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Organocatalytic conjugate addition of 2-arylacetates and 2-arylacetonitriles having an electron-withdrawing group to α,β-unsaturated ketones

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ABSTRACT

A catalytic conjugate addition reaction of 2-arylacetates and 2-arylacetonitriles having an electron-withdrawing group to α,β-unsaturated ketones has been established using pyrrolidine as a catalyst. The reagents having NO_2^-, CO_2Me-, and CN-functional groups on the aromatic ring can be used; the reaction with various α,β-unsaturated ketones provided the Michael addition products in good yields.

The conjugate addition reaction of carbon nucleophiles to electron-poor alkenes is a powerful tool for forming a carbon–carbon bond formation in organic synthesis; consequently, it helps generate a diverse array of products.[1] Versatile activated methylenes, such as 1,3-diketones, 1,3-dinitriles, ketoesters, malonate esters, and nitroesters are valuable nucleophiles for conjugate addition to ,β-unsaturated nitriles and carbonyls. In particular, this reaction has attracted attention in asymmetric organocatalytic reactions in recent years.[2] The adducts of conjugate addition provide synthetically useful blocks for the synthesis of biologically active natural products and pharmaceutical compounds.[3] However, despite belonging to an important class of nucleophiles, simple less reactive activated methylenes such as benzylesters are not employed in asymmetric organocatalytic reactions since they do not easily participate in conjugate addition of enones.[4,5]

A numerous natural products including rubioncolin B,[6] flustramine B,[7] (−)-siccanin,[8] and (−)-morphine[9] have a chiral center at the benzylic position. Many efforts have been made to introduce a stereogenic center at the benzylic position. Therefore, less reactive methylenes such as benzylesters to α,β-unsaturated carbonyls, which enables the leading intermediates to be used in the synthesis of natural products is of considerable importance. However, developing these methylenes as nucleophiles in an asymmetric organocatalytic reaction is still a challenging task. Herein, we report the conjugate addition of 2-arylacetates and 2-arylacetonitriles having an electron-withdrawing group to α,β-unsaturated ketones using an organocatalyst.

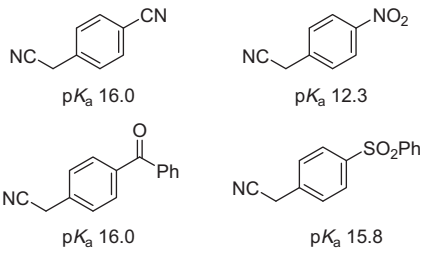

Figure 1. Benzylcyanide derivatives having an electron-withdrawing group.

Benzylcyanide (pK_a 22) and benzylester (ethyl 2-phenylacetate, pK_a 23) are less acidic than malonate esters (diethyl malonate, pK_a 16) and 1,3-dinitrile (malononitrile, pK_a 11), making it difficult to use them as nucleophiles in an organocatalytic conjugate addition reaction. However, addition of an electron-withdrawing group to the phenyl ring lowers the pK_a values of benzylcyanide and benzylester. The pK_a values for 4-(cyanomethyl)-benzonitrile and 2-(4-nitrophenyl)acetonitrile are 16 and 12, respectively (Fig. 1).[10] Thus, we envisioned that organocatalytic conjugate addition would be possible if benzylester containing an electron-withdrawing group was used instead of just benzylester. However, to the best of our knowledge, the use of this compound as nucleophile in conjugate addition reactions has never been reported.

The conjugate addition reaction of methyl 2-(4-nitrophenyl)acetate **2a** to (*E*)-4-phenylbut-3-en-2-one **3a** was selected as the model reaction (Table 1). The pyrrolidinyl tetrazole catalyst **1a** (Fig. 1) was initially examined as an organocatalyst in this reaction since this

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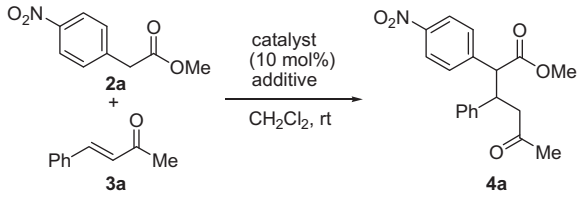
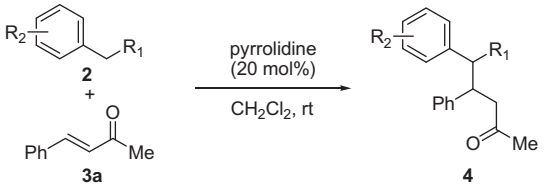
Table 1
Organocatalytic conjugate addition of methyl 2-(4-nitrophenyl)acetate (**2a**) to (*E*)-4-phenylbut-3-en-2-one (**3a**)[a]



Entry	Catalyst	Additive	Time (h)	Yield[b] (%)
1	**1a**	—	24	No rxn
2	**1a**	Bn_2NH (1 equiv)	24	No rxn
3[c]	**1a**	K_2CO_3 (1 equiv)	36	76
4	**1a**	Piperidine (1 equiv)	56	72
5	**1a**	Pyrrolidine (1 equiv)	12	89
6	**1a**	Pyrrolidine (10 mol %)	36	85
7	**1b**	Pyrrolidine (1 equiv)	12	91
8	**1b**	Pyrrolidine (10 mol %)	32	84
9	—	Pyrrolidine (1 equiv)	24	76
10	—	Pyrrolidine (10 mol %)	24	90

[a] Unless otherwise specified, the reaction was carried out in CH_2Cl_2 (0.5 M) with 1.5 equiv of **2a** relative to **3a** in the presence of 10 mol % catalyst and additive.
[b] Isolated yield after chromatographic purification.
[c] Performed in DMF.

Table 2
Organocatalytic conjugate addition of 2-arylacetate and 2-arylacetonitrile to (*E*)-4-phenylbut-3-en-2-one (**3a**)[a]



Entry	R_1	R_2	Product	Time (h)	Yield[b] (%)	dr[c]
1	CO_2Me	*p*-NO_2	**4a**	24	95	53:47
2	CO_2Me	*o*-NO_2	**4b**	48	64	60:40
3[d]	CO_2Me	*p*-CO_2Me	**4c**	48	54	54:46
4	CN	*p*-NO_2	**4d**	24	99	64:36
5	CN	o-NO_2	**4e**	24	71	53:47
6	CN	*p*-CO_2Me	**4f**	40	77	60:40
7[d]	CN	*o*-CO_2Me	**4g**	48	65	52:48
8	CN	*p*-CN	**4h**	24	90	64:36
9	CN	*o*-CN	**4i**	40	99	51:49
10	CN	H	**4j**	24	No rxn	

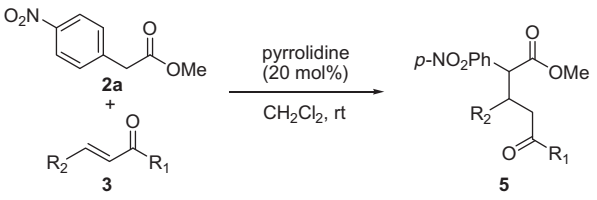
[a] Unless otherwise specified, the reaction was carried out in CH_2Cl_2 (0.5 M) with 1.5 equiv of **2** relative to **3a** in the presence of 20 mol % of pyrrolidine.
[b] Isolated yield after chromatographic purification.
[c] Determined by ^1H NMR analysis.
[d] 1 equiv of pyrrolidine was added.

catalyst **1a** has gave the product in good yield with high enantioselectivity for the conjugate addition reaction of malonate to α,β-unsaturated enones.[11] No reaction was observed in the absence of additive base and when dibenzylamine was used as a base after 24 h at room temperature (entries 1 and 2). The reaction proceeded to furnish the corresponding product **4a** in moderate yields using K_2CO_3 and piperidine as the base (entries 3 and 4). The pyrrolidine additive afforded the desired product **4a** with good reactivity (entries 5 and 6) even using of catalytic amount. Under these conditions, L-proline **1b** readily catalyzed the conjugate addition reaction of methyl 2-(4-nitrophenyl)acetate **2a** to (*E*)-4-phenylbut-3-en-2-one **3a** resulting in a good yield (entries 7 and 8).[12] However, unfortunately, the pyrrolidinyl tetrazole catalyst **1a** and L-proline **1b** did not provide the chiral product **4a** in this reaction. Additionally, we found that pyrrolidine alone could promote and even more catalyze this reaction without **1a** or **1b** (entries 9 and 10).[12]

Although this conjugate addition reaction does not achieve enantiocontrol, we decided to explore the scope of this new process. Firstly, this reaction proved to be general for a variety of benzylcyanides and benzylesters having an electron-withdrawing group **2**. As revealed in Table 2, the reactions proceeded in good yields in the case of both 2-arylacetate and 2-arylacetonitrile. Reagents having a CO_2Me-functional group on the aromatic ring showed relatively lower reactivities than those having NO_2^- and CN-functional groups (entries 3, 6 and 7). As expected, the conjugate addition reaction of 2-phenylacetonitrile (benzylcyanide) to (*E*)-4-phenylbut-3-en-2-one **3a** did not occur (entry 10).

The addition of methyl 2-(4-nitrophenyl)acetate **2a** to various α,β-unsaturated ketones **3** was also evaluated and some representative results are shown in Table 3. The conjugate addition of 2-(4-nitrophenyl)acetate **2a** to aromatic α,β-unsaturated methyl ketones exhibited good results. Significant structural variation in aromatic α,β-unsaturated methyl ketones was tolerated in this reaction, which occurred efficiently, independent of the nature of

Table 3
Organocatalytic conjugate addition of methyl 2-(4-nitrophenyl)acetate (**2a**) to α,β-unsaturated ketones[a]



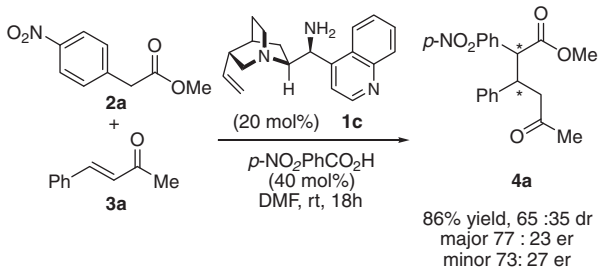
Entry	R_1	R_2	Product	Time (h)	Yield[b] (%)	dr[c]
1	Me	*p*-MePh	**5a**	24	99	53:47
2	Me	*p*-MeOPh	**5b**	48	79	53:47
3	Me	*p*-ClPh	**5c**	48	88	53:47
4	Me	*p*-BrPh	**5d**	48	93	53:47
5	Me	*p*-NO_2Ph	**5e**	48	63	58:42
6	Me	1-Naphthyl	**5f**	32	94	57:43
7	Me	2-Furyl	**5g**	48	60	55:45
8	$-(CH_2)_2-$		**5h**	24	93	59:41
9	$-(CH_2)_3-$		**5i**	24	99	52:48

[a] Unless otherwise specified, the reaction was carried out in CH_2Cl_2 (0.5 M) with 1.5 equiv of **2a** relative to **3** in the presence of 20 mol % of pyrrolidine.
[b] Isolated yield after chromatographic purification.
[c] Determined by ^1H NMR analysis

the substituents on the aromatic ring, where electron-donating (entries 1 and 2) and electron-withdrawing groups (entries 3–5) are presented. Furthermore, conjugate aromatic and heteroaromatic α,β-unsaturated methyl ketones can participate in the processes as well (entries 6 and 7). Finally, we confirmed that 2-cyclopenten-1-one and 2-cyclohexen-1-one were suitable for use in this reaction (entries 8 and 9).

We are also developing an asymmetric variant of this reaction. For example, the reaction of methyl 2-(4-nitrophenyl)acetate **2a** to (*E*)-4-phenylbut-3-en-2-one **3a** in the presence of catalyst **1c** furnished the corresponding product **4a** in good yields and with moderate enantioselectivities (Scheme 1).

In summary, we described organocatalytic conjugate addition reaction of 2-arylacetates and 2-arylacetonitriles having an



Scheme 1. Asymmetric organocatalytic conjugate addition of methyl 2-(4-nitrophenyl)acetate (**2a**) to (*E*)-4-phenylbut-3-en-2-one (**3a**).

electron-withdrawing group to α,β-unsaturated ketones using pyrrolidine as a catalyst.

The reagents having NO_2^-, CO_2Me-, and CN-functional group on the aromatic ring can be used and the reaction with various α,β-unsaturated ketones provided the Michael addition products in good yields. Current work focuses on expanding the scope of this reaction to other substrates such as α,β-unsaturated aldehydes and α,β-unsaturated nitriles, and on developing an efficient catalytic asymmetric variant.

Acknowledgments

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12. *General procedure for the synthesis of* **4** *and* **5**. To a solution of α,β-unsaturated ketones **3** (0.30 mmol) in CH_2Cl_2 (0.6 mL) at room temperature was added pyrrolidine (0.060 mmol) followed by addition of 2-arylacetate or 2-arylacetonitrile **2** (0.45 mmol). The resulting solution was stirred at room temperature until complete consumption of α,β-unsaturated ketones **3** was observed as determined by TLC. The resulting mixture was direct purified by silica gel chromatography to afford desired compounds **4** and **5**.
methyl 2-(4-nitrophenyl)-5-oxo-3-phenylhexanoate (**4a**). Prepared by the general procedure from (*E*)-4-phenylbut-3-en-2-one **3a** (44 mg, 0.30 mmol), methyl 2-(4-nitrophenyl)acetate **2a** (88 mg, 0.45 mmol) and pyrrolidine (52 μL, 0.060 mmol) in CH_2Cl_2 (0.6 mL) for 12 h to provide the desired compound as an white solid (major: 51 mg, 50% yield, R_f = 0.32 (EtOAc/hexanes = 1/3, v/v), minor: 46 mg, 45% yield, R_f = 0.22 (EtOAc/hexanes = 1/3, v/v)) after silica gel chromatography in 30% EtOAc/hexanes.
Major: mp 162–163 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23 (d, J = 8.8 Hz, 2H), 7.66 (d, J = 8.8 Hz, 2H), 7.24–7.35 (m, 5H), 4.06 (d, J = 11.2 Hz, 1H), 3.96 (ddd, J = 3.6, 9.6, 11.2 Hz, 1H), 3.42 (s, 3H), 2.71 (dd, J = 9.6, 16.8 Hz, 1H), 2.41 (dd, J = 3.6, 16.8 Hz, 1H), 1.86 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 206.1, 171.6, 147.7, 144.0, 140.7, 129.8, 128.7, 128.0, 127.4, 124.0, 57.3, 52.2, 46.8, 44.4, 30.7; MS m/z (%) 341 (M^+, 10), 309 (13), 283 (17), 237 (21), 195 (50), 147 (65), 43 (100); Anal. Calcd for $C_{19}H_{19}NO_5$: C, 66.85; H, 5.61; N, 4.10. Found: C, 66.93; H, 5.47; N, 4.01.
Minor: mp 132–133 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (d, J = 8.8 Hz, 2H), 7.31 (d, J = 8.8 Hz, 2H), 6.98–7.15 (m, 5H), 3.90–4.00 (m, 2H), 3.73 (s, 3H), 3.00 (dd, J = 8.4, 16.4 Hz, 1H), 2.87 (dd, J = 4.0, 16.4 Hz, 1H), 2.03 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 206.0, 172.3, 147.0, 144.1, 139.8, 129.6, 128.5, 128.0, 127.1, 123.4, 57.1, 52.6, 48.2, 44.7, 30.5; MS m/z (%) 341 (M^+, 11), 310 (15), 282 (13), 237 (22), 195 (48), 147 (64), 43 (100); Anal. Calcd for $C_{19}H_{19}NO_5$: C, 66.85; H, 5.61; N, 4.10. Found: C, 66.80; H, 5.78; N, 3.72.