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Enantioselective addition of anthrones to α,β-unsaturated aldehydes

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ABSTRACT

The first examples of enantioselective addition of anthrones to α,β-unsaturated aldehydes are disclosed. The reaction was performed at −40 °C achieving high yields and enantioselectivities.

Since the rediscovery of proline as organocatalyst by List et al.,[1] and the first example of imonium catalysis reported by MacMillan soon after in the Diels–Alder reaction,[2] the field of organocatalysis has grown exponentially. α,β-Unsaturated aldehydes have been widely used as Michael acceptors in a huge variety of reactions catalyzed by chiral secondary amines, achieving high levels of enantioselectivity.[3]

In our research group, we focused on the development of new asymmetric methodologies based on organocatalysis.[4] Interested by new methodologies that allow us to form C–C bonds in an enantioselective fashion, we turned our attention to the addition of anthrones to α,β-unsaturated aldehydes.

Anthrones usually behave as reactive dienes toward a variety of dienophiles, in the presence of base and in aprotic solvents, as first demonstrated by Rickborn and co-workers.[5] More recently, Tan and co-workers reported the enantioselective Diels–Alder cycloaddition of anthrones with maleimides catalyzed by chiral bicyclic guanidines which takes place with excellent yields and enantioselectivities (Scheme 1).[6]

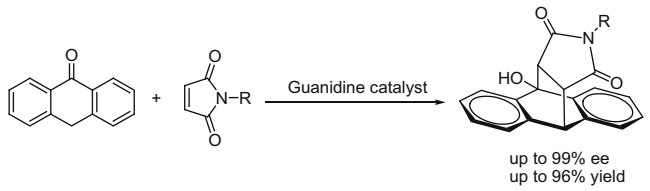
On the other hand, anthracenolate ion generated from the deprotonation of anthrone usually leads to consecutive double Michael reactions (Scheme 2a).[7]

In 2007, Shi et al. described a highly enantioselective addition of anthrones to nitroalkenes catalyzed by Cinchona alkaloid derivatives (Scheme 2b).[8]

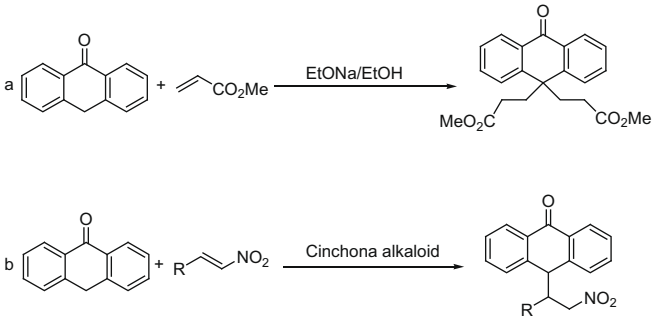
With this information in mind, and based on our previous experience in organocatalysis, we were interested to study the unprecedented addition of anthrones to α,β-aldehydes catalyzed by secondary amines in order to determine the nature of the addition (Scheme 3)

To our delight, when anthrone **1a** was added to cinnamaldehyde in toluene using different chiral amines as catalysts, only the Michael addition product was obtained (Table 1).

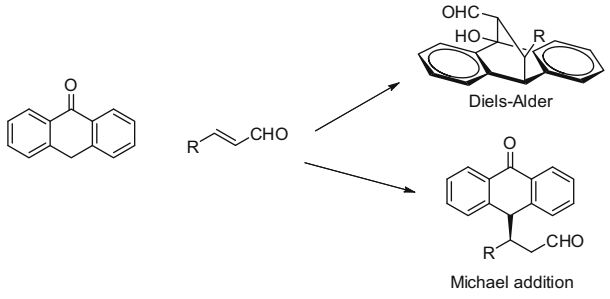
Next we decided to optimize the reaction conditions in order to achieve high yields and enantioselectivities. In an initial solvent



Scheme 1. Anthrone addition to maleimides.



Scheme 2. Michael addition of anthrones.



Scheme 3. Expected products.

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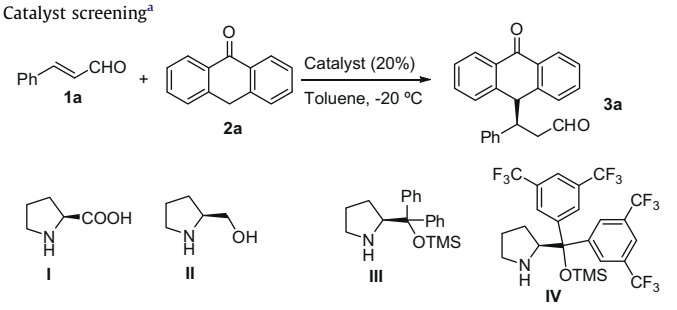
Table 1
Catalyst screening[a]



Entry	Catalyst	Time (h)	Conversion[b] (%)	ee[c] (%)
1	**I**	48	8	0
2	**II**	48	23	0
3	**III**	48	76	48
4	**IV**	48	Traces	n.d.

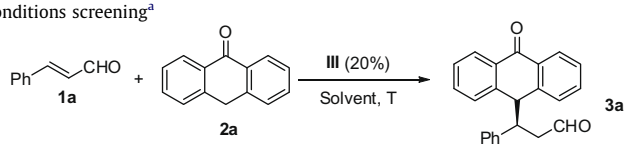
[a] Experimental conditions: A mixture of **1a** (0.25 mmol), catalyst (20%), and **2a** (0.30 mmol) in toluene (1 mL) was stirred at −20 °C for 48 h.
[b] Conversion determined by NMR analysis of the crude reaction.
[c] ee determined by chiral HPLC analysis.

screening, we found that amine **III** efficiently catalyzes the reaction at room temperature, although no significant enantioselective induction was observed (Table 2, entry 1). For this reason, we performed the reaction at lower temperature. We were pleased to find that at −40 °C the enantiomeric excess of the product was increased to 80% (Table 2, entry 5). Furthermore, the use of different additives such as acids (entry 6) and hydrogen bond donors (entry 7) did not bring about any positive effects in terms of yield or selectivity.

Once we found suitable reaction conditions for the enantioselective addition of anthrones to cinnamaldehyde, we studied the scope of the reaction with different unsaturated aldehydes, as shown in Table 3.

Gratifyingly, in all cases the anthrone addition took place with good yields and enantioselectivities. For example, when *para*-nitro cinnamaldehyde was used, the addition product was obtained in 75% yield and 78% ee (entry 3). Surprisingly, when 4-cyanocinnamaldehyde was used, the reaction proceeded extremely well, affording the final adduct **3b** in 85% yield and 99% ee (entry 2). When aliphatic unsaturated aldehydes were used, the reaction took place with high yields and enantioselectivities (entries 4–7). Further studies show that the final adducts racemize very fast, probably due to a retro-Michael process, especially when aromatic aldehydes are used. This could be the reason why we obtained better enantioselectivities with aliphatic aldehydes.

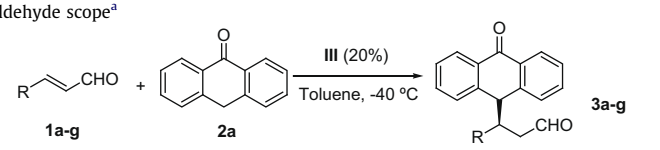
Table 2
Conditions screening[a]

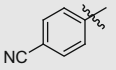
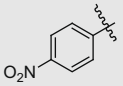


Entry	Solvent	*T*	Time (h)	Conversion [b] (%)	ee[c] (%)
1	Toluene	rt	3	100	4
2	Toluene	−20 °C	48	76	48
3	CH_2Cl_2	−30 °C	24	43	14
4	Toluene	−30 °C	72	48	63
5	Toluene	−40 °C	240	23	80
6[d]	Toluene	−40 °C	48	33	54
7[e]	Toluene	−40 °C	48	23	60

[a] Experimental conditions: A mixture of **1a** (0.25 mmol), catalyst (20%), and **2a** (0.30 mmol) in solvent (1 mL) was stirred at temperature reported in the table.
[b] Conversion determined by NMR analysis of the crude reaction.
[c] ee determined by chiral HPLC analysis.
[d] 0.2 mmol of benzoic acid added.
[e] 0.2 mmol of Schreiner's thiourea added.

Table 3
Aldehyde scope[a]



Entry	Product	R	Time	Yield[b] (%)	ee[c] (%)
1	**3a**		36 d	88	80
2[d]	**3b**		5 d	85	99
3	**3c**		36 d	75	78
4	**3d**	Me	10 d	95	94
5	**3e**	Et	10 d	82	96
6	**3f**	*n*-Pr	10 d	84	96
7	**3g**	*n*-Bu	10 d	92	86

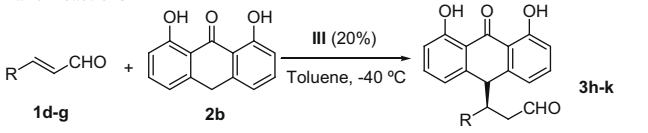
[a] Experimental conditions: A mixture of **1a–g** (0.25 mmol), catalyst **III** (20%), and **2a** (0.30 mmol) in toluene (1 mL) was stirred at −40 °C for the time reported in the table. After full conversion the crude product was purified by column chromatography.
[b] Isolated yield.
[c] ee determined by chiral HPLC analysis.
[d] Reaction run at −30 °C.

Spurred by these results, next we tried to expand this methodology to dithranols. It is well known that anthranols are more nucleophilic than anthrones, so that normally only 1,4 addition is observed. For example, Tan and coworkers reported that while anthrones react with maleimides affording the expected Diels–Alder adducts, dithranol only gives the 1,4-Michael addition.[6]

As expected, when dithranol was used in our reaction with α,β-unsaturated aldehydes, only Michael addition was observed. In order to study the scope of the process, dithranol **2b** was reacted with different aliphatic aldehydes as shown in Table 4. In all the examples, we obtained the final adducts in good yields and in very high enantioselectivities. Unfortunately, when aromatic aldehydes were used, only complex mixtures were obtained.

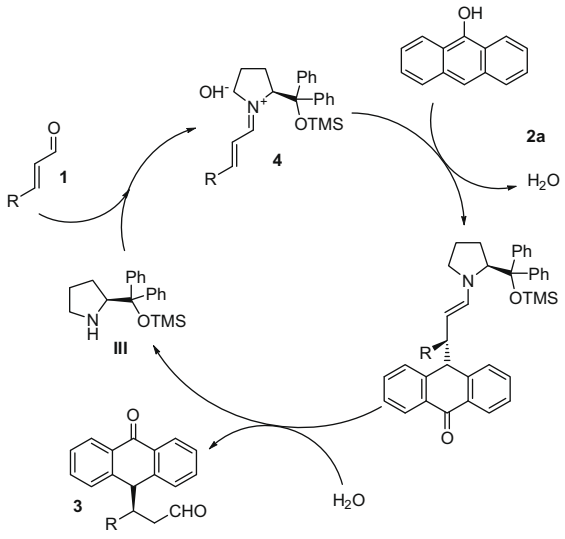
Tentatively, we assign the absolute configuration of adducts **3** by assuming that the mechanism and transition states are similar to those described for other organocatalytic Michael additions catalyzed by diphenylprolinol derivatives reported in the litera-

Table 4
Dithranol reactions[a]



Entry	Product	R	Time	Yield [b] (%)	ee[c] (%)
1	**3h**	Me	10 d	88	97
2	**3i**	Et	10 d	95	99
3	**3j**	*n*-Pr	10 d	93	99
4	**3k**	*n*-Bu	10 d	92	99

[a] Experimental conditions: A mixture of **1d–g** (0.375 mmol), catalyst **III** (20%), and **2b** (0.25 mmol) in toluene (1 mL) was stirred at −40 °C for the time reported in the table. After full conversion the crude product was purified by column chromatography.
[b] Isolated yield.
[c] ee determined by chiral HPLC analysis.



Scheme 4. Proposed mechanism and stereochemical outcome.

ture.[4c,9] Thus, efficient shielding of the Si-face of the chiral iminium intermediate **4** by the bulky aryl groups of chiral pyrrolidine **III**, leads to stereoselective Re-facial nucleophilic conjugate addition by anthrone in enol form, as shown in Scheme 4.

In summary, we have reported a highly chemo- and enantioselective anthrone addition to α,β-unsaturated aldehydes. The reaction is efficiently catalyzed by commercially available chiral pyrrolidine derivatives and gives the corresponding adducts in high yields and in moderate to excellent enantioselectivities.[10] Mechanistic studies, synthetic applications of this new methodology, and the discovery of new reactions based on this concept are ongoing in our laboratory.

Acknowledgments

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10. *Typical experimental procedure for the synthesis of compound* **3j**: To a stirred solution of catalyst **III** (16 mg, 0.05 mmol, 20 mol %) in toluene (1.0 mL), were added *E*-2-hexenal **1f** (37 mg, 0.375 mmol, 1.0 equiv), and dithranol **2b** (57 mg, 0.25 mmol, 1.0 equiv). The reaction mixture was vigorously stirred at −40 °C for 10 days. Next, the crude product was purified by silica gel chromatography (hexane/EtOAc mixtures) to give the corresponding dithranol derivative **3j**. Compound **3j**: Colorless oil. ^{1}H NMR (400 MHz. $CDCl_3$, TMS_{int}): δ (ppm) = 12.12 (d, J = 2.6 Hz, 2H), 9.56 (t, J = 1.6 Hz, 1H), 7.52–7.46 (m, 2H), 6.95–6.90 (m, 3H), 6.85–6.82 (m, 1H), 4.33 (d, J = 3.1 Hz, 1H), 2.50–2.41 (m, 1H), 2.29 (ddd, J^1 = 1.6 Hz, J^2 = 6.6 Hz, J^3 = 17.4 Hz, 1H), 2.03 (ddd, J^1 = 1.8 Hz, J^2 = 6.9 Hz, J^3 = 17.4 Hz, 1H), 1.38–1.20 (m, 4H), 0.86 (t, J = 7.1 Hz, 3H). ^{13}C NMR (100 MHz. $CDCl_3$): δ (ppm) = 201.3, 193.8, 162.6, 144.9, 144.2, 136.2, 136.1, 119.6, 119.5, 116.5, 116.4, 116.3, 45.1, 44.6, 44.1, 32.5, 20.5, 13.9. $[\alpha]_D^2$5 −5.7 (*c* 1.0, $CHCl_3$, 99% ee). HRMS(ESI): calcd for $[C_{20}H_{20}NaO_4]^+$: 347.1254; found: 347.1255. HPLC (Chiralpak® IC, 1 mL min^{-1}, hexanes:IPA 90:10, 254 nm): t_R = 17 min (major), 27 min (minor).