Highly Enantioselective and Regioselective Conjugate Addition of Nitromethane to 1,5-Diarylpenta-2,4-dien-1-ones Using Bifunctional Cinchona Organocatalysts

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Abstract: A general and efficient asymmetric organocatalytic 1,4-Michael addition of nitromethane to 1,5-diarylpenta-2,4-dien-1-ones (cinnamylideneacetophenones) catalyzed by 9-thiourea-9-(deoxy)-*epi*-hydroquinine has been developed. The reactions afforded excellent enantioselectivities (up to 99%), high yields (up to 97%), and exclusive regioselectivity.

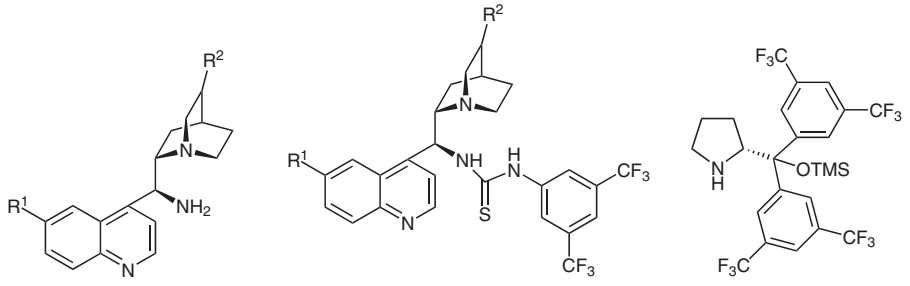
Key words: asymmetric catalysis, enantioselectivity, regioselectivity, ketones

The 1,4-Michael addition of nucleophiles to electron-deficient alkenes is one of the oldest and more useful carbon–carbon bond-forming reactions.[1] The key importance of this conjugate addition in organic synthesis has led to the development of a great number of asymmetric catalytic versions.[2] The term asymmetric organocatalysis covers a wide range of organic processes and methodologies providing efficient and environmentally friendly access to enantiomerically pure compounds, including many drugs and bioactive natural products, where the absence of metals is required.[3]

An attractive way to introduce chirality into a Michael addition is through the use of small chiral organic molecules. In particular, 9-amino-(9-deoxy)-*epi*-cinchona alkaloids **1**,[4] 9-thiourea-(9-deoxy)-*epi*-cinchona alkaloids **2**,[5] and diarylprolinol silyl ether **3**[6] (Figure 1) have been extensively used as organocatalysts in 1,4-Michael addition to α,β-unsaturated ketones.

Several electrophilic species can be suitable substrates for 1,4-Michael addition. Among them, α,β-unsaturated aryl ketones constitute a class of compounds that has receive less attention than the corresponding unsaturated alkyl ketones or aldehydes because the aromatic group can block the interaction of the carbonyl group with the catalyst. In our investigation, we were concerned with δ-aryl α,β,γ,δ-unsaturated aryl ketones (cinnamylideneacetophenones), compounds similar to chalcones but with an extra double bond. Nitromethane represents a versatile nucleophile that can be chemically transformed into a variety of functionally useful compounds. Addition of nitromethane to chalcones has been demonstrated[5a,j,7] but the addition of nitromethane to cinnamylideneacetophenones has received scant attention.[5j] In this case only one example has been described with δ-phenyl-α,β,γ,δ-unsaturated *N*-acylpyrrole ketone with 54% yield and 94% ee.

In this communication we present a general and efficient organocatalytic 1,4-Michael addition of nitromethane to different cinnamylideneacetophenones catalyzed by organocatalysts **1**–**3**. Our investigation began with the screening of chiral organocatalysts **1a**,[5a] **2a**,[5a] and **3** (Figure 1) to promote a conjugate addition of nitromethane to 1,5-diphenylpenta-2,4-dien-1-one (**4a**)[8a] under neat conditions to obtain (*E*)-3-(nitromethyl)-1,5-diphenylpent-4-en-1-one (**5a**, Table 1).



1a R^1 = OMe, R^2 = Et
1b R^1 = OMe, R^2 = CH=CH_2
1c R^1 = H, R^2 = CH=CH_2

2a R^1 = OMe, R^2 = Et
2b R^1 = OMe, R^2 = CH=CH_2
2c R^1 = H, R^2 = CH=CH_2

3

Figure 1

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Table 1 Catalyst Screening for the Addition of Nitromethane to **4a**[a]

4a **5a**

Entry	Catalyst	Additive	Yield (%)[b]	ee (%)[c]
1[d]	**1a**	$PhCO_2H$	–[e]	–
2[d]	**1a**	TFA	–[e]	–
3	**1a**	DMP	–[e]	–
4	**1a**	DBU	77	0
5	**2a**	DBU	51	13
6[f]	**2a**	DBU	83	4
7	**2a**	DMP	33	86
8[f]	**2a**	DMP	60	80
9	**2a**	–[g]	56	93
10[h]	**2a**	–[g]	40	88
11	**3**	$PhCO_2H$	–[e]	–
12	**3**	TFA	–[e]	–
13	**3**	DMP	–[e]	–
14	**3**	DBU	98	0

[a] Reactions were carried out using **4a** (15 mg, 0.064 mmol), 20 mol% of catalyst **1a**, **2a**, or **3** (0.013 mmol), 20 mol% of requisite additive (0.013 mmol), and 0.1 M solution of nitromethane (0.64 mL) at r.t. under a nitrogen atmosphere.
[b] Yield of isolated products after chromatography.
[c] Determined by chiral HPLC using a Chiralpak IA column.
[d] Conditions: 40 mol% of additive.
[e] No reaction was observed.
[f] Reaction was carried out with 40 mol% of catalyst and additive.
[g] Without additive.
[h] Reaction was carried out without nitrogen atmosphere.

Enantioselectivity and yield varied significantly according to the catalyst employed. No reaction was observed with catalysts **1a** (entries 1–3) and **3** (entries 11–13) and with only DBU reaction occurred in a nonenantioselective way (entries 4, 14). The main reason might be the fact that nucleophile is not efficiently activated by **1a** and **3**. Poor enantioselectivities were obtained for catalyst **2a** in combination with DBU (entries 5, 6). In contrast, the use of *trans*-2,5-dimethylpiperazine as additive led to promising results (entries 7, 8). In the absence of additive, catalyst **2a** afforded higher enantioselectivities (93%, entry 9) and 88% (entry 10). Therefore, this bifunctional thiourea group seems to be the best catalytic system for the addition of nitromethane to cinnamylideneacetophenone (**4a**) because the thiourea motif might be a very efficient tool in this Michael addition.

Next we tested the influence of the solvent on the reaction, with screening results summarized in Table 2. The variation of solvent had little effect on the enantioselectivity (entries 1–6) except in the case of the protic solvent methanol (entry 7). However, yields were influenced by the solvent; polar solvents such as MeOH (entry 7) or MeCN (entry 4) gave poor yields; whereas less polar solvents such as CH_2Cl_2 (entry 2), $CHCl_3$ (entry 3), THF (entry 5), or toluene (entry 6) gave rise to better yields. Dichloromethane (entry 2) gave a result comparable with the neat conditions (entry 1).

Table 2 Solvent Effect on the Organocatalyzed 1,4-Addition of Nitromethane to **4a**[a]

Entry	Catalyst	Solvent	Yield (%)[b]	ee (%)[c]
1	**2a**	neat	56	93
2	**2a**	CH_2Cl_2	50	90
3	**2a**	$CHCl_3$	42	92
4	**2a**	MeCN	19	90
5	**2a**	THF	39	90
6	**2a**	toluene	39	86
7	**2a**	MeOH	23	76

[a] Reactions were carried out at 0.1 M solution of **4a** (15 mg, 0.064 mmol), 20 mol% of catalyst **2a** (0.013 mmol), 20 mol% of adequate additive (0.013 mmol), and nitromethane (5.4 mmol, 0.29 mL) in 0.35 mL of solvent at r.t. for 7 d under a nitrogen atmosphere.
[b] Yield of isolated products after chromatography.
[c] Determined by chiral HPLC using a Chiralpak IA column.

After selecting 9-thiourea-(9-deoxy)-*epi*-hydroquinine **2a** without any additive as the most efficient catalyst and nitromethane as solvent, the influence of catalyst loading and concentration conditions were investigated (Table 3). We started at neat conditions with 20 mol% of catalyst **2a** in a 0.1 M solution of substrate. When the reaction temperature was raised to 40 °C (entry 2) and molecular sieves were added (entry 3), good ee and acceptable yields were obtained. Increasing the molar concentration of substrate (entries 4–6) improved the reaction yield and the enantioselectivity was retained. The best reaction conditions were achieved with 0.3 M solution of substrate and 30 mol% of catalyst (entry 7), resulting in excellent yield (97%) and high enantioselectivity (96%). A recrystallization of the material so obtained raised the ee to 99%. The *R*-configuration was confirmed by single-crystal X-ray diffraction data[9] and this is in accordance with theoretical studies developed by Soós and Pápai.[10] Lowering the reaction temperature to –10 °C did not improve the ee values (entry 8). Increasing the amount of catalyst to 40 mol% caused the ee values to decrease (entries 9, 10). Finally, we investigated the conjugate additions of nitromethane to **4a** with different *epi*-thiourea cinchona alkaloids such as **2b**[5a] and **2c**[11] (Figure 1), although poor results were obtained (entries 11, 12).

With the established optimized conditions, the scope of the reaction for different cinnamylideneacetophenones **4b–h**[8,12] was investigated (Table 4). Results show that the

Table 3 Optimization of Reaction Conditions for Asymmetric Conjugate Addition of Nitrometane to **4a** Using Catalysts **2a–c**[a]

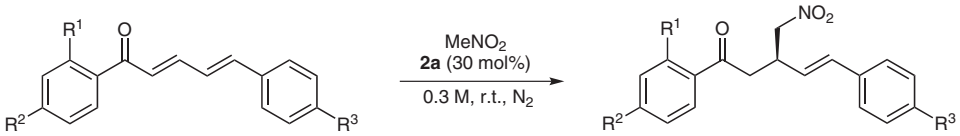
Entry	2	Catalyst load (mol%)	Concentration [M]	Yield (%)[b]	ee (%)[c]
1	**2a**	20	0.1	56	93
2[d]	**2a**	20	0.1	77	90
3[e]	**2a**	20	0.1	65	91
4	**2a**	20	0.2	65	93
5	**2a**	20	0.3	78	93
6	**2a**	20	0.4	87	90
7	**2a**	30	0.3	97	96[f,g]
8[h]	**2a**	30	0.3	82	93
9	**2a**	40	0.1	60	87
10[e]	**2a**	40	0.1	70	85
11	**2b**	30	0.3	64	91[i]
12	**2c**	30	0.3	74	76[i]

[a] Reactions were carried out using **4a** (15 mg, 0.064 mmol), catalyst **2a–c** and nitromethane for 7 d under a nitrogen atmosphere.
[b] Yield of isolated products after chromatography.
[c] Determined by chiral HPLC using a Chiralpak IA column.
[d] Reaction was carried out at 40 °C.
[e] With 10 mg of 4 Å MS.
[f] >99% ee after recrystallization.
[g] The absolute configuration of (*R*)-**5a** was determined by chiral HPLC and X-ray analysis.[8]
[h] Reaction was carried out at –10 °C.
[i] Configuration of (*R*)-**5a** was determined by chiral HPLC.

synthesis of new (*R*,*E*)-1,5-diaryl-3-(nitromethyl)-5-pent-4-en-1-ones **5b–h**[13] took place with high levels of enantioselectivity (87–99%) independent of the nature and position of substituents. These compounds could be recrystallized and their ee raised to 99%. However, the reaction yield was influenced by the substitution on the aryl rings (19–92%). Derivatives with electron-withdrawing and electron-donating substitutents at the *para* position of the δ-aryl group were examined. When an electron-withdrawing substitution was present (entry 1), a moderate yield was obtained. This result can be explained by a charge density decreasing in the α,β,γ,δ-unsaturated ketone system, which implies that the hydrogen-bonding interaction between the catalyst **2a** and the carbonyl group of **4b** is more labile. When an electron-donating group was present (entry 2), a high yield and enantioselectivity were observed. In this case, the charge density increases in the system and the hydrogen-bonding is stronger. Different substitutions present in the *para* position of the ketone aryl group (entries 3–5), did not significantly affect the enantioselectivity and isolated yield. *ortho*-Substitution in the aryl group proximal to the ketone decreased the yield significantly (entries 6, 7). Presumably, the OH and NH_2 substituents can form intramolecular hydrogen bonds to the ketone group and hinder the interaction between the ketone and the catalyst.

The crystal structure of compound (*R*)-**5a**[9] (Figure 2) was found in the chiral orthorhombic $P2_12_12_1$ space group. Even though the absolute configuration of the molecules could not be unequivocally determined using solely single-crystal X-ray diffraction data (due to the presence of only light atoms in the compounds, i.e., $Z < Si$), this was

Table 4 Scope of the Enantioselective Addition of Nitromethane to 1,5-Diarylpenta-2,4-dien-1-ones **4b–h** Organocatalyzed by **2a**[a]



Entry	4	R^1	R^2	R^3	5 (yield, %)[b]	ee (%)[c]
1	**4b**	H	H	NO_2	**5b** (66)	88[d,e]
2	**4c**	H	H	OMe	**5c** (91)	>99[e]
3	**4d**	H	Me	H	**5d** (83)	90[d,e]
4	**4e**	H	OMe	H	**5e** (81)	93[d,e]
5	**4f**	H	Cl	H	**5f** (92)	94[d,e]
6	**4g**	OH	H	H	**5g** (33)	90[e]
7	**4h**	NH_2	H	H	**5h** (19)	87[e]

[a] Reactions carried out using **4b–h** (0.128 mmol), 30 mol% of catalyst **2a** (22.9 mg, 0.038 mmol) in 0.3 M solution of nitromethane (0.47 mL) under nitrogen atmosphere for 7 d at r.t.
[b] Yield of isolated products after chromatography.
[c] Determined by chiral HPLC using a Chiralpak IA column.
[d] ee >99% after recrystallization.
[e] *R*-Configuration was determined by chiral HPLC.

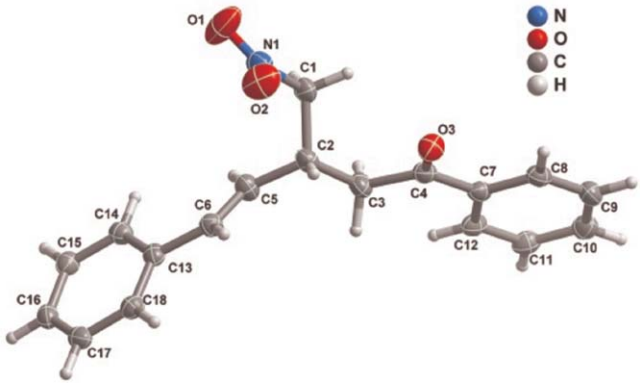


Figure 2 Schematic representation of the molecular units present in compound (*R*)-**5a**. Nonhydrogen atoms are represented as thermal ellipsoids drawn at the 50% probability level and hydrogen atoms as spheres with arbitrary radii.

resolved by taking into consideration data from the synthesis and results from chiral HPLC separation.

In summary, we have developed a general organocatalytic 1,4-Michael addition of nitromethane to different 1,5-diarylpenta-2,4-dien-1-ones in the presence of 9-thiourea-9-(deoxy)-*epi*-hydroquinine. Excellent levels of enantiomeric excess (up to 99%) and isolated yields (up to 97%) have been achieved for a wide range of substrates and exclusive regioselectivity was obtained with no δ-addition being observed.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(9) Further details on the single-crystal X-ray diffraction studies are given as Electronic Supporting Information. This compound crystallized as colorless prisms, in the orthorhombic P212121 space group with $Z = 4$.
Crystal Data for (*R*)-5a
$C_{18}H_{17}NO_3$, $M = 295.33$, $T = 150$ (2) K, $a = 5.59290$ (10) Å, $b = 11.9990$ (3) Å, $c = 23.0093$ (5) Å, $V = 1544.14$ (6) Å^3, μ(MoKα) = 0.087 mm^{-1}, $D_c = 1.270$ g cm^{-3}, crystal size of $0.14 \times 0.12 \times 0.10$ mm^3. Of a total of 35216 reflections collected, 2411 were independent ($R_{int} = 0.0233$). Final

$R1 = 0.0360$ [$I > 2\sigma(I)$] and $wR2 = 0.0969$ (all data). Data completeness to theta = 29.13°, 99.8%. Data have been deposited at the Cambridge Crystallographic database: CCDC 739749

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(12) **Synthesis of (*E*,*E*)-1-(2-Aminophenyl)-5-phenylpenta-2,4-dien-1-one (4h)**
Sodium hydride (265 mg, 11 mmol) was added to a solution of 2′-aminoacetophenone (675 mg, 5.0 mmol) in dry THF (15.5 mL), and the mixture was cooled to r.t. Cinnamaldehyde (792 mg, 6.0 mmol) in dry THF (20 mL) was added, and the reaction mixture was stirred for 12 h and then poured into a mixture of H_2O (20 mL) and ice (20 g) and acidified with HCl to pH ~2. The solid obtained was filtered, taken up in CH_2Cl_2 and washed with H_2O. The organic layer was dried and concentrated, and the residue was purified by silica gel column chromatography with a 1:1 mixture of light PE–CH_2Cl_2 as eluent. The residue was recrystallized from EtOH. Orange solid (573 mg, 46% yield); 113–114 °C. ^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 7.79 (dd, 1 H, ^3J = 8.5 Hz, ^4J = 1.5 Hz, H-6′), 7.58–7.48 (m, 3 H, H-3, H-2″,6″), 7.40–7.25 (m, 4 H, H-3″,5″, H-4′, H-4″), 7.18 (d, 1 H, $^3J_{trans}$ = 14.8 Hz, H-2), 7.08–6.94 (m, 2 H, H-4, H-5), 6.70–6.66 (m, 2 H, H-3′, H-5′), 6.31 (br s, 2 H, NH_2) ppm. ^{13}C NMR (125.77 MHz, $CDCl_3$): δ = 191.7 (C-1), 150.9 (C-2′), 143.0 (C-3), 140.7 (C-4), 136.3 (C-1″), 134.2 (C-4′), 130.9 (C-6′), 129.0 (C-4″), 128.8 (C-3″,5″), 127.2 (C-2″,6″, C-5), 126.5 (C-2), 119.1 (C-1′), 117.3 (C-5′), 115.9 (C-3′) ppm.

(13) **General Procedure for Enantioselective Addition of Nitromethane to Cinnamylideneacetophenones 4a–h: Synthesis of 5a–h**
1,5-Diarylpenta-2,4-dien-1-ones **4a**–**h** (0.128 mmol) and thiourea catalyst **2a** (22.9 mg, 0.038 mmol) were dissolved in nitromethane (0.47 mL) under a nitrogen atmosphere. The mixture was stirred for 7 d at r.t. The resulting solution was evaporated and purified by column chromatography eluting with hexane–EtOAc (9:1). The purified material was crystallized to obtain compounds **5a**–**h**.

Selected Data for (*R*,*E*)-3-(Nitromethyl)-1,5-diphenylpent-4-en-1-one [(*R*)-5a]
White solid (36.7 mg, 97% yield); 105–107 °C (hexane–EtOAc). ^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 7.96 (d, 2 H, ^3J = 7.5 Hz, H-2′,6′), 7.60 (t, 1 H, ^3J = 7.5 Hz, H-4′), 7.48 (t, 2 H, ^3J = 7.5 Hz, H-3″,5″), 7.34–7.21 (m, 5 H, H-2″,6″, H-3″,5″, H-4″), 6.58 (d, 1 H, $^3J_{trans}$ = 15.9 Hz, H-5), 6.17 (dd, 1 H, $^3J_{trans}$ = 15.9 Hz, ^3J = 8.6 Hz, H-4), 4.72 (ABX, 1 H, $^2J_{AB}$ = 12.2 Hz, $^3J_{AX}$ = 5.9 Hz, H-1A‴), 4.62 (ABX, 1 H, $^2J_{AB}$ = 12.2 Hz, $^3J_{BX}$ = 7.4 Hz, H-1B‴), 3.81–3.70 (m, 1 H, H-3), 3.30 (d, 2 H, ^3J = 6.5 Hz, H-2) ppm. ^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 197.0 (C-1), 136.5 (C-1′), 136.2 (C-1″), 133.6 (C-4′), 133.4 (C-5), 128.8 (C-3′,5′), 128.6 (C-3″,5″), 128.1 (C-2′,6′), 128.0 (C-4″), 126.5 (C-4), 126.4 (C-2″,6″), 78.8 (C-1‴), 40.3 (C-2), 37.3 (C-3) ppm. HRMS (ESI$^+$): *m/z* calcd for $[C_{18}H_{17}NO_3 + H]^+$: 296.1281; found: 296.1279. Anal. Calcd for $[C_{18}H_{17}NO_3 + H]^+$: C, 73.20; H, 5.80; N, 4.74. Found: C, 73.17; H, 5.82; N, 4.79. HPLC (*i*-PrOH–hexane = 10:90, flow rate 0.7 mL/min, λ = 254 nm): t_R(minor) = 18.31 min; t_R(major) = 20.70 min (ee = 96%), after recrystallization (ee >99%).

Selected Data for (*R*,*E*)-1-(4-Chlorophenyl)-3-(nitromethyl)-5-phenylpent-4-en-1-one [(*R*)-5f]
White solid (38.8 mg, 92% yield); 147–148 °C (hexane–EtOAc). ^{1}H NMR (300.13 MHz, $CDCl_3$, 20 °C): δ = 7.89 (AA′BB′, $^3J_{AB}$ = 8.6, Hz, $^4J_{AA'}$ = 2.4 Hz, $^5J_{AB'}$ = 1.9 Hz, 2 H, H-2′,6′), 7.46 (AA′BB′, $^3J_{AB}$ = 8.6, Hz, $^4J_{BB'}$ = 2.4 Hz, $^5J_{AB'}$ = 1.9 Hz, 2 H, H-3′,5′), 7.32–7.24 (m, 5 H, H-3″,5″, H-2″,6″, H-4″), 6.58 (d, $^3J_{trans}$ = 15.8 Hz, 1 H, H-5), 6.15 (dd, $^3J_{trans}$ = 15.8 Hz, ^3J = 8.5 Hz, 1 H, H-4), 4.71 (ABX, $^2J_{AB}$ = 12.1 Hz, $^3J_{BX}$ = 6.0 Hz, 1 H, H-1A‴), 4.61 (ABX, $^2J_{AB}$ = 12.1 Hz, $^3J_{BX}$ = 7.1 Hz, 1 H, H-1B‴), 3.79–3.68 (m, 1 H, H-3), 3.30 (dd, ^2J = 17.7 Hz, ^3J = 6.5 Hz, 1 H, H-2A), 3.24 (dd, ^2J = 17.7 Hz, ^3J = 6.5 Hz, 1 H, H-2B) ppm. ^{13}C NMR (125.77 MHz, $CDCl_3$, 20 °C): δ = 195.8 (C-1), 140.1 (C-4′), 136.0 (C-1″), 134.7 (C-1′), 133.6 (C-5), 129.4 (C-2′,6′), 129.1 (C-3′,5′), 128.6 (C-3″,5″), 128.0 (C-4″), 126.4 (C-2″,6″), 126.2 (C-4), 78.8 (C-1‴), 40.3 (C-2), 37.3 (C-3) ppm. HRMS (ESI$^+$): *m/z* calcd for $[C_{18}H_{16}ClNO_3 + Na]^+$: 352.0711; found: 352.0710. Anal. Calcd for $[C_{18}H_{16}ClNO_3 + Na]^+$: C, 65.56; H, 4.89; N, 4.25. Found: C, 65.27; H, 4.92; N, 4.21. HPLC (*i*-PrOH–hexane = 10:90, flow rate 0.7 mL/min, λ = 254 nm): t_R(minor) = 24.31 min; t_R(major) = 28.95 min (ee = 94%), after recrystallization (ee > 99%).