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Organocatalytic Asymmetric Deconjugative Michael Additions

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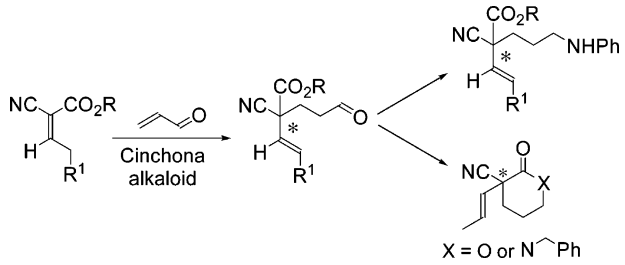

The organocatalytic allylic C−C bond-forming addition of activated alkylidenes to acrolein has been achieved with good yield and regio- and enantioselectivity. Chiral tertiary amines in the form of cinchona alkaloid catalysts are used to give allyl intermediates that exhibit unusual α-selectivity in the C−C bond-forming step. The products are transformed into a large range of intermediates that are difficult to access via alternative methods, using different oxidative and reductive protocols.

The Michael reaction is one of the most ubiquitous in all of organic chemistry, and developing this C−C bond-forming reaction remains an important challenge in organic synthesis. Various methods exist to carry out this conjugate addition reaction in an enantioselective, catalytic manner,[1] and recent advances in the field of asymmetric Michael reactions have seen additions to α,β-unsaturated ketones, esters, amides, and nitroalkenes.[2] Although the addition to α,β-unsaturated aldehydes can be accomplished utilizing iminium ions[3] and is included in Wynberg's seminal work with β-ketoesters,[4] to the best of our knowledge, few other catalytic asymmetric methods exist.[5]

As part of our recent research on organocatalyzed asymmetric reactions,[6] we have introduced a new concept exploiting the latent nucleophilic reactivity of activated alkylidenes **1** for creating enantioselective, allylic C−N[6i] and C−C[2n] bonds with excellent regio- and stereocontrol. The synthetic appeal of enantioenriched alkenes as intermediates in complex molecule synthesis is well-known,[7] and the most widely used approach to these alkenes is that of π-allyl-metal complexes that can undergo nucleophilic addition.[8] Our complementary organocatalytic concept relies on the deprotonation of an allylic hydrogen atom by a chiral base to give a delocalized allylic anion (Scheme 1). The anion formed can then attack electrophiles from the γ- or α-position leading to **2** or **3**, respectively. In our previous studies, attack has always come exclusively from the γ-position.[2n,6i] Our work utilizes the cinchona alkaloids[6d−m] as chiral bases for the formation of these chiral ion pairs, as they are readily available and easy to derivatize.

We now wish to report our first findings of attack from the α-position of this chiral ion pair, leading to an enantioselective organocatalytic deconjugative Michael reaction of alkylidene cyanoacetates[9] with acrolein, yielding a quaternary stereocenter.

We began our investigation by studying the reaction between the alkylidene cyanoacetate **4a** and acrolein **5** in the presence of Et_3N (Table 1, entry 1). The reaction was found to take place cleanly, with good conversion to the α-substituted product **6a**. The "simple" alkaloid quinine **I** gave reasonable enantiomeric excess (entry 2) under our reaction conditions (−20 °C in CH_2Cl_2). The opposite enantiomer could be accessed by using the

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SCHEME 1. Organocatalytic Asymmetric Electrophilic Addition to Allylic Systems

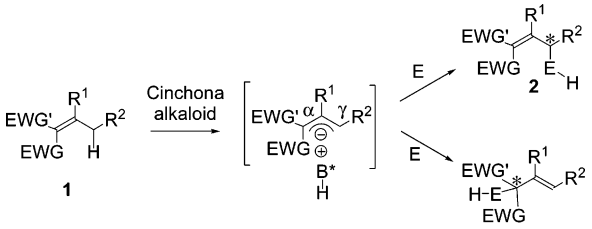
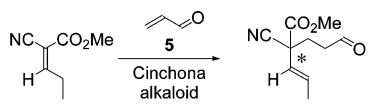
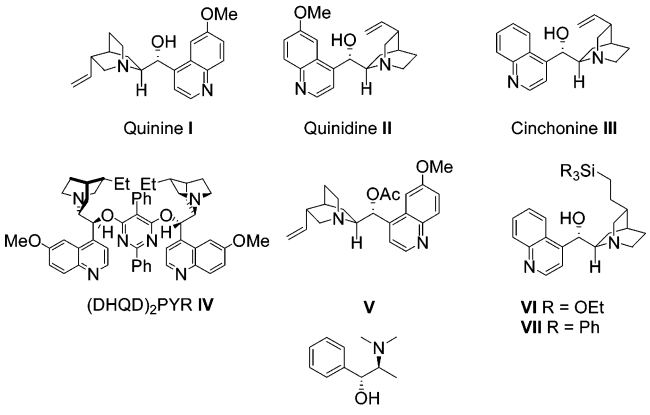


TABLE 1. Initial Screening of Catalysts for the Reaction of Alkylidene Cyanoacetate 4a with Acrolein 5 in the Presence of Various Achiral and Chiral Bases as the Catalysts[a]



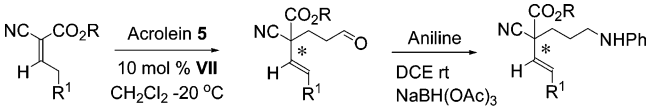


entry	catalyst	temp. (°C)	time (h)	conv.[b] (%)	ee[b] (%)
1	Et_3N	−20	19	85	
2	quinine **I**	−20	20	36	−35
3	quinidine **II**	−20	20	80	+38
4	cinchonine **III**	−20	20	31	+49
5	$(DHQD)_2PYR$ **IV**	−20	20		
6	**V**	−20	18		
7	**VI**	−20	23	71	+58
8	**VII**	−20	23	85	+59
9	**VII**	−30	65	43[c]	+55
10	*N*-methyl ephedrine **VIII**	−20	19	21	+29

[a] Reaction performed at a 0.125 mmol scale (**4a**) with 1.5 equiv of **5** and 10 mol % of catalyst in CH_2Cl_2. [b] Determined by chiral GC analysis of the crude mixture. [c] 3.0 equiv of **5** used.

quasi-enantiomer quinidine **II**, which gave similar enantioselectivity and better reactivity (entry 3). Cinchonine **III** showed an improvement in enantioselectivity, giving 49% ee, albeit with perturbed reactivity (entry 4). During the course of our initial screening, it became apparent that the oxygen atom on the C9 position of the cinchona alkaloid backbone needed to be unsubstituted for good conversion to occur under any reaction conditions (compare entries 2−4 with 5 and 6). With this information in mind, a screening of catalysts showed that **VI** or **VII** (derived from cinchonine using a Pt-catalyzed hydrosilation reaction)[10] was the most effective catalyst at −20 °C,

TABLE 2. Reaction Scope with Respect to Nucleophiles 4a−j[a]



entry	ester (R)	R^1	time (h)	conv. (%)	yield[b] (%)	ee[c] (%)
1	**4a**, Me	Me	23	**6a**, 81[d]	**7a**, 44	56
2	**4b**, Me	*n*-Hex	26	**6b**, 76[d]	**7b**, 52	56
3	**4c**, Me	allyl	26	**6c**, 77[d]	**7c**, 54	51
4	**4d**, Me	$(CH_2)_3OTBS$	24	**6d**, 72[d]	**7d**, 55	53
5	**4e**, Me	*i*-Pr	70	**6e**, 77[d]	**7e**, 63	50
6	**4f**, Me	*t*-Bu	192	**6f**, 77[d]	**7f**, 59	40
7	**4g**, Me	Bn	18	**6g**, 85[e]	**7g**, 39	39
8	**4h**, *i*-Pr	Me	19	**6h**, 95[d]	**7h**, 52	55
9	**4i**, Bn	Et	24	**6i**, 81[e]	**7i**, 39	53
10	**4j**, *t*-Bu	Et	73	**6j**, 74[e]	**7j**, 45	40

[a] Reactions were performed at a 0.25 mmol scale (**4**) with 1.5 equiv of **5**, using 10 mol % of catalyst **VII** in CH_2Cl_2 at 0.125 M. [b] For reaction times, see Supporting Information. [c] Determined by CSP−HPLC analysis. [d] Determined by chiral GC analysis. [e] Determined by ^1H NMR analysis of the crude mixture.

giving 71 and 85% conversion with 58 and 59% ee, respectively (entries 7 and 8). Lowering the temperature to −30 °C resulted in comparable enantioselectivity but greatly diminished the reactivity (43% conversion and 55% ee, entry 9). Other chiral tertiary amino alcohols such as *N*-methylephidrine **VIII** could also perform the reaction, albeit with low conversion and modest enantioselectivity (entry 10).

The scope of the asymmetric allylic C−C bond-forming reaction was probed using a range of activated alkylidene cyanoacetates **4a**−**j**, reacting with acrolein **5**. The use of 1.5 equiv of **5** and dilution to 0.125 M (Table 2, entry 1) was found to be beneficial to the reaction rate without decreasing the enantioselectivity. Although good conversions were observed for **4a**, the conversion was 81% by chiral GC analysis and 85% by ^1H NMR analysis after 23 h (Table 2, entry 1), the product could not be isolated in a correspondingly high yield (53%). This loss of product was attributed to a lack of stability of the initial Michael reaction products **6a**−**j** to column chromatography. Numerous methods were examined to give stable derivatives of **6a**, and the most reliable method was a simple reductive amination using $NaBH(OAc)_3$ and aniline in 1,2-dichloroethane (DCE) to give the desired secondary amines (**7a**−**j**),[11] which could be isolated in good yield with no loss of stereochemical information. This protocol was used to isolate all further catalytic reactions.

The first site of the alkylidene cyanoacetates to be modified was the allylic position, while keeping the methyl ester constant. Thus, the benchmark reaction where R^1 = Me gave 44% yield (over two steps) and 56% ee (Table 2, entry 1). Increasing the alkyl chain length by using an *n*-hexyl, allyl, or TBS-protected *n*-propanol group gave similar enantioselectivity, and compounds **7b**−**d** were obtained with 56, 51, and 53% ee, respectively (entries 2−4). Increasing the steric bulk of the allylic position with an *i*-propyl group gave longer reaction times, as expected (70 h, 63% yield, and 50% ee, entry 5). When the bulk was increased further with a *tert*-butyl group, the

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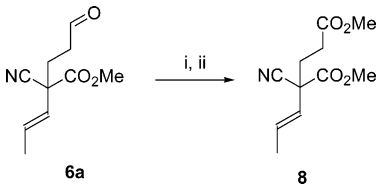
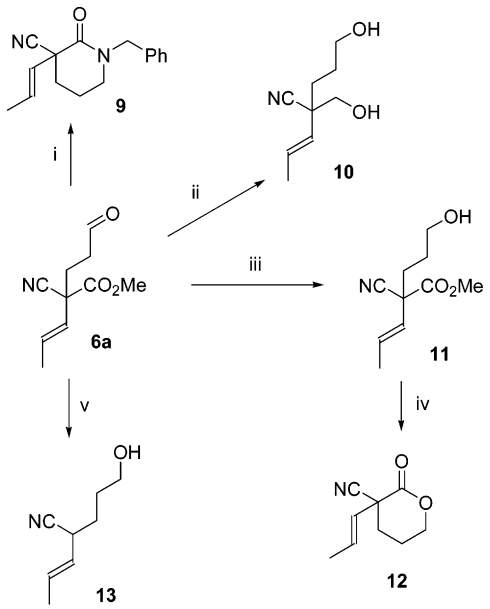
SCHEME 2. Oxidative Transformation of Michael Product 6a[a]



[a] Conditions: (i) $NaClO_2$, KH_2PO_4, 2-methyl-2-butene, *t*-BuOH/H_2O, rt, 90 min; (ii) $TMSCHN_2$, 30% MeOH in toluene, rt, 20 min.

SCHEME 3. Reductive Transformations of Michael Product 6a[a]



[a] Conditions: (i) benzylamine, $NaBH(OAc)_3$, 1,4-dioxane, rt; (ii) $NaBH_4$, CH_2Cl_2/MeOH, −20 °C; (iii) $NaCNBH_3$, 20% CH_3CO_2H in THF, −20 °C; (iv) SiO_2, DCE, 70°C; (v) $LiAlH_4$, THF, −78 °C.

reaction progressed sluggishly to give **7f** in 77% conversion after 192 h. Compound **7f** was isolated in 59% yield and a moderate 40% ee (entry 6). The use of a benzyl group gave similar reactivity (18 h to give 85% conversion) to the benchmark reaction, and **7g** was obtained in 39% yield with 39% ee (entry 7).

The tolerance of this organocatalytic Michael reaction to various ester groups in the alkylidene cyanoacetates was then investigated. An *i*-propyl ester group gave 52% yield and 55% ee, while both benzyl and *tert*-butyl esters gave similar yields (39 and 45%), with the benzyl ester giving 53% ee and the *tert*-butyl ester giving 40% ee (entries 8−10).

Many synthetic manipulations of the highly functionalized Michael product **6** could be envisioned. When oxidative conditions are used, the crude aldehyde **6a** can be transformed to the corresponding methyl ester in good yield (48% three steps) via the carboxylic acid with no loss of stereochemical information (Scheme 2).

As well as the reductive amination with $NaBH(OAc)_3$ and aniline used to isolate the catalytic products (**6a**−**j**), other reductive conditions were examined (Scheme 3). All reactions were performed on the crude Michael product **6a**, and with the exception of product **13**, the enantiomeric excess was maintained. Interestingly, the replacement of aniline with benzylamine under otherwise similar reductive reaction conditions resulted in a mixture of the corresponding amine (not isolated) and lactam **9**. To obtain the lactam in useful yield, a solvent screening was carried out (see Supporting Information) revealing that 1,4-dioxane greatly favored the formation of the lactam (39%, three steps). At −20 °C, $NaBH_4$ gave a facile reduction of both the aldehyde and ester functionality to yield diol **10** (49%, two steps). Pleasingly milder reductive conditions (see Scheme 3) could be employed to furnish alcohol **11** in good yield (58% two steps) without touching the methyl ester. Alcohol **11** allows the formation of lactone **12** using silica (23%).[12]

The stronger reducing agent $LiAlH_4$ rapidly resulted in the decarboxylation of **6a** giving cyano alcohol **13** (52%, two steps) at low temperature (−78 °C); only decomposition of **6a** was obtained at higher temperatures. As the decarbonylation step leads to a loss of chirality at the quaternary center, the replacement of chiral catalyst **VII** by Et_3N in the initial Michael reaction would lead to a useful synthetic methodology for the creation of cyano alcohols, which are structurally similar to **13**.

In conclusion, we have developed the first example of nucleophilic attack from the α-position of an allylic chiral ion pair derived from activated alkylidenes using an easy to prepare cinchona alkaloid catalyst. These highly functionalized catalytic products could be manipulated to give a wide range of useful intermediates that are difficult to obtain via other procedures.

Experimental Section

Representative Procedure for the Enantioselective Addition of Alkylidene Cyanoacetates 4a−j to Acrolein 5 using VII as Catalyst: Alkylidene cyanoacetate **4a**−**j** (0.25 mmol) was dissolved in CH_2Cl_2 (2 mL) and to this acrolein **5** (0.375 mmol, 27.8 μL) was added to a glass vial equipped with a magnetic stirring bar. The mixture was cooled to −78 °C, and at this temperature catalyst **VII** (10 mol %, 0.025 mmol, 13.8 mg) was added. The resulting mixture was placed at −20 °C for the time specified in Table 2 in the main text. The mixture was then cooled to −78 °C and passed quickly through a short pad of Iatrobeads (elute Et_2O) to remove the catalyst. All transformations are carried out on the crude product from this point, and yields quoted are for two or three steps.

2-Cyano-2-(3-oxo-propyl)-pent-3-enoic Acid Methyl Ester 6a. ^1H NMR ($CDCl_3$) δ 9.77 (s, 1H), 6.08 (dq, J = 6.6, 15.4 Hz, 1H), 5.41 (dd, J = 1.6, 15.4 Hz, 1H), 3.81 (s, 3H), 2.56−2.72 (m, 2H), 2.29−2.37 (m, 1H), 2.15−2.23 (m, 1H), 1.77 (dd, J = 1.7, 6.6 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ 199.2, 167.8, 131.3, 124.3, 117.1, 53.8, 50.8, 39.4, 29.5, 17.6. (26 mg, 53% overall yield). The pure product was obtained by flash chromatography on Iatrobeads eluting with CH_2Cl_2 to remove **4a**, followed by CH_2Cl_2/Et_2O 10/1 to give **6a** as a clear oil. MS calcd for $C_{10}H_{13}NO_3$ $[M+Na]^+$, 218.08; found, 218.1 (the compound is too unstable for determination of the exact mass). $[\alpha]^{20}_D$ +20.6 (c = 1.0, CH_2Cl_2, 52% ee). GC Chrompak CP-Chirasil Dex CB-column. Temperature program: from 70 °C to 140 °C at a rate of 10 °C/min, maintained temperature for 5 min, then to 180 °C at a rate of 10 °C/min. τ_{major} = 11.3 min, τ_{minor} = 11.1 min (56% ee).

Representative Procedure for the Reductive Amination of 6a−j with Aniline and $NaBH(OAc)_3$: The crude Michael product **6a**−**j** (0.25 mmol scale reaction) was dissolved in dry DCE (1 mL). Aniline (22.8 μL, 0.25 mmol) and $NaBH(OAc)_3$ (74 mg, 3.5 mmol) were added, and the heterogeneous mixture was stirred under argon at room temperature for 18−20 h. Saturated $NaHCO_3$ (1 mL) was then added, and the mixture was extracted with EtOAc (3 × 1 mL).

(12) Alvarez, E.; Cuvigny, T.; Herve du Penhoat, C.; Julia, M. *Tetrahedron* **1985**, *44*, 119.

The combined organic layers were dried (Na_2SO_4) and evaporated to give a yellow oil. The crude amine was purified by flash chromatography on SiO_2 (eluent: 5−10% EtOAc in hexane) to give **7a**−**j** as clear oils.

2-Cyano-2-(3-phenylamino-propyl)-pent-3-enoic Acid Methyl Ester 7a. The title compound was obtained according to the general procedure (reaction time 18 h) as a colorless oil, yield 44% (two steps). ^{1}H NMR ($CDCl_3$) δ 7.19 (t, J = 8.4 Hz, 2H), 6.72 (t, J = 7.3, 1H), 6.60 (d, J = 7.7 Hz, 2H), 6.09 (dq, J = 6.6, 15.4 Hz, 1H), 5.45 (dd, J = 1.7, 15.4 Hz, 1H), 3.80 (s, 3H), 3.64 (broad s, 1H), 3.17 (t, J = 6.8 Hz, 2H), 2.17 (m, 1H), 1.94 (m, 1H), 1.83 (m, 1H), 1.78 (dd, J = 1.6, 6.5 Hz, 3H), 1.70 (m, 1H). ^{13}C NMR ($CDCl_3$) δ 168.3, 147.9, 130.5, 129.2, 124.9, 117.6, 117.4, 112.7, 53.6, 51.6, 43.0, 35.1, 25.2, 17.6. HRMS calcd for $C_{16}H_{20}N_2O_2$ [M + H]$^+$, 273.1598; found, 273.1593. $[\alpha]^{20}_D$ +16.3 (c = 1.0 CH_2Cl_2, 56% ee). The ee was determined by HPLC using a Chiralcel OD column [hexane/*i*-PrOH (90:10)]; flow rate 1.0 mL/min; τ_{major} = 24.6 min, τ_{minor} = 19.9 min (56% ee).

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Supporting Information Available: Experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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