Chiral Brønsted Acids and Their Calcium Salts in Catalytic Asymmetric Mannich Reactions of Cyclic 1,3-Diketones

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Abstract: Asymmetric calcium-catalyzed direct Mannich reactions of 1,3-dicarbonyl compounds with imines have been developed. The reactions proceed under mild conditions and provide the corresponding products with high enantiomeric excess.

Key words: Mannich reaction, organocatalysis, calcium, BINOL phosphoric acid, amino acid

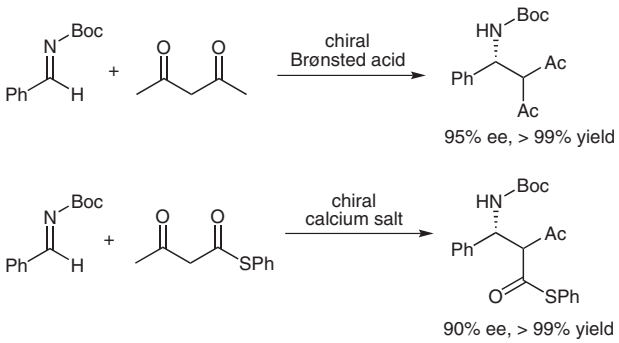
Mannich reaction represent one of the most important methods for the preparation of β-amino carbonyl compounds which are important and versatile building blocks for the synthesis of an assortment of heterocyclic compounds, natural products and biologically active nitrogen-containing compounds. In this context the development of asymmetric variants of this transformation is of great importance and has received considerable attention.[1]

In recent years chiral metal-free BINOL-derived phosphoric acids have been shown to be versatile and powerful chiral Brønsted acid catalysts for a great number of asymmetric transformations.[2–4]

An efficient, asymmetric BINOL phosphoric acid catalyzed Mukaiyama-type Mannich reaction of ketene silyl acetals and aldimines has been developed by Akiyama.[5] Terada reported the Mannich-type reaction of acetylacetone with aldimine using the same catalyst.[6a–e] The chiral Brønsted acid catalyzed multicomponent Mannich reaction has been described by Gong and Zhu,[7] and the development of vinylogous Mannich reactions using chiral BINOL phosphates has been reported by Schneider and Akiyama.[8] Our group has previously successfully developed a dual Brønsted acid catalyzed Mannich–Michael reaction providing isoquinuclidines as well as a Brønsted acid assisted enantioselective Brønsted acid catalyzed direct Mannich reaction[9] of ketones with *N*-aryl aldimines.[10]

Recently Ishihara and co-workers[6f] found that the chiral calcium salts[11] derived chiral phosphoric acids effectively catalyze the direct Mannich reaction (Scheme 1).[12]

In view of these results, we herein report an extension of the Brønsted acid and chiral calcium salt catalyzed Mannich reactions by employing a different type of carbonyl donor. We were especially interested in the application of cyclic dicarbonyl compounds, such as pyrone and cyclohexadiones.



Scheme 1 Brønsted acid catalyzed Mannich reaction

Thus, our initial examination focused on the addition of pyrone **2** to *N*-Boc-protected aldimine **3a** employing various calcium-derived salts from BINOL and $[H_8]$-BINOL phosphoric acids. As shown in Table 1, both the catalyst structure and the temperature had a significant impact on the reaction outcome. Of the various catalysts tested (Table 1, entries 1–20), the best enantioselectivities were obtained with the 3,3′-(2,4,6-triisopropyl)-substituted calcium salt catalyst Ca[**1h**]$_2$.[13] Interestingly, even the mono(2,4,6-triisopropyl)-substituted catalyst provided the Mannich product with a good enantiomeric excess of 65%. The optimal reaction temperature was found to be –40 °C. Higher temperatures gave reduced enantioselectivities and lowering of the temperature beyond –40 °C resulted in prolonged reaction time.

Further optimizations concentrated on the reaction solvent. The results obtained are shown in Table 2. The calcium-catalyzed enantioselective addition of pyrone **2** to aldimine **3a** proceeded in various common solvents including toluene, CH_2Cl_2, $CHCl_3$, trifluorotoluene or dibutyl ether.

Performing the reaction in toluene afforded the product **4a** with good enantioselectivity (86% ee; Table 2, entry 1). Lowering the amount of the catalyst to 2.5 mol% resulted in a drop in the chemical yield to 22% but without affecting the selectivity of the reaction (86% ee; Table 2, entry 2). This indicates that substrate inhibition plays a role in this transformation. However, the best enantioselectivity was achieved when dibutyl ether was employed as the reaction medium and the corresponding Mannich adduct **4a** was obtained with high enantiomeric excess (88% ee; Table 2, entry 6). Performing the reaction with metal-free BINOL phosphoric acid resulted in lower enantioselectivity (60% ee; Table 2, entry 7 vs. entry 6).

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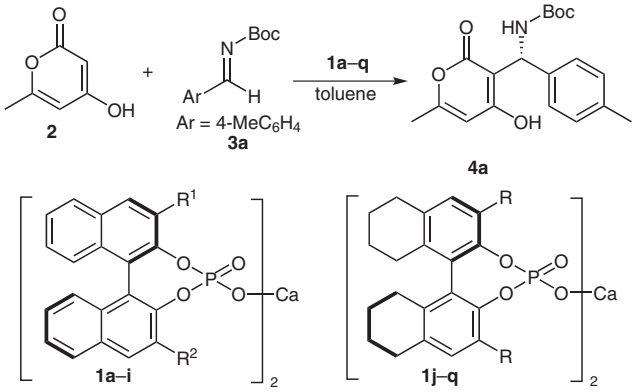
Table 1 Screening of Catalysts and Reaction Temperature[a]



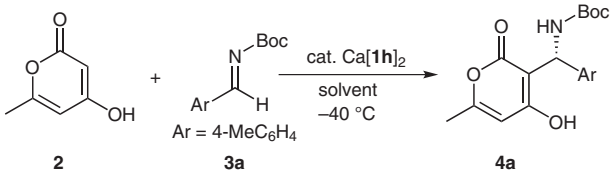
Ca[**1a**]$_2$: $R^1 = R^2$ = Ph
Ca[**1b**]$_2$: $R^1 = R^2$ = 2-naphthyl
Ca[**1c**]$_2$: $R^1 = R^2$ = 4-$O_2NC_6H_4$
Ca[**1d**]$_2$: $R^1 = R^2$ = 9-phenanthryl
Ca[**1e**]$_2$: $R^1 = R^2$ = 9-anthracenyl
Ca[**1f**]$_2$: $R^1 = R^2$ = 3,5-$(CF_3)_2C_6H_3$
Ca[**1g**]$_2$: $R^1 = R^2$ = 3,4,5-$F_3C_6H_2$
Ca[**1h**]$_2$: $R^1 = R^2$ = 2,4,6-(*i*-Pr)$_3C_6H_2$
Ca[**1i**]$_2$: R^1 = H, R^2 = 2,4,6-(*i*-Pr)$_3C_6H_2$

Ca[**1j**]$_2$: R = Ph
Ca[**1k**]$_2$: R = 2-naphthyl
Ca[**1l**]$_2$: R = 1-naphthyl
Ca[**1m**]$_2$: R = 9-phenanthryl
Ca[**1n**]$_2$: R = 4-biphenyl
Ca[**1o**]$_2$: R = 3,5-$(CF_3)_2C_6H_3$
Ca[**1p**]$_2$: R = 4-$MeOC_6H_4$
Ca[**1q**]$_2$: R = $SiPh_3$

Entry	Catalyst **1**	Temp (°C)	ee (%)[b]
1	Ca[**1a**]$_2$	–40	41
2	Ca[**1b**]$_2$	–40	37
3	Ca[**1c**]$_2$	–40	11
4	Ca[**1c**]$_2$	–70	9
5	Ca[**1d**]$_2$	–40	22
6	Ca[**1e**]$_2$	–40	73
7	Ca[**1f**]$_2$	–40	22
8	Ca[**1f**]$_2$	–70	14
9	Ca[**1g**]$_2$	–40	37
10	Ca[**1h**]$_2$	–40	86
11	Ca[**1i**]$_2$	–40	65
12	Ca[**1j**]$_2$	–40	20
13	Ca[**1k**]$_2$	–40	22
14	Ca[**1l**]$_2$	–40	16
15	Ca[**1m**]$_2$	–40	19
16	Ca[**1n**]$_2$	r.t.	13
17	Ca[**1n**]$_2$	–40	19
18	Ca[**1o**]$_2$	–40	32
19	Ca[**1p**]$_2$	–40	15
20	Ca[**1q**]$_2$	–40	4

[a] Reaction conditions: pyrone **2** (1.0 equiv), aldimine **3a** (1.5 equiv), Ca[**1a**]$_2$–Ca[**1q**]$_2$ (5 mol%), at 0.1 M solution in toluene.
[b] Determined by HPLC analysis on a chiral column (CHIRALPAK AD-H).

Table 2 Evaluation of Different Solvents[a]



Entry	Solvent	Yield (%)[b]	ee (%)[c]
1	toluene	52	86
2[d]	toluene	22	86
3	$CHCl_3$	62	82
4	CH_2Cl_2	41	70
5[e]	trifluorotoluene	30	70
6	dibutyl ether	49	88
7[f]	dibutyl ether	53	60

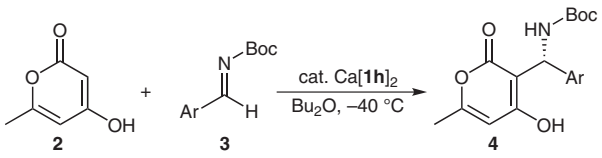
[a] Reaction conditions: pyrone **2** (1.0 equiv), aldimine **3a** (1.5 equiv), Ca[**1h**]$_2$ (5 mol%), at 0.1 M solution at –40 °C for 72 h.
[b] Isolated yields after column chromatography.
[c] Determined by HPLC analysis on chiral column (CHIRALPAK AD-H).
[d] The reaction was performed with 2.5 mol% catalyst.
[e] The reaction was performed at r.t.
[f] The reaction was performed with 10 mol% phosphoric acid **1h**.

Having established the optimal reaction conditions, we next turned our attention to the scope of this reaction.[14,15] As shown in Table 3, the calcium-catalyzed asymmetric Mannich reaction of pyrone **2** with *N*-Boc-aldimines **3** provided the corresponding products **4a–d** in moderate yields but with good enantioselectivities. Better yields were typically obtained when the reaction was conducted in $CHCl_3$, however, this in turn led to slightly lower enantioselectivities. Again, in the absence of calcium significantly lower enantioselectivities were obtained (Table 3, entry 3 vs. entry 2 and entry 6 vs. entry 5).

Having demonstrated that a highly enantioselective calcium-catalyzed Mannich reaction can be performed with pyrones as carbonyl donor we considered whether it would be possible to extend this procedure to cyclic dicarbonyl compounds, such as 1,3-cyclohexadione. By applying the same reaction conditions, we explored the Mannich reaction of 1,3-cyclohexadione **5** with different *N*-Boc-aldimines **3**. The results are summarized in Table 4. The reaction proceeded well, again providing the corresponding products with good enantioselectivities.[14]

In summary we have developed an asymmetric calcium-catalyzed direct Mannich reaction of cyclic 1,3-dicarbonyl compounds with different *N*-Boc-protected aldimines. The chiral calcium catalysts are derived from BINOL phosphoric acids which have also shown to be catalysts for this reaction. In addition to existing methods, we were able to demonstrate that carbonyl donors, such as cyclohexadione as well as pyrone, can be applied in asymmetric Mannich reactions and that the corresponding products,

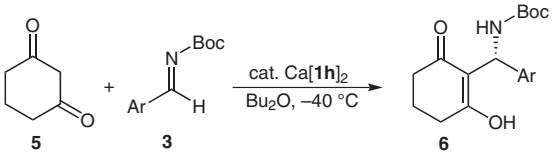
Table 3 Substrate Scope for the Asymmetric Mannich Reaction



Entry[a]	Product	Ar	Yield (%)[b]	ee (%)[c]
1	**4a**	4-MeC_6H_4	49	88
2[d]	**4a**	4-MeC_6H_4	62	82
3[d,e]	**4a**	4-MeC_6H_4	45	39
4	**4b**	3-ClC_6H_4	43	76
5	**4c**	2-BrC_6H_4	55	86
6[e]	**4c**	2-BrC_6H_4	43	73
7[d]	**4c**	2-BrC_6H_4	67	84
8	**4d**	Ph	43	52

[a] Reaction conditions: pyrone **2** (1.0 equiv), aldimine **3** (1.5 equiv), 5 mol% Ca[**1h**]$_2$, at 0.1 M solution in dibutyl ether at –40 °C for 60–72 h.
[b] Isolated yields after column chromatography.
[c] Determined by HPLC analysis on a chiral column (CHIRALPAK AD-H).
[d] The reaction was performed in $CHCl_3$.
[e] The reaction was performed with 10 mol% phosphoric acid **1h**.

Table 4 Substrate Scope[a]



Entry[a]	Product	Ar	Yield (%)[b]	ee (%)[c]
1	**6a**	4-MeC_6H_4	47	73
2	**6c**	2-BrC_6H_4	49	83
3[d]	**6c**	2-BrC_6H_4	53	72
4[e]	**6c**	2-BrC_6H_4	48	62
5	**6e**	4-$CF_3C_6H_4$	48	88

[a] Reaction conditions: 1,3-cyclohexadione (**5**; 1.0 equiv), aldimine **3** (1.5 equiv), 5 mol% Ca[**1h**]$_2$, at 0.1 M solution in dibutyl ether at –40 °C for 60–72 h.
[b] Isolated yields after column chromatography.
[c] Determined by HPLC analysis on a chiral column (CHIRALPAK AD-H).
[d] The reaction was performed with 10 mol% phosphoric acid **1h**.
[e] The reaction was performed in $CHCl_3$.

which are valuable intermediates in organic synthesis, can be obtained with good enantiomeric excess.

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(14) The absolute configuration of the products was obtained from X-ray crystal structure analysis of compound **6c**. On the basis of this structure the absolute configuration was assigned to be the *S* configuration.

(15) **General Procedure for Direct Mannich Reaction**: In a typical experiment pyrone **2** or 1,3-cyclohexadione (**5**; 1.0 equiv), aldimine **3** (1.5 equiv), and the calcium catalyst (5 mol%) were suspended in Bu_2O in a screw-capped vial and the resulting mixture was allowed to stir at –40 °C for 60–72 h. Purification of the crude product by column chromatography on silica gel afforded the corresponding product **4** or **6**.

(*R*)-*tert*-Butyl(4-hydroxy-6-methyl-2-oxo-2*H*-pyran-3-yl)(*p*-tolyl)methylcarbamate (4a): Isolated by column chromatography (CH_2Cl_2–acetone, 10:1) as a white solid in 49% yield and 88% ee. The ee was determined by HPLC using Chiralpak AD-H column [(*n*-hexane–*i*-PrOH, 90:10), flow rate: 0.6 mL/min; major enantiomer: t_R = 29.59 min; minor enantiomer: t_R = 22.07 min]; $[\alpha]_D$ –6.1 (*c* = 1.84, CH_2Cl_2); mp 173–175 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.22 (d, *J* = 8.0 Hz, 2 H), 7.02 (d, *J* = 8.0 Hz, 2 H), 6.79 (d, *J* = 12.0 Hz, 1 H), 6.05 (d, *J* = 12.0 Hz, 1 H), 5.88 (s, 1 H), 3.41 (s, 1 H), 2.23 (s, 3 H), 2.07 (s, 3 H), 1.39 (s, 9 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.10, 164.94, 161.74, 157.40, 137.67, 136.82, 129.09, 126.12, 102.60, 100.84, 81.11, 28.48, 21.05, 19.85. IR (KBr): 3359, 2980, 1700, 1651, 1530, 1161, 884, 783 cm^{-1}. MS (EI): *m*/*z* (%) = 345 (2) [M$^+$], 339 (30), 251 (41), 230 (58), 200(100), 145 (64), 77 (92).

(*R*)-*tert*-Butyl(2-hydroxy-6-oxocyclohex-1-enyl)(*p*-tolyl)-methylcarbamate (6a): Isolated by column chromatography (CH_2Cl_2–acetone, 10:1) as a white solid in 47% yield and 73% ee. The ee was determined by HPLC using Chiralpak AD-H column [(*n*-hexane–*i*-PrOH, 92:8), flow rate: 0.6 mL/min; major enantiomer: t_R = 20.23 min; minor enantiomer: t_R = 17.98 min]; $[\alpha]_D$ +4.43 (*c* = 0.75, CH_2Cl_2); mp 132–134 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.60 (br s, 1 H), 7.19 (d, *J* = 8.0 Hz, 2 H), 7.00 (d, *J* = 8.0 Hz, 2 H), 6.82 (d, *J* = 9.9 Hz, 1 H), 5.99 (d, *J* = 9.9 Hz, 1 H), 2.45 (t, *J* = 6.0 Hz, 2 H), 2.22 (s, 5 H), 1.79–1.89 (m, 2 H), 1.35 (s, 9 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.73, 157.32, 136.00, 128.80, 125.92, 116.22, 80.60, 48.78, 37.02, 29.64, 28.54, 21.15, 20.62. IR (KBr): 3455, 2922, 1710, 1490, 1165, 1025, 779 cm^{-1}. MS (EI): *m*/*z* (%) = 331 (56) [M$^+$], 266 (58), 239 (92), 194 (100), 116 (58), 78 (52), 70 (98).