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Asymmetric Calcium Catalysis: Highly Enantioselective Carbonyl-Ene and Friedel–Crafts Reactions for the Synthesis of Quaternary α-Hydroxy Esters Bearing a Trifluoromethyl Group

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Introduction

The development of efficient catalytic asymmetric reactions that allow the preparation of enantiopure organic molecules still constitutes a major challenge in organic chemistry. Considerable attention has been devoted to the development of new routes or methods to access these compounds. Most existing methods rely on the application of chiral transition metal catalysts, and a variety of highly enantioselective reactions have been reported. Recently, chiral alkaline-earth metal catalysts have been found to be promising alternative catalysts in chemical transformations.[1,2,3a,b] Among the chiral alkaline-earth metal catalysts reported, chiral calcium catalysts are of great interest as they can readily be prepared and exhibit outstanding stereoselective induction.[1d]

During the synthesis of chiral 2,2′-dihydroxy-1,1′-binaphthyl (binol)-derived *N*-triflylphosphoramides **1** we observed the formation of calcium salts **2**.[3b,7b] This was at first sight intriguing as no calcium derivatives were used in the synthesis or work-up procedure. However, we noticed that silica gel contains traces of calcium and thus the purification by column chromatography was responsible for the formation of the chiral calcium complexes. The calcium salts **2** turned out to be less effective catalysts, and this may be due to the chelating properties of the triflylphosphoramide ligands (Figure 1). Acidic workup resulted in the chiral triflylphosphoramides, which are highly acidic Brønsted acid catalysts **1** that generally exhibit higher reactivity and selectivity.[3d] Similar observations have also been made for the corresponding chiral phosphoric acids **3**[4,5] and their calcium salts **4** in imine activations.[2f] However, in this case, often only little difference in reactivity has been observed and stereoselectivities of the acid and calcium salt are comparable.[6,2f]

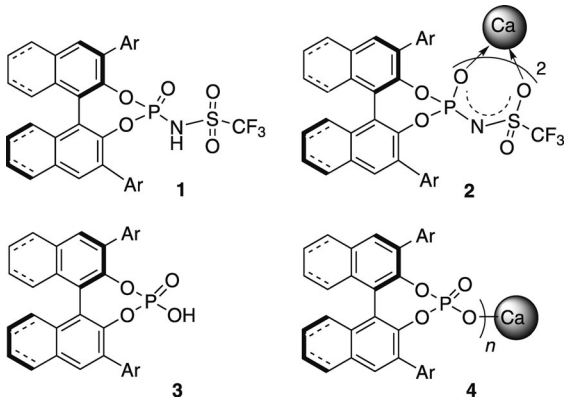

Figure 1. Chiral binol-derived Brønsted acids and their calcium salts.

Results and Discussion

Recently, we reported a highly enantioselective carbonyl-ene reaction[7–9] using various styrene derivatives. In this reaction, the calcium phosphoramide complexes **2** were poor catalysts, while the metal-free phosphoramides **1** proved to be highly effective Brønsted acid catalysts.[7b]

However, the high acidity of the triflylphosphoramides **1** (pK_a 6–7 in acetonitrile) led to by-product formation through elimination, and in certain cases, styrene dimerization was observed. In order to suppress the side reactions we decided to employ milder catalysts.[7b]

Here we report a highly enantioselective carbonyl-ene reaction of trifluoropyruvate with styrene derivatives catalyzed by a chiral calcium phosphate catalyst. We began our studies by examining various binol-derived phosphoric acid catalysts (pK_a 13-14 in acetonitrile) and their calcium salts. Interestingly, the calcium salts showed both better reactivity and selectivity in the reaction of methylstyrene with trifluoropyruvate and the corresponding α-hydroxy-α-trifluoromethyl esters were obtained in good yields and with excellent enantioselectivities if the reactions were performed in aromatic solvents (Table 1). Of various binol and [H_8]-binol phosphoric acid-derived calcium salts tested, the Ca[**4e**]$_n$ showed the best results, thus providing the desired product in 90% *ee* (Table 1, entry 5). Lower yields and enantioselectivities were obtained when the reactions were carried out in *o*-xylene (65% yield, 87% *ee*) or CF_3-benzene (66% yield, 82% *ee*; Table 1, entries 6 and 7). Lowering the reac-

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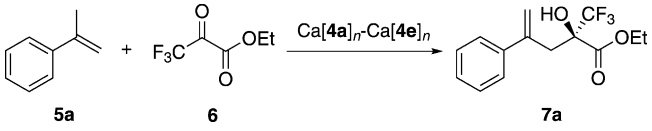
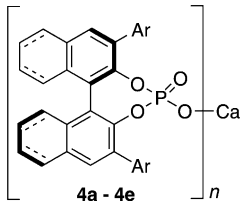
Table 1. Optimization of the enantioselective carbonyl-ene reaction.[a]





Ca[**4a**]$_n$: Ar = 4-MeO-phenyl
Ca[**4b**]$_n$: Ar = 3,5-$(CF_3)_2$-phenyl
Ca[**4c**]$_n$: Ar = 4-biphenyl [H_8]
Ca[**4d**]$_n$: Ar = 2-naphthyl [H_8]
Ca[**4e**]$_n$: Ar = 4-MeO-phenyl [H_8]

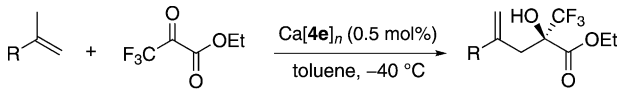
Entry	Ca[**4**]$_n$ [mol%]	Solvent	T [°C]	Yield [%][b]	*ee* [%][c]
1	Ca[**4a**]$_n$ (1)	toluene	−20	53	67
2	Ca[**4b**]$_n$ (1)	toluene	−20	52	3
3	Ca[**4c**]$_n$ (1)	toluene	−20	53	84
4	Ca[**4d**]$_n$ (1)	toluene	−20	49	64
5	Ca[**4e**]$_n$ (0.5)	toluene	−20	72	90
6	Ca[**4e**]$_n$ (0.5)	o-xylene	−20	65	87
7	Ca[**4e**]$_n$ (0.5)	CF_3-benzene	−20	66	82
8	Ca[**4e**]$_n$ (0.5)	toluene	−40	68	94
9	Ca[**4e**]$_n$ (0.5)	toluene	−60	60	94

[a] Reaction conditions: **5a** (1.5 equiv), **6** (1.0 equiv), Ca[**4a**]$_n$–Ca[**4e**]$_n$ (0.5–1 mol%), in 0.25 M solution of solvent for 48 h. [b] Yield of the isolated product after column chromatography. [c] Determined by HPLC analysis on a chiral column (CHIRALPAK AS-H).

tion temperature to −40 °C gave the product in higher enantiomeric excess but lower chemical yield (68% yield, 94% *ee*; Table 1, entry 8 vs. entry 5). Further decrease in the reaction temperature to −60 °C did not improve the enantioselectivity of the reaction (Table 1, entry 9). Importantly, the mild reaction conditions and neutral acidity resulted in no by-product formation, and neither elimination nor dimerization of styrene was observed.

Having established the optimal reaction conditions, we next focused on the scope of this first asymmetric calcium-catalyzed carbonyl-ene reaction (Table 2). In general, different styrene derivatives (**5a–j**) bearing electron-donating and electron-withdrawing substituents could effectively be employed in this mild calcium-catalyzed procedure and the desired α-hydroxy-α-trifluoromethyl esters were isolated in good yields and with excellent enantioselectivities (Table 2, entries 1–10). Interestingly, just 0.5 mol% of catalyst was sufficient for a successful reaction.

Table 2. Scope of the chiral calcium phosphate-catalyzed carbonyl-ene reaction.[a]

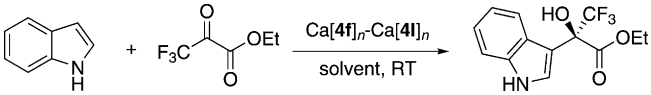


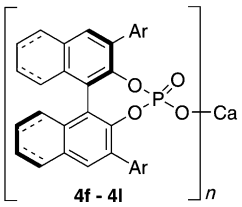
Entry	R	**7**	Yield [%][b]	*ee* [%][c]
1	Ph	**7a**	68	94
2	*p*-MeC_6H_4	**7b**	62	89
3	*m*-MeC_6H_4	**7c**	56	90
4	*p*-EtC_6H_4	**7d**	68	84
5	*p*-*t*BuC_6H_4	**7e**	68	84
6	*p*-*i*PrC_6H_4	**7f**	77	86
7	*m,p*-$Me_2C_6H_3$	**7g**	75	91
8	*p*-FC_6H_4	**7h**	53	95
9	2-naphthyl	**7i**	50	91
10	6-tetralinyl	**7j**	75	87

[a] Reaction conditions: **5** (1.5 equiv), **6** (1.0 equiv), Ca[**4e**]$_n$ (0.5 mol%), in 0.25 M solution of toluene at −40 °C for 48 h. [b] Yield of the isolated product after column chromatography. [c] Determined by HPLC analysis on a chiral column.

Based on this success and to further explore the synthetic utility of chiral calcium binol phosphate catalysts we decided to also examine the asymmetric Friedel–Crafts alkylation.[10,11] The calcium-catalyzed reaction of indole **8a** with ethyl trifluoropyruvate **6** was selected as the model reaction. The influence of the catalyst structure, catalyst loading, and solvents are summarized in Table 3. Our initial experiments were conducted at room temperature using various calcium binol phosphate cataylsts such as Ca[**4f**]$_n$–Ca[**4l**]$_n$. Among the chiral calcium catalysts evaluated, 1-naphthyl-substituted [H_8]-binol calcium phosphate Ca[**4k**]$_n$ was the best catalyst, providing the corresponding product **9a** in good yield and good enantioselectivity (Table 3, entry 6). By lowering the catalyst loading to 2 mol% resulted in a slight reduction in the *ee* without affecting the chemical yield (Table 3, entry 8 vs. entry 6). Next we investigated the effect of reaction media (Table 3, entries 8–14). In general, the reaction can

Table 3. Optimization of the enantioselective Friedel–Crafts alkylation.[a]





Ca[**4f**]$_n$: Ar = 2,4,6-(*i*Pr)$_3$-phenyl
Ca[**4g**]$_n$: Ar = 1-naphthyl
Ca[**4h**]$_n$: Ar = 2-naphthyl
Ca[**4i**]$_n$: Ar = 9-anthracenyl
Ca[**4j**]$_n$: Ar = 9-phenanthryl
Ca[**4k**]$_n$: Ar = 1-naphthyl [H_8]
Ca[**4l**]$_n$: Ar = 9-phenanthryl [H_8]

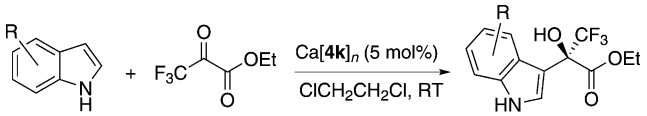
Entry	Ca[**4**]$_n$ [mol%]	Solvent	Yield [%][b]	*ee* [%][c]
1	Ca[**4f**]$_n$ (5)	CH_2Cl_2	93	49
2	Ca[**4g**]$_n$ (5)	CH_2Cl_2	83	50
3	Ca[**4h**]$_n$ (5)	CH_2Cl_2	98	49
4	Ca[**4i**]$_n$ (5)	CH_2Cl_2	85	45
5	Ca[**4j**]$_n$ (5)	CH_2Cl_2	82	63
6	Ca[**4k**]$_n$ (5)	CH_2Cl_2	83	77
7	Ca[**4l**]$_n$ (5)	CH_2Cl_2	89	73
8	Ca[**4k**]$_n$ (2)	CH_2Cl_2	83	72
9	Ca[**4k**]$_n$ (5)	$ClCH_2CH_2Cl$	90	83
10[d]	Ca[**4k**]$_n$ (5)	$ClCH_2CH_2Cl$	92	46
11	Ca[**4k**]$_n$ (5)	$CHCl_3$	87	76
12	Ca[**4k**]$_n$ (5)	CF_3-benzene	93	69
13	Ca[**4k**]$_n$ (5)	Toluene	83	58
14	Ca[**4k**]$_n$ (5)	benzene	66	42

[a] Reaction conditions: indole **8a** (1.0 equiv), **6** (1.5 equiv), Ca[**4f**]$_n$–Ca[**4l**]$_n$ (5 mol%), in 0.26 M solution of solvent at room temperatutre for 30 min. [b] Yield of the isolated product after column chromatography. [c] Determined by HPLC analysis on a chiral column (CHIRALPAK OD-H). [d] The reaction was performed at −30 °C for 24 h.

be performed in various solvents in the presence of catalytic amounts of the catalyst Ca[**4k**]$_n$, thus giving the product in good to excellent yields. The choice of the solvents showed noticeable impact on the enantioselectivity. With catalyst Ca[**4k**]$_n$ higher enantiomeric excess was obtained when the reactions were performed in halogenated solvents. The best result in terms of chemical yield and enantioselectivity was obtained when the reaction was carried out in dichloroethane and the product was isolated in 90% yield and 83% enantiomeric excess (Table 3, entry 9). Lowering the reaction temperature from room temperature to −30°C resulted in prolonged reaction time and lower enantiomeric excess (Table 3, entry 10 vs. entry 9).

With the optimal reaction conditions in hand, the scope of the asymmetric calcium phosphate-catalyzed Friedel–Crafts alkylation was investigated (Table 4). The reaction generally proceeds well with various indoles bearing electron-withdrawing or electron-donating groups to afford the products in excellent yields and with enantiomeric excesses up to 89%. Interestingly, the calcium salts compare favorably to the earlier reported metal-free Brønsted acid catalysts.[12]

Table 4. Scope of the asymmetric Friedel–Crafts alkylation.[a]



8 **6** **9**

Entry	R	9	Yield [%][b]	*ee* [%][c]
1	H	**9a**	92	83
2	5-F	**9b**	94	84
3	5-Cl	**9c**	93	84
4	5-Br	**9d**	98	85
5	5-I	**9e**	98	79
6	5-CN	**9f**	90	87
7	6-F	**9g**	96	89
8	6-Cl	**9h**	98	87
9	5-CH_3	**9i**	99	82
10	5-OCH_3	**9j**	98	82
11	7-CH_3	**9k**	99	87
12	7-C_2H_5	**9l**	98	84

[a] Reaction conditions: indole **8** (1.0 equiv), **6** (1.5 equiv), Ca[**4k**]$_n$ (5 mol%), in 0.26 M solution of dichloroethane at room temperature for 30 min. [b] Yield of the isolated product after column chromatography. [c] Determined by HPLC analysis on a chiral column.

Conclusions

In summary, we here report the first asymmetric calcium-catalyzed addition reactions of styrene as well as indole derivatives to trifluoropyruvates. The corresponding products are obtained in high yields and with good to excellent enantioselectivities. The procedure allows direct access to biologically relevant fluorine-containing molecules, which are of interest for medicinal and agrochemical chemistry. The synthesis of quaternary stereocenters still remains a challenge in organic synthesis. Thus, the newly developed transition-metal-free protocol addresses this challenge and provides a valuable and mild method for the generation of esters comprising an α-trifluoromethyl as well as α-hydroxy moiety, a substitution pattern which mimics a carboxylic acid.

Experimental Section

General Procedure for the Enantioselective Carbonyl-Ene Reaction of Trifluoropyruvate with α-Methyl Styrene

In a screw capped reaction tube, a mixture of α-methyl styrene **5** (0.3 mmol, 1.5 equiv) and catalyst Ca[**4e**]$_n$ (0.5 mol%) was dissolved in toluene (0.8 mL) and ethyl trifluoropyruvate **6** (0.2 mmol, 1.0 equiv) was added at −40°C. The resulting solution was stirred for 48 h. The crude reaction mixture was directly charged on silica gel and purified by column chromatography (*n*-hexane/ethyl acetate, 95.5) to afford the desired product **7**.

General Procedure for the Enantioselective Friedel–Crafts Alkylation of Indole with Trifluoropyruvate

Indole **8** (0.077 mmol, 1.0 equiv), catalyst Ca[**4k**]$_n$ (5 mol%), and ethyl trifluoropyruvate **6** (0.116 mmol, 1.5 equiv) were suspended in dichloroethane (0.3 mL) in a screw capped vial. The resulting mixture was allowed to stir at room temperature for 30 min. The crude reaction mixture was directly purified by column chromatography on silica gel (*n*-hexane/dichloromethane/ethyl acetate, 10:9:1) to give the desired product **9**.

Acknowledgements

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Keywords: 1,2-addition reactions · asymmetric synthesis · brønsted acids · calcium · chirality

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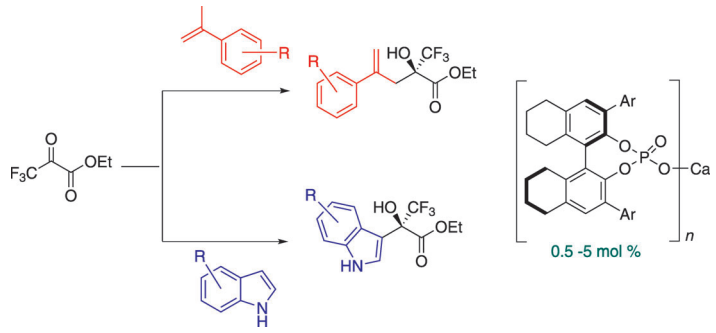

Enantioselective calcium-catalyzed addition reactions of styrene and indole derivatives with trifluoropyruvates have been developed. The alkaline-earth metal-catalyzed reactions proceed smoothly to afford the corresponding products in high yields and with good to excellent enantioselectivities under mild reaction conditions.

Asymmetric Catalysis

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Asymmetric Calcium Catalysis: Highly Enantioselective Carbonyl-Ene and Friedel–Crafts Reactions for the Synthesis of Quaternary α-Hydroxy Esters Bearing a Trifluoromethyl Group