Proline catalyzed enantioselective Michael additions of unmodified ketones to arylidenes

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A range of proline-catalyzed Michael additions of unmodified ketones to arylidenes have been examined to yield optically active \(\gamma\)-cyanoketones in excellent to moderate yields with low enantioselectivities.

Keywords: Michael additions, \(\gamma\)-cyanoketones, arylidenes, enantioselectivities, \(L\)-proline

The use of \(L\)-proline for the development of enantioselective catalytic protocols in organic synthesis has received much attention. \(L\)-Proline-based catalytic system for asymmetric Michael reactions includes the asymmetric conjugate addition of nitroacetate, malonates, nitroalkanes, and recently pyrroles to \(\alpha,\beta\)-unsaturated carbonyl compounds\(^{1,2}\). In such cases, carbonyl compounds are modified to more reactive species such as enol or enamine equivalents, which required additional synthetic steps, stoichiometric amount of base, additional reagents, etc. Michael additions of unmodified carbonyl compounds to nitro olefins using \(L\)-proline as a functional catalyst were recently reported with very low yields and very low enantioselectivities, \textit{i.e.} enantiomeric excess (ee). The current study explores the \(L\)-proline catalyzed Michael additions of unmodified ketones to arylidenes.

Asymmetric catalysis of organic reactions is one of the main research fields in chemistry\(^5\). Although for many years, asymmetric catalysis was conceptually linked to the use of chiral transition-metal complexes, processes catalyzed by metal-free small organic molecules have recently received significant attention\(^6\). Generally, the substrates are activated by non-covalent interactions, and in this manner, synthetically highly valuable enantioselective transformations are possible by applying well-defined low-molecular weight non-metallic catalysts\(^7\).

The Michael addition reaction is one of the most general and versatile methods for the formation of carbon-carbon bonds in organic synthesis. It is not surprising that the development of enantioselective catalytic protocols for this type of reaction has received much attention. Efforts aimed at achieving asymmetric versions of the process by using chiral organo-catalysts have been explored intensively in recent years\(^6\). Among these organo-catalysts, aminocatalysts have recently gained considerable attention, particularly in asymmetric synthesis\(^10\). Several valuable and broadly applicable transformations, including, Aldol, Michael, Mannich, and Diels-Alder reactions are amenable to aminocatalysis. Previous aminocatalytic Michael reactions are amenable to aminocatalysis.

The stoichiometric use of enamines as nucleophiles in the Michael reaction has been pioneered by Stork et al.\(^{11}\). Seebach \textit{et al.} have thoroughly studied the Michael reactions of preformed enamines with nitro olefins\(^{12}\). Enamine catalysis, however, has been rarely used so far, and no intermolecular examples are known\(^{13}\). Proline has been found to be effective for enamine-based direct catalytic asymmetric aldo\(^{14,15}\), Mannich\(^{16,17}\), Diels-Alder\(^{18,19}\), and \(\alpha\)-amination reactions\(^{20,21}\). \(L\)-Proline and other pyrrolidine-based catalytic systems for asymmetric Michael reactions have also been described\(^{22-24}\). Proline-catalyzed versions of enamine-related reactions have been studied recently. Generally, in Michael reactions, carbon nucleophiles that contain an active methylene center such as malonic acid esters, \(\beta\)-keto esters, nitroalkanes, etc. have been studied\(^{25,26}\). Proline-catalyzed Michael additions of ketones to nitrostyrene were examined by Enders \textit{et al.}\(^{24}\) to obtain optically...
active γ-nitro ketones in medium to excellent yields and up to 97% de of the syn-diastereomers and 76% ee. List and his co-workers also reported the proline-catalyzed Michael addition of unmodified ketones to nitro olefins to provide γ-nitro ketones in moderate enantioselectivity with excellent yields. In most cases, trans-β-nitrostyrene was employed as Michael acceptor. The use of L-proline in the Michael-type reaction of a range of ketones with nitro-olefins has been the subject of two recent independent studies using DMSO or methanol as the solvent; and it was noted that there was a need to improve the enantioselectivities of the reactions or lower the reaction times. Herein, we report the L-proline catalyzed Michael additions of unmodified ketones, 1 to arylidenes, 2 as Michael acceptors which were prepared by Knoevenagel condensation of benzaldehyde with active methylene compounds to give γ-cyano ketones, 3 (Scheme I). The Michael reaction of three different arylidenes with six different ketones was studied. All reactions gave the products in very good yields but with low enantioselectivities. To the best of our knowledge, this is the first report of the utilization of arylidenes as Michael acceptors in the catalytic asymmetric Michael reactions.

Results and Discussion

As a model reaction, we studied the L-proline (10 mol %) catalyzed Michael reaction of acetyl acetone 1a with 2-benzylidenemalononitrile 2a in methanol at room temperature to give 2-(3-oxo-2-acyl-1-phenylbutyl)malononitrile 3a in high yields (94%). But as expected the diastereoselectivity and enantioselectivity were low. Next, the reaction between 3-pentanone 1c with 2-benzylidenemalononitrile 2a in methanol was studied at room temperature to give 2-(3-oxo-2-methyl-1-phenylpentyl)malononitrile 3c. To improve the enantiomeric excess, the reaction was performed with dimethyl sulfoxide (DMSO) and acetonitrile. The use of DMSO gave the product in low yield and the enantioselectivity was slightly increased. With acetonitrile, the enantioselectivity was slightly enhanced but the yield was very low. As has been observed previously, the reaction in methanol gave improved enantioselectivity over DMSO (Ref.24). In the hope of enhancing the enantioselectivity, the reaction was carried out at 0°C. Unfortunately, no beneficial effect was observed. It was also found that reducing the amount of catalyst lowered the yield significantly and had little effect on the enantioselectivities. The optimal amount of catalyst was found to be 15 mol% (Ref.23). Higher the polarity of the solvent, the enantioselectivity was found to be increased.

The optimum reaction conditions for the enantioselective Michael addition of arylidenes were established and a series of analogues which bear various substituents on the terminal double bond of arylidenes, which are derived by condensing benzaldehyde with various active methylene compounds such as, α-cyanoacetamide, ethyl α-cyanoacetate, diethyl malonate, etc were screened. A range of ketones and arylidenes were tested using

![Scheme I](image-url)
these optimization conditions and the results are shown in Table I. Under these conditions, it was found that the yields were generally good (82%) to (96%) and with ee’s ranging from 35% to 57%. The Michael addition of benzylidene cyanoacetamide 2b with ketones 1a, 1b, proceeded with 40-53% ee to afford adducts 3g-h in high yields (entries 7-8). Under, the same conditions, no product was observed with 1a and benzylidene diethylmalonate. For the Michael addition of benzylidene cyanoacetate, the reactivity of 1a was low and the desired product was obtained in very low yield of 10%. However, the

Table I—Michael additions of ketones to arylidenes

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<sup>a</sup> Based on the isolated product.

<sup>b</sup> Determined by chiral HPLC
Michael addition of 2-pentanone 1j with 2e gave high yield (96%) but duration of the reaction was long (7 days).

Experimental Section

All chemicals were used without further purification and all the aldehydes, ketones and metal acetates were obtained from Merck and Aldrich. Infrared (IR) spectra were recorded on Shimadzu FT-IR spectrophotometer in the range of 200-4000 cm⁻¹. All the samples were run on a sodium chloride plate as a liquid film. Infrared (IR) spectra were recorded on Shimadzu FT-IR spectrophotometer. The enantiomeric excess (ee) of the reaction products had the physical constants and NMR spectra in accord with the published data.

2-(Oxoo-3-methyl-2-acetyl-1-phenylpropyl)malononitrile, 3a: Colourless oil; Yield 94%; [α]D = +11.0° (c = 0.10, CHCl₃); ¹H NMR (CDCl₃, 300 MHz): δ 7.19-7.38 (m,5H), 4.50 (s,1H), 4.44 (s,1H), 2.31 (s,1H), 2.06 (s,3H), 1.64 (s,3H). ¹⁳C NMR (CDCl₃, 75 MHz): δ 199.1, 157.4, 143.1, 129.4, 127.9, 127.6, 119.2, 115.0, 62.5, 39.7, 30.0, 19.0; ESI-HRMS Calcd for C₁₅H₁₄N₂O₂ + Na: 277.1104, Found 277.1099; 87% ee determined by HPLC on AS-H column, hexane-isopropanol (70:30), 1.0 mL min⁻¹, UV: 254 nm, t_min = 13.886 min, t_major = 16.383 min.

2-(Oxoo-2-benzoyl-1-diphenylpropyl)malononitrile, 3b: Colourless oil; Yield 92%; [α]D = +11.0° (c = 0.10, CHCl₃); ¹H NMR (CDCl₃, 300 MHz): δ 7.48-7.38 (m,10H), 4.50 (s,1H), 4.44 (s,1H), 2.31 (s,1H), 2.06 (s,3H), 1.64 (s,3H). ¹⁳C NMR (CDCl₃, 75 MHz): δ 199.1, 157.4, 143.1, 129.4, 127.9, 127.6, 119.2, 115.0, 62.5, 39.7, 30.0, 19.0; ESI-HRMS Calcd for C₂₀H₁₆N₂O₂ + Na: 339.0357, Found 339.1002; 87% ee determined by HPLC on AS-H column, hexane-isopropanol (70:30), 1.0 mL min⁻¹, UV: 254 nm, t_min = 11.879 min, t_major = 13.322 min.

2-(Oxoo-2-methyl-1-phenylpentyl)malononitrile, 3c: Colourless oil; Yield 90%; [α]D = -34.0° (c = 0.45, CHCl₃); ¹H NMR (CDCl₃, 300 MHz): δ 7.38-7.46 (m,5H), 4.50 (s,1H), 4.44 (d, J = 5.1 Hz, 1H), 3.43(dd, J = 12.4 Hz, J = 5.0 Hz, 1H), 3.31 (dq, J = 9.6 Hz, J = 7.1 Hz, 1H), 2.76 (dq, J = 18.1 Hz, J = 7.2 Hz, 1H), 2.58 (dq, J = 18.0 Hz, J = 7.3 Hz, 1H), 1.15 (t, J = 7.1 Hz, 1H), 1.01 (d, J = 7.3 Hz, 3H); ¹³C NMR (CDCl₃, 75 MHz): δ 213.7, 134.8, 129.1, 129.0, 128.2, 111.5, 111.3, 47.2, 46.6, 34.9, 27.0, 16.4, 7.6; ESI-HRMS Calcd for C₂₀H₁₆N₂O₂: 239.1243, Found 239.1087; 87% ee determined by HPLC on OJ-H column, hexane-isopropanol (70:30), 1.0 mL min⁻¹, UV: 254 nm, t_min = 12.339 min, t_major = 15.397 min.

2-(Oxoo-1,3-diphenylpropyl)malononitrile, 3d: Spectral data are identical to authentic sample and to those previously reported1.2

2-(1-p-Methoxyphenyl-3-oxo-3-phenylpropyl)malononitrile, 3e: Spectral data are identical to authentic sample and to those previously reported.

2-(3-p-Chlorophenyl-3-oxo-3-phenylpropyl)malononitrile, 3f: Colourless oil; Yield 88%; [α]D = -45.0° (c = 0.20, CHCl₃); ¹H NMR (CDCl₃, 300 MHz): δ 7.88 (d, J = 8.2 Hz, 2H), 7.45 (d, J = 8.2 Hz, 2H), 7.39 (s, 5H), 4.59 (d, J = 5.2 Hz, 1H), 3.90-3.94
(m, 1H), 3.56-3.69 (m, 2H); $^{13}$C NMR (CDCl$_3$, 75 MHz): $\delta$ 195.4, 140.8, 136.3,134.0,129.5, 129.4, 129.3, 127.9,111.7, 111.6, 41.1, 40.1, 28.7; ESI-HRMS Calcd for C$_{15}$H$_7$ClN$_2$O – H: 307.8726, Found 307.7462; 53% ee determined by HPLC on AS-H column, hexane-isopropanol (70:30), 0.8 mL min$^{-1}$, UV: 254 nm, $t_{\text{minor}}$ = 13.307 min, $t_{\text{major}}$ = 16.906 min.

2-(3-Oxo-3-methyl-2-acetyl-1-phenylpropyl)cya-noacetamide, 3g: White solid; Yield 86%; $[\alpha]_D$ = -12.5$^\circ$ (c = 0.20, CHCl$_3$); $^1$H NMR (DMSO-d$_6$, 300 MHz): $\delta$ 9.37 (s, 1H), 7.27-7.40 (m, 5H), 4.20 (d, $J$ = 5.1 Hz, 1H), 3.92 (dd, $J$ = 12.4 Hz, $J$ = 5.0 Hz, 1H), 2.50 (d, $J$ = 7.3 Hz, 1H), 1.82 (s, 3H), 1.37 (s, 3H); $^{13}$C NMR (CDCl$_3$, 75 MHz): $\delta$ 196.4, 164.9, 161.9, 145.2, 135.5, 133.4, 130.8, 130.0, 129.6, 129.3, 129.1, 128.9, 128.7, 128.3, 126.8, 126.1, 115.7, 115.3, 114.3, 40.7, 40.5; ESI-HRMS Calcd for C$_{15}$H$_{16}$N$_2$O$_2$-H: 271.2418, Found 271.2316; 88% ee determined by HPLC on OD-H column, hexane-isopropanol (70:30), 1.0 mL min$^{-1}$, UV: 254 nm, $t_{\text{minor}}$ = 12.312 min, $t_{\text{major}}$ = 19.071 min.

2-(3-Oxo-3-methyl-2-benzoyl-1-phenylpropyl)cyanoacetamide, 3h: Colourless oil; Yield 82%; $[\alpha]_D$ = +11.0$^\circ$ (c = 0.10, CHCl$_3$); $^1$H NMR (CDCl$_3$, 300 MHz): $\delta$ 9.40 (s, 1H), 7.86-7.96 (m, 3H), 7.58-7.61 (m, 1H), 7.45-7.51 (m, 3H), 7.16-7.41 (m, 3H), 4.94 (d, $J$ = 5.2 Hz, 1H), 4.26 (d, $J$ = 7.0 Hz, 1H), 4.06 (dd, $J$ = 12.4 Hz, $J$ = 5.0 Hz, 1H), 1.18 (s, 3H); $^{13}$C NMR (CDCl$_3$, 75 MHz): $\delta$ 196.0, 163.9, 139.5, 138.5, 133.3, 129.2, 128.8, 128.5, 127.9, 127.4, 117.1, 83.4, 52.4, 48.8, 42.4, 41.6, 23.9; ESI-HRMS Calcd for C$_{19}$H$_{15}$N$_2$O$_3$: 357.1348, Found 357.1394; 87% ee determined by HPLC on AS-H column, hexane-isopropanol (70:30), 1.0 mL min$^{-1}$, UV: 254 nm, $t_{\text{minor}}$ = 14.546 min, $t_{\text{major}}$ = 16.213 min.

2-(3-Oxo-3-methyl-1-phenylpentyl)cyanoacetate, 3i: White solid; Yield 96%; $[\alpha]_D$ = -12.5$^\circ$ (c = 0.20, CHCl$_3$); $[\alpha]_D$ = -1.6 (c = 1.0, CHCl$_3$); $^1$H NMR (DMSO-d$_6$, 300 MHz): $\delta$ 7.27-7.33 (m, 5H), 4.21 (d, $J$ = 7.3 Hz, 1H), 3.92-3.95 (m, 1H), 3.11 (m, 2H), 2.34-2.44 (m, 3H), 1.54-1.57 (m, 3H), 0.89 (t, $J$ = 7.1 Hz, 1H); $^{13}$C NMR (CDCl$_3$, 75 MHz): $\delta$ 208.4, 165.1, 139.4, 138.3, 129.1, 129.0, 128.1, 115.7, 63.1, 45.4, 44.1, 40.7, 17.3, 13.9; ESI-HRMS Calcd for C$_{17}$H$_{15}$NO$_3$ + Na: 310.2391, Found 310.1987; 88% ee determined by HPLC on OD-H column, hexane-isopropanol (70:30), 1.0 mL min$^{-1}$, UV: 254 nm, $t_{\text{minor}}$ = 15.876 min, $t_{\text{major}}$ = 19.253 min.

Conclusion

In conclusion, a novel proline-catalyzed Michael reaction of unmodified ketones to arylidines has been developed. Important features of this reaction are that yields are typically excellent and the reactions are operationally simple and do not require inert atmosphere, temperature manipulations, metal salts, or preformed enolate equivalents. The improvement of the enantioselectivity of this new reaction is in progress.

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References