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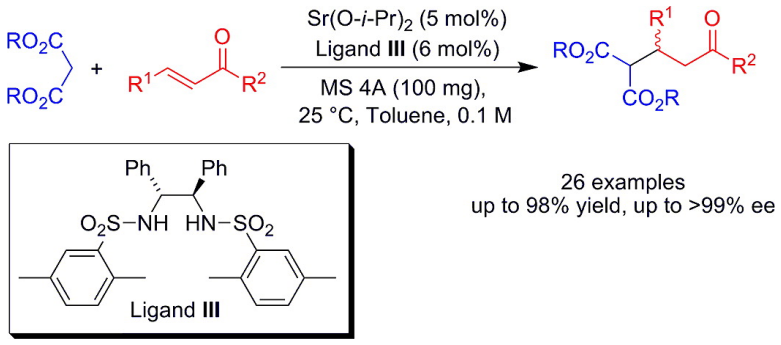

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Strontium-Catalyzed Highly Enantioselective Michael Additions of Malonates to Enones

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Strontium is the fifteenth most abundant element in the earth's crust (384 ppm),[1] it commonly occurs in nature as the form of the sulfate mineral celestite ($SrSO_4$) and the carbonate strontianite ($SrCO_3$). Despite its availability, there are few reports of its use as catalyst in organic transformations.[2] Herein we describe the first report of an asymmetric strontium catalyst.

The catalytic asymmetric Michael reaction is one of the most powerful carbon−carbon bond-forming reactions, which enables access to a variety of optically active building blocks from catalytic amounts of chiral information.[3] There are several reports of the catalytic asymmetric conjugate addition of malonates to enones, where different types of catalysts such as chiral metal complexes,[4] chiral ionic liquids,[5] phase-transfer catalysts,[6] organocatalysts,[7] and L-proline salts[8] have been employed. However, when chalcone derivatives are used, there are only a few reports enjoying limited success. High selectivity was achieved by Maruoka et al.[6a] using an *N*-spiro quaternary ammonium salt as a phase-transfer catalyst; however, an excess of malonate (4 equiv) was used. Using a cinchona thiourea organocatalyst, Wang et al.[7a] reported excellent selectivities, but also in this case an excess of malonate was used (5.6 equiv) and longer reaction times (from 72 to 144 h) were needed. Therefore, development of a truly efficient catalyst that provides a solution to these problems is a goal of considerable importance.

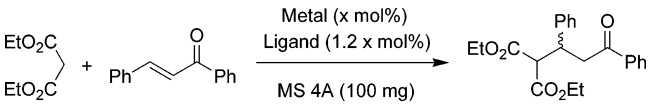
We have recently reported the asymmetric 1,4-addition reactions of glycine derivatives with α,β-unsaturated carbonyl compounds catalyzed by a chiral calcium complex featuring bisoxazoline ligand **I**.[9] Our first attempts to extend this system to the Michael addition of diethyl malonate (**1b**) to chalcone (**2a**) were unsuccessful (Table 1, entry 1). After careful screening of ligands, we found that a complex prepared from Ca(O-*i*-Pr)$_2$ and the sulfonamide ligand **III**[10] in toluene afforded the desired Michael adduct in moderate selectivity (entry 4). To our delight, changing the metal alkoxide to Sr(O-*i*-Pr)$_2$ gave the desired product in high yield with excellent enantioselectivity (entry 5).

Next we explored the scope of the reaction under the optimized reaction conditions. First, we examined the effect of the ester substituent (R) of the malonates (Table 2). The results show that the reactions proceeded smoothly in high yields with good to excellent enantioselectivities. We found that di-*n*-propyl malonate was an optimal Michael donor both in terms of reactivity and selectivity (entry 3). Investigation of the effect of the catalyst loading (entries 3−6) revealed that even with only 0.5 mol % of the catalyst the reaction proceeded to afford the product in good yield with excellent selectivity (72% yield, 97% ee, entry 6).

With these results in hand, we next surveyed the α,β-unsaturated ketone substrates. As shown in Table 3, the strontium-catalyzed conjugate addition reaction was also applicable to a wide variety of chalcones **2b**−**u** in high yields with excellent ee values.[12]

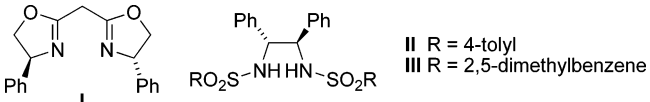
The system tolerated electron-withdrawing (entries 1−3, 5−7, and 10−14), electron-donating (entries 4 and 15), or both substituents (entries 8 and 9) in the aromatic groups R^1 and R^2, with little effect on the yield or the selectivity. High selectivity was also obtained in the reactions with heteroaromatic substituents (entries 16−18). The use of *N*-acylpyrrole **2s** afforded the Michael adduct with remarkable selectivity (99% ee, entry 18), thus giving an access

Table 1. Effect of Metal Sources and Chiral Ligands[a]



1b **2a** **3ba**

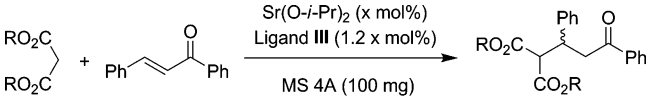
entry	metal (*x* mol %)	ligand	solvent	time (h)	yield (%)[b]	ee (%)[c]
1[d]	Ca(O-*i*-Pr)$_2$ (10%)	**I**	THF	24	47	4
2[d]	Ca(O-*i*-Pr)$_2$ (10%)	**II**	THF	24	47	49
3[d]	Ca(O-*i*-Pr)$_2$ (10%)	**III**	THF	24	89	52
4[e]	Ca(O-*i*-Pr)$_2$ (5%)	**III**	toluene	18	58	65
5[e]	Sr(O-*i*-Pr)$_2$ (5%)	**III**	toluene	18	91	97
6[e]	Ba(O-*i*-Pr)$_2$ (5%)	**III**	toluene	18	80	76
7[e]	Ba(O-*t*-Bu)$_2$ (5%)	**III**	toluene	18	82	70
8[e]	Ba(O-*t*-Bu)$_2$ (5%)	**III**	THF	18	15	33
9[d]	Mg(O-*t*-Bu)$_2$ (10%)	**III**	toluene	18	9	30



I **II** R = 4-tolyl
III R = 2,5-dimethylbenzene

[a] The catalyst was prepared at room temperature for 2 h and then the substrates (0.3 mmol of **2a** and 1.2 equiv of **1b**) were added without removal of volatiles. MS = molecular sieves. [b] Isolated yields. [c] Determined by chiral HPLC analysis (see Supporting Information). [d] Reaction run at 0 °C. [e] Reaction run at 25 °C.

Table 2. Conjugate Addition Reactions of Malonates **1a**−**1f** to **2a**[a]



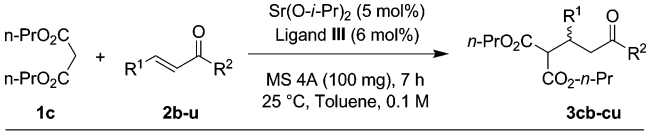
1a-f **2a** **3aa-3fa**

entry	Sr(O-*i*-Pr)$_2$ (mol %)	R	time (h)	yield (%)[b]	ee (%)[c] (configuration)
1	5	Me	24	65	94 (S)[d]
2	5	Et	18	91	97 (S)[d]
3	5	*n*-Pr	7	92	99
4	2.5	*n*-Pr	7	90	99
5[e]	1	*n*-Pr	9	70	97
6[f]	0.5	*n*-Pr	24	72	97
7	5	*i*-Pr	21	83	89
8	5	*n*-Bu	3	85	96
9	5	Bn	18	85	84

[a] Unless otherwise stated, see footnote in Table 1. [b] Isolated yields. [c] Determined by chiral HPLC analysis. [d] Absolute configuration was determined by comparison of the optical rotation with the value previously reported.[4k,11] [e] Reaction conducted with 0.75 mmol of **2a** and 1.2 equiv of **1c**. [f] Reaction conducted with 1.5 mmol of **2a** and 1.2 equiv. of **1c**, 0.2 M concentration in toluene.

10.1021/ja710332h CCC: $40.75

Table 3. Conjugate Addition Reactions of **1c** to Enones **2b**−**u**[a]

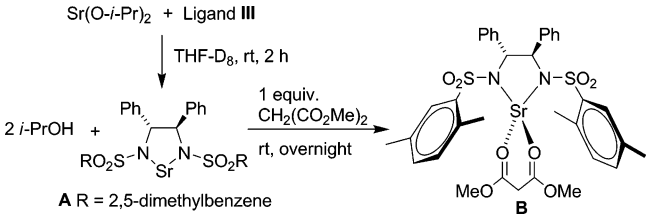


1c **2b-u** **3cb-cu**

entry	R^1	R^2	adduct	yield (%)[b]	ee (%)[c]
1	2-ClC_6H_4	Ph	**3cb**	76	92
2	4-ClC_6H_4	Ph	**3cc**	93	97
3	4-FC_6H_4	Ph	**3cd**	92	98
4	4-$MeOC_6H_4$	Ph	**3ce**	80	>99
5	4-$NO_2C_6H_4$	Ph	**3cf**	98	96
6	3-$NO_2C_6H_4$	Ph	**3cg**	94	94
7	4-FC_6H_4	4-FC_6H_4	**3ch**	91	96
8	4-$MeOC_6H_4$	4-FC_6H_4	**3ci**	81	>99
9	3,4-di-$MeOC_6H_3$	4-FC_6H_4	**3cj**	61	96
10	4-ClC_6H_4	4-FC_6H_4	**3ck**	97	97
11	2-ClC_6H_4	4-FC_6H_4	**3cl**	80	93
12	4-FC_6H_4	4-MeC_6H_4	**3cm**	90	98
13	Ph	4-ClC_6H_4	**3cn**	98	99
14	Ph	4-FC_6H_4	**3co**	92	99
15	Ph	4-$MeOC_6H_4$	**3cp**	85	99
16	2-thienyl	2-thienyl	**3cq**	73	97
17[d]	5-methylfuran-2-yl	Ph	**3cr**	71	96
18[e]	Ph	1-pyrrolyl	**3cs**	93	99
19[f]	Ph	−CH=CHPh	**3ct**	97	86
20[f]	−CH=CHPh	Ph	**3cu**	62	97

[a] Unless otherwise stated, see footnote in Table 1. [b] Isolated yields. [c] Determined by chiral HPLC analysis. [d] Reaction time 48 h. [e] Reaction time 24 h. [f] Reaction run using 2.2 equiv of malonate **1c**.

Scheme 1



to an important enantiopure chiral building block that can be further transformed.[4a] In addition, when *trans*,*trans*-dibenzylideneacetone (**2t**) or cinnamylideneacetophenone (**2u**) were used, the adduct resulting from one single Michael addition was obtained exclusively, even when 2.2 equiv of dipropyl malonate were employed (entries 19 and 20). The product can thus be further functionalized at the unreacted double bond.[12]

To elucidate the structure of the catalyst, we have conducted NMR spectroscopic studies. Sr(O-*i*-Pr)$_2$ (0.15 mmol) was reacted with 1 equiv of ligand **III** in deuterated THF (0.75 mL) for 2 h (Scheme 1). After this time, the $^{13}C\{^1H\}$ NMR spectrum shows evidence of the coordination of the ligand, and appearance of free *i*-PrOH. At room temperature, the peaks corresponding to the strontium bis(sulfonamide) complex **A** are considerably broadened, indicating a possible conformational equilibrium,[13] whereas the peaks of the free *i*-PrOH are sharp (see Supporting Information). After that, 1 equiv of dimethyl malonate (**1a**) was added, and the mixture was stirred overnight. After this time the $^{13}C\{^1H\}$ spectrum shows three new peaks resonating at δ 174.6, 64.6, and 49.7, which are consistent with those of coordinated dimethyl malonate to Sr.[14]

In summary, we have developed a novel strontium based catalyst, prepared from readily available Sr(O-*i*-Pr)$_2$ and a simple bis-sulfonamide type ligand. To the best of our knowledge, this is the first example of an asymmetric transformation catalyzed by a chiral strontium complex. This catalyst effectively promoted the conjugate addition of malonates to a wide variety of chalcone derivatives, providing an access to several useful synthetic building blocks with high optical purity. Moreover, in contrast to previous reports, this reaction system does not require an excess amount of nucleophile or long reaction times, the reactions are performed at room temperature and the catalyst loading can be reduced to 0.5 mol %. Further investigations to clarify the exact catalyst structure, as well as to further expand the substrate scope, are now in progress in our laboratories.

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Supporting Information Available: Experimental procedures and product characterization. This material is available free of charge via the Internet at http://pubs.acs.org.

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