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Catalytic Use of Strontium Hexamethyldisilazide in the Asymmetric Michael Addition of Malonate to Chalcone Derivatives

Shū Kobayashi,* Miyuki Yamaguchi, Magno Agostinho, and Uwe Schneider
Department of Chemistry, School of Science, The University of Tokyo, Hongo, Bunkyo-ku, Tokyo 113-0033
Graduate School of Pharmaceutical Sciences, The University of Tokyo, Hongo, Bunkyo-ku, Tokyo 113-0033
The HFRE Division, ERATO, Japan Science Technology Agency (JST), Hongo, Bunkyo-ku, Tokyo 113-0033

(Received December 26, 2008; CL-081221; E-mail: shu_kobayashi@chem.s.u-tokyo.ac.jp)

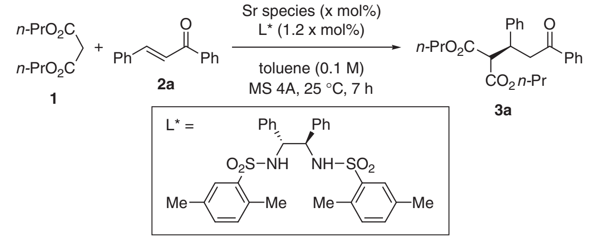
Strontium hexamethyldisilazide, combined with a chiral bis(sulfonamide) ligand, was found to be very effective for the catalytic asymmetric Michael addition of malonate to chalcone derivatives.

The Michael addition is among the most important carbon–carbon bond transformations. Over the past few years, this reaction has attracted much attention and significant advances in the development of catalytic enantioselective protocols have been achieved.[1] In this context, asymmetric 1,4-additions of malonates to enones catalyzed by chiral ionic liquids,[2] phase-transfer catalysts[3] or organocatalysts,[4] and proline salts[5] have been reported, while interestingly, many examples of chiral metal-based catalysts have also been published for this type of transformation.[6,7] Among those, however, only few examples were based on the use of inexpensive and readily available alkaline earth metals.[6c–6g] In addition, a large excess of malonate (4–6 equiv) is typically required when chalcones are used as electrophiles.[3a,4a] During our on-going efforts toward truly effective metal catalysis for catalytic asymmetric carbon–carbon bond formation, we have recently reported the first chiral strontium catalyst.[8] While the abundant group 2 element[9] strontium is very appealing for metal catalysis, only sporadic examples of its synthetic use are known.[10]

In our earlier work,[8] strontium isopropoxide [Sr(O*i*-Pr)$_2$] as the Brønsted base, combined with a chiral bis(sulfonamide) ligand, proved to be most effective for asymmetric 1,4-additions. We report here another strontium source, strontium hexamethyldisilazide [Sr(HMDS)$_2$],[10a,11] which is a new, more effective catalyst precursor for asymmetric catalysis.

In initial experiments using di-*n*-propylmalonate (**1**) and chalcone (**2a**) in toluene at room temperature, we examined several strontium salts, combined with the chiral bis(sulfonamide) ligand[12] shown in Table 1. Compared with our previous best result employing Sr(O*i*-Pr)$_2$ (Entry 1),[8] the corresponding commercially available acetate, chloride, iodide, and hydroxide salts displayed both significantly lower catalytic activity and asymmetric induction (Entries 2–5). On the other hand, Sr(HMDS)$_2$, as a stronger Brønsted base, proved to be most efficient in terms of chemical yield and optical purity (Entry 6); interestingly, with this precursor the catalytic loading could be decreased to 2 mol % with only marginal loss in enantiomeric excess (Entries 7 and 8). At this stage, we ascribe the better results with Sr(HMDS)$_2$ to more effective formation of the chiral catalyst. With this new, more efficient catalyst precursor in hand, we continued our investigations to further improve this strontium catalysis.

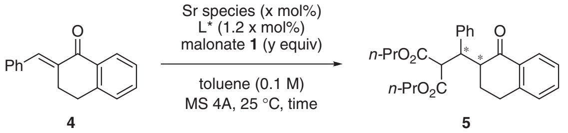
Table 1. Screening of various strontium sources



Entry	Sr species	x/mol %	Yield/%[a]	ee/%[b]
1	Sr(O*i*-Pr)$_2$	5	92	99
2	Sr(OAc)$_2$	5	7	36
3	SrCl$_2$	5	6	−11
4	SrI$_2$	5	11	−8
5	Sr(OH)$_2$	5	4	8
6	Sr(HMDS)$_2$	5	97	99
7[c]	Sr(HMDS)$_2$	3	99	98
8[c]	Sr(HMDS)$_2$	2	96	96

[a]Isolated yields. [b]Determined by chiral HPLC analysis. [c]Reaction time: 12 h.

Table 2. Use of a cyclic chalcone derivative

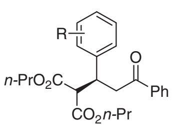


Entry	Sr species (x/mol %)	**1** (y equiv)	Time /h	Yield[a] /%	dr[b] /%	ee[c] /%
1	Sr(O*i*-Pr)$_2$ (5)	2.5	86	50	97:3	80
2	Sr(O*i*-Pr)$_2$ (5)	5.0	86	92	97:3	66
3	Sr(O*i*-Pr)$_2$ (10)	1.2	168	40	97:3	88
4	Sr(HMDS)$_2$ (10)	1.2	48	38	97:3	95
5	Sr(HMDS)$_2$ (5)	1.2	48	26	98:2	95
6	Sr(HMDS)$_2$ (10)	2.5	48	50	97:3	94
7[d]	Sr(HMDS)$_2$ (6)	1.2	48	86	98:2	60

[a]Isolated yields. [b]Determined by ^{1}H NMR analysis. The relative configuration was not assigned. [c]Determined by chiral HPLC analysis. [d]Concentration: 1 M.

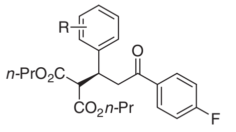
We first investigated the use of a less reactive cyclic chalcone derivative **4** as the Michael acceptor (Table 2). Sr(O*i*-Pr)$_2$ as the Brønsted base provided the desired product **5** with high diastereoselectivity (97%) and an enantiomeric excess of up to 88% (Entries 1–3); unfortunately, under the best conditions the reaction was very slow (168 h) and the yield was low (40%;

Table 3. Scope for acyclic chalcones employing Sr(HMDS)$_2$[a,b,c]



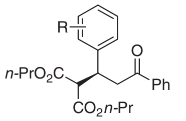
3b R = 2-Cl: 82% yield, 95% ee

3c R = 4-Cl: 93% yield, 97% ee



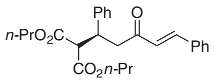
3f R = 2-Cl: 92% yield, 93% ee

3g R = 4-F: 94% yield, 98% ee



3d R = 3-NO$_2$: 86% yield, 96% ee

3e R = 4-NO$_2$: 81% yield, 97% ee



3h 95% yield, 90% ee

[a] Conditions: Sr(HMDS)$_2$ (5 mol %), L* (6 mol %), toluene (0.1 M), MS 4A, 25 °C, 7 h. [b] Isolated yields. [c] Determined by chiral HPLC analysis.

Entry 3). Importantly, Sr(HMDS)$_2$ proved to be a better catalyst precursor in terms of both asymmetric induction (up to 95% ee) and reaction time (48 h; Entries 4–7). The best result so far obtained produced Michael adduct **5** with 97% ds and 94% ee (Entry 6). It is noted that much higher enantioselectivities were obtained by using Sr(HMDS)$_2$ compared with Sr(O*i*-Pr)$_2$, and that this is the first example of the use of Sr(HMDS)$_2$ as a catalyst for C–C bond formation.

Next, we examined the scope for several acyclic chalcones[13] by using Sr(HMDS)$_2$ as the Brønsted base (Table 3). In all cases, the reactions proceeded well to afford the corresponding Michael adducts **3b**–**3h** in high yields with excellent enantioselectivities (Table 3). In addition, Sr(HMDS)$_2$ proved to be a more efficient catalyst precursor than Sr(O*i*-Pr)$_2$ with respect to both chemical yields and optical purities.[8]

In conclusion, we have discovered Sr(HMDS)$_2$ as an unprecedented Brønsted base for catalytic asymmetric 1,4-additions.[14] The use of this strontium amide salt, combined with a chiral bis(sulfonamide) ligand, was shown to be more efficient than the use of Sr(O*i*-Pr)$_2$ with respect to substrate scope of both acyclic and cyclic chalcones. Most remarkably, the catalytic system proved to be excellent under very mild conditions that are: (1) the reaction proceeds at room temperature; (2) an external base is not required; (3) an excess of malonate is not needed. Further investigations to clarify catalyst structure and mechanism as well as to develop novel Sr-catalyzed carbon–carbon bond-forming reactions are now underway in our laboratories.

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This paper is dedicated to Professor Ryoji Noyori on the occasion of his 70th birthday.

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14 Typical experimental procedure for the Sr-catalyzed Michael addition: In a flame-dried 30-mL flask, a suspension of Sr(HMDS)$_2$ (6.1 mg, 0.015 mmol, 5 mol %), chiral ligand L* (9.9 mg, 0.018 mmol, 6 mol %), and MS 4A (100 mg) in dry toluene (1.0 mL) was stirred for 2 h at room temperature under an argon atmosphere. After this period, solutions of di-*n*-propyl malonate (**1**; 67.1 μL, 0.36 mmol, 1.2 equiv) in toluene (1.0 mL) and the corresponding chalcone **2** or **4** (0.30 mmol) in toluene (1.0 mL) were successively added. After the indicated reaction time, the crude mixture was quenched with sat. aq NH$_4$Cl (10 mL). After addition of CH$_2$Cl$_2$, the organic layer was separated and the aqueous layer was extracted with CH$_2$Cl$_2$ (three times). The combined organic layers were then dried over anhydrous Na$_2$SO$_4$, filtered and concentrated under reduced pressure. The corresponding crude product was purified by preparative thin-layer chromatography (PTLC; hexane–ethyl acetate) to afford the desired product **3** or **5**.