them, the introduction of different central metals to control the reaction enantioselectivity in a specific way has attracted more and more attention.[8] The unique characteristics of metal ions in atomic radius and electronic property altered their coordination pattern even with the same chiral ligand. This provides the possibility of the existence of different transition states, which offered more opportunities for modification leading to both enantiomerically enriched products. As part of our continuing efforts toward reactions catalyzed by *N*,*N*′-dioxide-metal complexes,[9] we report here the first example of $AgAsF_6$/$Sm(OTf)_3$ controlled reversal of enantioselectivity in asymmetric Friedel−Crafts alkylation of indoles and β,γ-unsaturated α-ketoesters using the same chiral starting material. Moreover, the reaction could even be carried out with as low as 0.01 mol % catalyst loading to give the desired products in good to excellent yields and enantioselectivities.

As novel ligands, chiral *N*,*N*′-dioxides complexed with different metals such as In(III),[9a] Sc(III),[9b,i] La(III),[9c] Ni(II),[9d,f] Fe(II),[9g] Cu(I),[9e] and Cu(II)[9h] have shown powerful catalytic capability in various reactions. According to the initial experiment, $Sm(OTf)_3$ and AgOTf gave the most promising results of 28% and 48% ee, respectively (Table 1, entry 1 vs 2). The opposite configuration obtained obviously proved the decisive role of central metals in effective stereocontrol of the reaction products. Given the rare application of Sm(III) in asymmetric catalytic reaction[10] as well as the availability of L-ramiprol acid, the starting material of the ligands **1a**−**1d** (Figure 1), in one single enantiomer, we decided to optimize both reaction systems simultaneously in order to expand the utility of this reaction. Subsequent investigation of the reaction parameters such as ligand, temperature, substrate concentration, and catalyst loading gave the optimal conditions: 10 mol % $AgAsF_6$-**1a** as the catalyst, −20 °C in 2.0 mL of THF for the (*S*)-isomer (82% yield and 85% ee), and 0.5 mol % complex of **1b**-$Sm(OTf)_3$ as catalyst, −20 °C in 0.6 mL of CH_2Cl_2 for the (*R*)-isomer (96% yield and 98% eeTable 1, entries 8 and 15).[11]

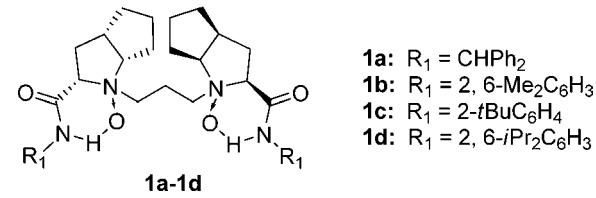
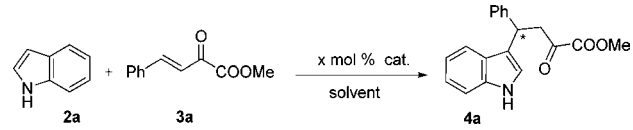


Figure 1. *N*,*N*′-Dioxide ligands evaluated.

Table 1. Catalytic Enantioselective Friedel−Crafts Reaction of Indole **2a** with β,γ-Unsaturated α-Ketoester **3a** in the Presence of Catalysts[a]



entry	L	metal	solvent	x (mol %)	yield (%)[b]	ee (%)[c]
1	**1a**	$Sm(OTf)_3$	THF	10	91	28 (*R*)
2	**1a**	AgOTf	THF	10	53	48 (*S*)
3	**1a**	$AgSbF_6$	THF	10	60	64 (*S*)
4	**1a**	$AgAsF_6$	THF	10	59	70 (*S*)
5	**1b**	$AgAsF_6$	THF	10	47	49 (*S*)
6	**1c**	$AgAsF_6$	THF	10	47	29 (*S*)
7	**1d**	$AgAsF_6$	THF	10	61	42 (*S*)
8[d,e]	**1a**	$AgAsF_6$	THF	10	82	85 (*S*)
9	**1a**	$Sm(OTf)_3$	CH_2Cl_2	10	99	62 (*R*)
10	**1b**	$Sm(OTf)_3$	CH_2Cl_2	10	99	90 (*R*)
11	**1c**	$Sm(OTf)_3$	CH_2Cl_2	10	86	81 (*R*)
12	**1d**	$Sm(OTf)_3$	CH_2Cl_2	10	83	65 (*R*)
13[d]	**1b**	$Sm(OTf)_3$	CH_2Cl_2	10	98	98 (*R*)
14[d,f]	**1b**	$Sm(OTf)_3$	CH_2Cl_2	10	93	94 (*R*)
15[d,g]	**1b**	$Sm(OTf)_3$	CH_2Cl_2	0.5	96	98 (*R*)

[a] Unless otherwise noted, reactions were carried out with ligand (10 mol %), metal (10 mol %), **2a** (0.25 mmol), and **3a** (0.25 mmol) in solvent (0.3 mL) at 0 °C for 24 h. [b] Isolated yield. [c] Determined by chiral HPLC analysis. The absolute configuration was determined by comparing with literature data.[4] [d] Reaction was carried out at −20 °C. [e] The solvent was 2.0 mL. [f] The solvent was 1.0 mL. [g] 0.5 mmol **3a** and 0.6 mL CH_2Cl_2 were used.

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(8) For examples of metals-controlled reversal of reaction enantioselectivity, see :(a) Ghosh, A. K.; Mathivanan, P.; Cappiello, J. *Tetrahedron Lett.* **1996**, *37*, 3815. (b) Sibi, M. P.; Shay, J. J.; Liu, M.; Jasperse, C. P. *J. Am. Chem. Soc.* **1998**, *120*, 6615. (c) Sibi, M. P.; Chen, J. *J. Am. Chem. Soc.* **2001**, *123*, 9472. (d) Yabu, K.; Masumoto, S.; Yamasaki, S.; Hamashima, Y.; Kanai, M.; Du, W.; Curran, D. P.; Shibasaki, M. *J. Am. Chem. Soc.* **2001**, *123*, 9908. (e) Shibata, N.; Ishimaru, T.; Nagai, T.; Kohno, J.; Toru, T. *Synlett* **2004**, 1703. (f) Mao, J. C.; Wan, B. S.; Zhang, Z. J.; Wang, R. L.; Wu, F.; Lu, S. W. *J. Mol. Catal. A: Chem.* **2005**, *225*, 33. (g) Kim, H. Y.; Shih, H.-J.; Knabe, W. E.; Oh, K. *Angew. Chem., Int. Ed.* **2009**, *48*, 7420. (h) Spangler, K. Y.; Wolf, C. *Org. Lett.* **2009**, *11*, 4724.

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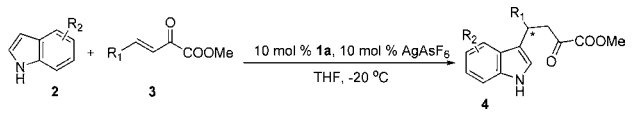
Under the optimal conditions, the substrate scope for the (*S*)-enantiomer of indole α-ketoesters **4** was investigated using 10 mol % complex of $AgAsF_6$-**1a** as catalyst. As presented in Table 2, the catalytic enantioselective Friedel−Crafts alkylation reaction proceeded well for many differently substituted β,γ-unsaturated α-ketoesters and indoles, independent of the electron-donating or electron-attracting character of the substituents (up to 90% ee). Moreover, heteroaromatic and fused ring substrates were also applicable, giving the desired indole esters with the same enantioselectivity of 84% ee (Table 2, entries 7 and 8).

Table 2. $AgAsF_6$ Catalyzed Enantioselective Frediel-Crafts Reaction of Indoles **2** with β,γ-Unsaturated α-Ketoesters **3**[a]

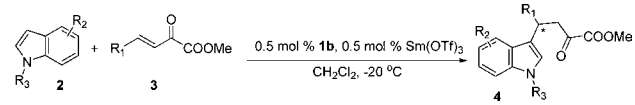


entry	R_1	R_2	time (h)	yield (%)[b]	ee (%)[c]
1	Ph	H	68	82	85 (95)[d] (*S*)[e]
2	3-BrC_6H_4	H	51	75	86 (92)[d]
3	2-ClC_6H_4	H	64	91	90
4	2,4-$Cl_2C_6H_3$	H	51	94	88
5	4-FC_6H_4	H	51	77	85 (91)[d]
6	4-BrC_6H_4	H	51	73	83 (99)[d] (*S*)[e]
7	2-thienyl	H	93	51	84
8	2-naphthyl	H	93	62	84 (90)[d]
9	Ph	5-Me	64	70	81
10	Ph	5-F	64	68	85
11	Ph	5-Cl	68	80	85 (96)[d]
12	Ph	5-Br	68	75	85 (90)[d]

[a] Unless otherwise noted, reactions were carried out with **1a** (10 mol %), $AgAsF_6$ (10 mol %), **2** (0.25 mmol), and **3** (0.25 mmol) in THF (2.0 mL) at −20 °C. See Supporting Information for details. [b] Isolated yield. [c] Determined by chiral HPLC analysis. See Supporting Information for details. [d] After a single recrystallization. [e] The absolute configuration was determined by comparing with literature data.[4]

We then turned our attention to the preparation of (*R*)-α-ketoester isomers **4** in the presence of 0.5 mol % $Sm(OTf)_3$-**1b**. Various indoles and β,γ-unsaturated α-ketoesters were also evaluated, giving the corresponding antipodes with excellent enantioselectivities (up to 98% ee). As shown in Table 3, the enantioselectivity of the reaction was found to be insensitive to both the steric and electronic properties of substituents on the phenyl ring (Table 3, entries 1−13), and different substituted α-ketoesters **4** were isolated in good yields and excellent enantiomeric ratios. In addition, heteroaromatic α-ketoester also reacted well with indole to deliver the desired product in 87% yield with 98% ee (Table 3, entry 14). The methyl protected indole exhibited little influence on the reaction:, 86% yield and 93% ee could be obtained (Table 3, entry 15). Just like the $AgAsF_6$ system, indoles with either electron-withdrawing or electron-donating substituents at different positions were also competent substrates, providing the Friedel−Crafts alkylation products with up to 99% yield and 98% ee (Table 3, entries 16−22).

Table 3. $Sm(OTf)_3$ Promoted Alternative Enantioselective Frediel-Crafts Reaction of indoles **2** with β,γ-Unsaturated α-Ketoesters **3**[a]



entry	R_1	R_2	R_3	time	yield (%)[b]	ee (%)[c]
1	Ph	H	H	15 min	96	98 (*R*)[f]
2	3-BrC_6H_4	H	H	20 min	98	98
3	2-ClC_6H_4	H	H	15 h	99	95
4	2,4-$Cl_2C_6H_3$	H	H	22 h	94	97
5	4-ClC_6H_4	H	H	3 h	96	93
6	4-FC_6H_4	H	H	22 h	99	96
7	4-BrC_6H_4	H	H	3 h	90	92 (*R*)[f]
8	4-$NO_2C_6H_4$	H	H	39 h	77	90
9	4-CNC_6H_4	H	H	15 h	92	95
10	4-PhC_6H_4	H	H	15 h	91	90
11	4-$MeOC_6H_4$	H	H	36 h	93	96
12	4-MeC_6H_4	H	H	22 h	96	96
13[d]	3-MeC_6H_4	H	H	23 h	83	97
14	2-thienyl	H	H	36 h	87	98
15	Ph	H	Me	1 h	86	93
16	Ph	2-Me	H	1 h	99	98
17[e]	Ph	4-OMe	H	1 h	83	92
18	Ph	5-F	H	58 h	90	95
19	Ph	5-Cl	H	58 h	82	90
20	Ph	6-OMe	H	30 min	99	95
21	Ph	7-Me	H	27 h	99	98
22	Ph	7-Et	H	10 h	99	96

[a] Unless otherwise noted, reactions were carried out with **1b** (0.5 mol %), $Sm(OTf)_3$ (0.5 mol %), **2** (0.5 mmol), and **3** (0.5 mmol) in CH_2Cl_2 (0.6 mL) at −20 °C. See Supporting Information for details. [b] Isolated yield. [c] Determined by chiral HPLC analysis. See Supporting Information for details. [d] The catalyst was 1 mol %. [e] 0.3 mL of CH_2Cl_2 was used. [f] The absolute configuration was determined by comparing with literature data.[4]

On the basis of the previous excellent works on Ag(I) complexes, as well as the low coordination number of Ag(I),[12] we consider that the bidentate coordination of Ag(I) with two oxygen atoms of *N*-oxide is preferred for the $AgAsF_6$-**1a** complex. As shown in **TS-1**, indole attacked the *β-si* face of the ester leading to the desired product with *S* configuration. However, a different transition state was proposed according to our previous study on the X-ray single crystal structure of *N*,*N*′-dioxide−Sc(III) complex.[9i] As rare earth metals bear similar coordination patterns,[13] it is

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(11) See Supporting Information for details.

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suggested that the use of **1b** and $Sm(OTf)_3$ in the Friedel−Crafts reaction is likely to generate a hexacoordinate $Sm(OTf)_3$-derived transition state, in which not only the oxygens of *N*-oxide but also carbonyl oxygens coordinated with Sm(III) in a tetradentate manner (Figure 2, **TS-2**). Moreover, one *N*-oxide is located *trans* to the carbonyl oxygen of the ester, while other oxygens such as the two carbonyl oxygens of amides, another *N*-oxide, and the one at the α position of the ester are accommodated in the same plane. This arrangement resulted in the attack of indole to the *β-re* face of the Michael acceptor, which provides the access to *R*-configured indole derivatives.

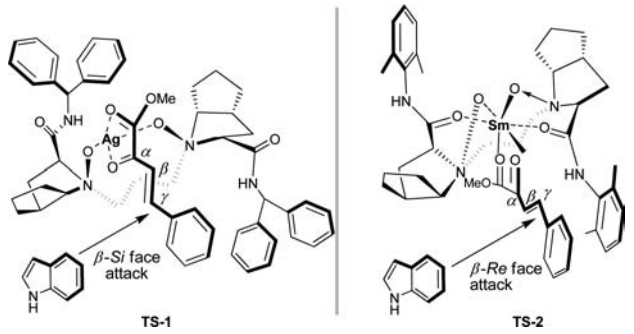
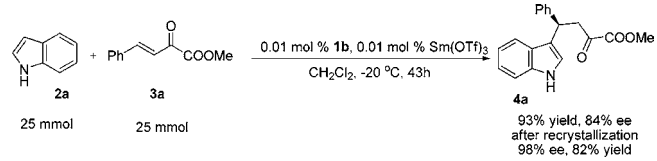


Figure 2. Proposed transition states for $AgAsF_6$-**1a** and $Sm(OTf)_3$-**1b**.

To exploit the potential of the current catalyst system, the reaction was scaled up to 25 mmol of the starting material only in the presence of 0.01 mol % of complex $Sm(OTf)_3$-**1b** as the catalyst. The corresponding product (*R*)-**4a** could also be isolated in a remarkable yield of 93% (7.12 g) with 84% ee. After a simple recrystallization,[11,14] the enantioselectivity could be increased to 98% ee with 82% yield (5.82 g, Scheme 1). As far as we know, this is to date the lowest catalyst loading reported for the Friedel−Crafts alkylations of indoles, thus demonstrating one of the advantages for this catalyst system.

Scheme 1. Scaled-up Version of Friedel−Crafts Alkylation of Indole **2a** with *β*,*γ*-Unsaturated α-Ketoester **3a**



In summary, we have developed an efficient catalytic enantioselective Friedel−Crafts alkylation of indole and *β*,*γ*-unsaturated α-ketoester. Just through changing the central metals, the reversal of enantioselectivity in the Friedel−Crafts alkylation of different indoles with a variety of *β*,*γ*-unsaturated α-ketoesters has been achieved using ligands **1a** and **1b** derived from the same chiral starting material. Both enantiomers can be obtained in good to excellent enantioselectivities. Furthermore, it should be highlighted that this catalytic procedure allows the lowering of catalyst loading to 0.01 mol % of $Sm(OTf)_3$-**1b** without considerable loss in reactivity and enantioselectivity. Further investigations on the mechanism of this catalytic system are still in progress.

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Supporting Information Available: Experimental procedures, spectral and analytical data for the reaction products. This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) Recrystallization was carried out in CH_2Cl_2 and petroleum ether (CH_2Cl_2/petroleum ether = 1:4).