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Catalytic Asymmetric Protonation of Chiral Calcium Enolates via 1,4-Addition of Malonates

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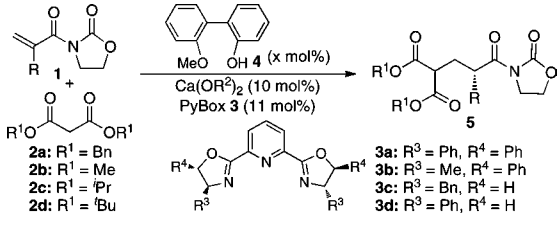
Since the pioneer report of Duhamel and Plaquevent regarding the first asymmetric protonation of lithium enolates,[1] asymmetric protonation has become a fascinating method for organic chemists to build tertiary chiral carbon centers.[2] Indeed, over the past 30 years several methods have been developed to introduce hydrogen atoms stereoselectively. After the first stoichiometric systems were successfully designed,[2b] the most challenging step was the development of a catalytic asymmetric protonation of enolates. This synthetic milestone was first achieved by Fehr[3a] and followed by others, furnishing efficient processes, although the substrate scope was relatively limited.[3] On the other hand, all of these methods required stoichiometric formation of enolates or surrogates such as silicon enolates. An attractive alternative is catalytic formation of chiral enolates *in situ* through addition to ketenes[4] or as a result of Michael addition of nucleophiles. This last strategy mainly employed basic catalysis that required nucleophilic substrates with a low pK_a value, such as thiols.[5,6] The addition of stronger nucleophiles, such as radicals[7a] and π-nucleophiles,[7b] was successfully achieved using Lewis acid catalysis. Finally, 1,4-addition of organometallic compounds catalyzed by transition metals also provided the desired chiral enolates, which were protonated enantioselectively.[8]

During our studies on chiral alkaline earth metal catalysts, we have found that anionic calcium[9a] and strontium[9b] complexes, as well as neutral chiral calcium complexes,[9c] were suitable catalysts to promote highly selective asymmetric 1,4-additions of malonates or glycine derivatives. However, the potential of the catalytic chiral enolates resulting from the additions has not been examined to date. Herein, we describe catalytic asymmetric protonation of chiral calcium enolates.

Scheme 1. Catalytic Asymmetric Protonation of Chiral Calcium Enolates



Our approach was based on catalytic formation of a calcium enolate via 1,4-addition of malonate to a Michael acceptor bearing an achiral template,[10] which can coordinate to the calcium center to rigidify the enolate and control its geometry. Initially, we selected the addition of malonate **2** to imide **1a** (R = Me) as models and screened several types of ligands with $Ca(O^iPr)_2$ as catalysts (Scheme 1). We were pleased to find that pyridinebisoxazoline (PyBox) **3a**−**d** gave the desired product **5a** in acceptable yields with promising enantioselectivity (Table 1). A survey of ligands showed that Ph-PyBox **3d** was the most promising in terms of enantioselectivity.[11] Moreover, several reaction parameters were examined to improve the yield and the selectivity, and it was found that dibenzyl malonate gave the best selectivity in toluene (entry 5). Primary, secondary, and tertiary alkyl malonates gave racemic products or had very low enantioselectivities (entries 6, 7, and 8).

Table 1. Ligand and Malonate Screening[a]

Entry	Ligand	R^1	Solvent	Yield (%)[b]	ee (%)
1	**3a**	Bn (**2a**)	THF	39	35
2	**3b**	Bn (**2a**)	THF	38	21
3	**3c**	Bn (**2a**)	THF	49	9
4	**3d**	Bn (**2a**)	THF	34	35
5	**3d**	Bn (**2a**)	Toluene	60	49
6	**3d**	Me (**2b**)	Toluene	80	2
7	**3d**	^{i}Pr (**2c**)	Toluene	86	3
8	**3d**	^{t}Bu (**2d**)	Toluene	83	11

[a] The reaction of **1a** (R = Me, 0.20 mmol) with **2** (0.28 mmol) was performed at 0 °C for 24 h in the presence of the chiral calcium catalyst prepared from $Ca(O^iPr)_2$ (0.020 mmol, 10 mol %) and **3** (0.022 mmol, 11 mol %). [b] Isolated yield.

Table 2. Effect of Calcium Salts[a]

Entry	$Ca(OR^2)_2$	*x*	Solvent	*t*, °C	Yield (%)[b]	ee (%)[c]
1	$Ca(O^iPr)_2$	0	Toluene	0	60	49
2	$Ca(O^iPr)_2$	10	Toluene	0	86	74
3	$Ca(O^iPr)_2$	10	Toluene	−20	33	84
4	$Ca(OEt)_2$	10	Toluene	0	86	83
5	$Ca(OEt)_2$	10	Toluene	−20	41	91
6	$Ca(OMe)_2$	10	Toluene	0	85	83
7[d]	$Ca(OEt)_2$	10	CPME	−20	63	92
8[d,e]	$Ca(OEt)_2$	10	CPME	−20	75	94
9[d,e,f]	$Ca(OEt)_2$	10	CPME	−20	90	95

[a] The reaction of **1a** (R = Me, 0.20 mmol) with **2a** (0.28 mmol) was performed for 24 h in the presence of the chiral calcium catalyst prepared from $Ca(OR^2)_2$ (0.020 mmol, 10 mol %), **3d** (0.022 mmol, 11 mol %), and phenol **4** (*x* mol %), unless otherwise noted. [b] Isolated yield. [c] Determined by HPLC analysis using a chiral column. [d] **2a** was slowly added over 10 h. [e] The reaction was conducted for 48 h. [f] EtOH (200 mol %) was added as an additive.

To further improve the enantioselectivity, we carefully examined calcium salts, which were previously found to be crucial for chiral induction (Table 2).[9c] Interestingly, it was found that the use of 10 mol % of phenol **4** with $Ca(O^iPr)_2$ showed a significant increase in the selectivity from 49% enantiomeric excess (ee) to 74% ee at 0 °C (entries 1 and 2). This promising selectivity was further improved to 84% ee at −20 °C despite a decrease in the yield to 33% (entry 3). A survey of calcium alkoxides showed that $Ca(OEt)_2$ was the best salt and that the selectivity reached 91% ee at −20 °C (entry 5). Moreover, the use of cyclopentyl methyl ether (CPME) as the

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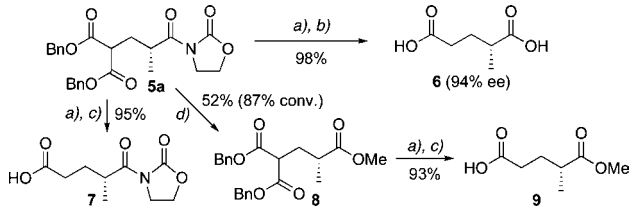
solvent combined with the slow addition of malonate[12] provided **5a** with high selectivity in acceptable yields (entry 7). A simple extension of the reaction time to 48 h gave the product in good yield with excellent selectivity (entry 8). Finally, ethanol was found to be an effective additive for obtaining a high yield and high enantioselectivity. The yield was increased to 90%, and the enantioselectivity reached 95% ee (entry 9).[11]

With this new and efficient process in hand, the scope of the reaction was surveyed. Access to both enantiomers was found to be possible with the same level of enantioselectivity (entry 2). Interestingly, the catalyst loading could be decreased to 5 mol % without significant loss of reactivity and selectivity (entry 1). 1,4-Adducts containing allylic derivatives gave excellent results with high selectivity up to 96% ee (entries 3−6). Alkynyl derivatives **5f**−**5h** were obtained in good yields with excellent selectivity (entries 7−9). The gram scale (2 mmol) reaction was possible without any loss of reactivity and enantioselectivity (entry 7). It is noted that, according to previous methods, access to these products required the use of diastereoselective alkylation using chiral auxiliaries.[13] On the other hand, despite several attempts, the aryl substitution of the Michael acceptor gave only moderate selectivity, albeit with good reactivity (R = Ph, entry 10).

We then conducted some mechanistic investigations to clarify the reaction pathway.[11] For the real catalyst, the existence of a mixed Ca alkoxy aryloxide is plausible as well as the existence of phenol in the presence of $Ca(OEt)_2$. A survey of phenols revealed that the phenol moiety might be involved in the deprotonation step, supported by a relationship between the acidity of the corresponding phenol and the basicity of the aryloxide. This information also suggested that the protonation step is the rate-determining step. However, all our attempts to characterize the mixed calcium salt were unsuccessful. Therefore, the sole function of phenol as a proton source cannot be denied at this stage. Finally, labeling experiments confirmed the reaction pathway and excluded a protonation through an internal proton return[14] by ethanol coordinated to the calcium center. With all these experimental observations, a mechanism involving the existence of a monomeric mixed calcium salt complexed with the PyBox ligand has been proposed.[11]

Finally, the synthetic potential of the protonated adduct was demonstrated. The adduct **5a** was readily converted to **6**, **7**, **8**, and **9** in high yields without losing optical purity. These transformations also led us to determine the absolute configuration of **5a** (*R*) by analogy with the literature data (Scheme 2).[11]

Scheme 2. Synthetically Useful Transformations of the Products[a]



[a] (a) H_2, Pd/C, rt; (b) 6 M HCl, 110 °C 5 h; (c) toluene 120 °C, 5 h; (d) MeONa (cat.), MeOH −20 °C, 30 min.

In conclusion, catalytic asymmetric protonation of chiral calcium enolates was performed. Chiral calcium enolates were prepared *in situ* from imides **1** and malonates **2** via 1,4-addition in the presence of catalytic amounts of $Ca(OEt)_2$, Ph-PyBox **3d**, and achiral phenol **4** and were smoothly protonated to afford the adducts **5** bearing tertiary asymmetric carbons in high yields with high enantioselectivity. It should be noted that the hydrogen atom represents the smallest element in the periodic table and its asymmetric introduction with high selectivity requires excellent chiral environments. Further investigations to extend these powerful chiral calcium enolates to the introduction of other functionalities and to apply this strategy in multistep synthesis are now ongoing.

Table 3. Substrate Scope[a]

Entry	R	5	Yield (%)[b]	ee (%)[c]
1	Me (**1a**)	**5a**	90 (88)[j]	95 (92)[j]
2[d]	Me (**1a**)	**5a**	72	94
3	Allyl (**1b**)	**5b**	86	96
4[e,f]	Prenyl (**1c**)	**5c**	85	93
5	*cis*-$CH_2CH{=}CHCl$ (**1d**)	**5d**	96	95
6[f,g]	Cinnamyl (**1e**)	**5e**	85	94
7[h]	$CH_2{-}C{\equiv}C{-}Ph$ (**1f**)	**5f**	88 (93)[k]	94 (93)[k]
8	$CH_2{-}C{\equiv}C{-}CH_2OBn$ (**1g**)	**5g**	77	93
9	$CH_2{-}C{\equiv}C{-}Bu$ (**1h**)	**5h**	91	94
10[i]	Ph (**1i**)	**5i**	72	48

[a] The reaction of **1** (0.20 mmol) with **2a** (0.28 mmol) was performed in CPME at −20 °C for 48 h in the presence of the chiral calcium catalyst prepared from $Ca(OEt)_2$ (0.020 mmol, 10 mol %), **3d** (0.022 mmol, 11 mol %), phenol **4** (0.020 mmol, 10 mol %), and EtOH (0.40 mmol, 200 mol %), unless otherwise noted. **2a** was slowly added over 10 h. [b] Isolated yield. [c] Determined by HPLC analysis using a chiral column. [d] The reaction was conducted for 24 h with (*R*,*R*)-**3d**. [e] 0.06 M. [f] The reaction was conducted for 72 h. [g] Mixed solvent (CPME/THF = 2/1) was used. [h] Mixed solvent (CPME/toluene = 4/1) was used. [i] Mixed solvent (toluene/DCM = 4/1) at 0.06 M for 24 h. [j] The reaction was carried out in the presence of 5 mol % of the catalyst. [k] 2 mmol scale.

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Supporting Information Available: Experimental procedure, mechanistic studies, and characterization of the products. This material is available free of charge via the Internet at http://pubs.acs.org.

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