Enantioselective organocatalytic Michael additions to acrylic acid derivatives: generation of all-carbon quaternary stereocentres†

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Acrylic esters, thioesters and *N*-acryloyl pyrrole have been identified as effective electrophiles in the enantioselective Michael addition reaction with β-keto ester pro-nucleophiles catalysed by a cinchona alkaloid derived bifunctional organocatalyst; enantiomeric excesses of up to 98% and yields of up to 96% can be obtained for a range of Michael acceptors and pro-nucleophiles.

The asymmetric Michael addition of acidic methine pro-nucleophiles to electron deficient alkenes is a direct and powerful method for the production of all-carbon quaternary stereogenic centers bearing pendant functionality amenable to further derivatisation. Since Wynberg's description[1] of the cinchona alkaloid catalysed addition of cyclic β-keto esters to methyl vinyl ketone, several examples of catalytic asymmetric Michael additions of carbon acids to the simplest, β-unsubstituted Michael acceptors leading to adducts in high enantiomeric excess have been reported. α,β-Unsaturated ketones,[2,3] acrolein,[2,3] acrylonitrile[4] vinyl sulfones[4] and ethylidene bisphosphonate esters[5] are all effective electrophiles using both metal-[2] and metal-free catalysis.[3–5] Asymmetric Michael additions to acrylate derivatives leading to adducts with tertiary stereogenic centres in moderate to high enantiomeric excesses are known through chiral phase transfer catalysis,[6] however, the direct formation of acrylate Michael adducts bearing fully substituted quaternary stereogenic centres in high enantiomeric excess under catalytic metal-free conditions has, to our knowledge, yet to be reported, despite the synthetic potential of such a methodology.[6e,7] Through employment of cinchona alkaloid-derived bifunctional organocatalysts developed in our, and other, laboratories (Fig. 1),[8–10] we believed the discovery of a highly enantioselective variant was plausible and accordingly began investigations.

Initial studies were required to assess the reactivity profile of various acrylate esters. Indanone-derived β-keto ester **2** was chosen as the test pro-nucleophile on the basis of its high reactivity in other Michael addition reactions. Ethyl acrylate **3a**, ethyl thioacrylate **3b** and 1-naphthylthioacrylate **3c** were then screened in the reaction using 3 equivalent of Michael acceptor and DABCO (1,4-diazabicyclo[2.2.2]octane) at 10 mol% as catalyst. The results are presented in Table 1.

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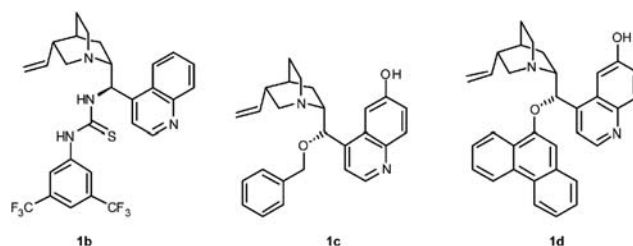

Fig. 1 Bifunctional cinchona alkaloid-derived organocatalysts.

With either ethyl acrylate **3a** and ethyl thioacrylate **3b** none of the desired Michael adducts were observed after stirring in CH_2Cl_2 at room temperature for 7 days. However, with 1-naphthylthioacrylate **3c** rapid and clean conversion to the desired Michael adduct **4c** was observed (entry 3, >95% conversion after 30 min). With suitable reactivity established, attention turned towards the development of the catalytic asymmetric variant. An encouraging 40% ee was observed using 10 mol% catalyst **1b**,[8a–c] however this could be increased significantly to 82% by the use of catalyst **1c**[4a,8f–i] instead. Optimisation of this result by examination of various reaction parameters resulted in a further increase of ee to 90%; finally, a change of catalyst to the slightly bulkier phenanthrene substituted catalyst **1d**[4a,8f–i] further increased the ee to 96%.

Table 1 Reactivity and optimisation studies[a]

2

3a: X = O, R = Et
3b: X = S, R = Et
3c: X = S, R = 1-naphthyl

4a: X = O, R = Et
4b: X = S, R = Et
4c: X = S, R = 1-naphthyl

Entry	E⁺	Cat.	Solv.	c^b/M	T/°C	Conv.[c] (%)	ee[d] (%)
1	**3a**	**1a**	CH_2Cl_2	1	r.t.	0	—
2	**3b**	**1a**	CH_2Cl_2	1	r.t.	0	—
3	**3c**	**1a**	CH_2Cl_2	1	r.t.	>95	—
4	**3c**	**1b**	CH_2Cl_2	1	r.t.	>95	40
5	**3c**	**1c**	CH_2Cl_2	1	r.t.	>95	82
6	**3c**	**1c**	CH_2Cl_2	1	0	>95	86
7	**3c**	**1c**	CH_2Cl_2	1	−20	>95	88
8	**3c**	**1c**	CH_2Cl_2	0.33	−20	>95	90
9	**3c**	**1c**	PhMe	0.33	−20	>95	82
10	**3c**	**1c**	THF	0.33	−20	>95	74
11	**3c**	**1d**	CH_2Cl_2	0.33	−20	>95	96

[a] Reaction was carried out using 3 equivalents of Michael acceptor and 10 mol% catalyst: see ESI† for experimental details and full optimisation table. [b] Concentration of **2**. [c] Determined by ¹H NMR analysis. [d] Determined by HPLC.

The tolerance of these optimised reaction conditions towards a variety of pro-nucleophiles was then investigated (Table 2). Substituted indanone esters **5** and **6** gave comparable results to those obtained using indanone ester **2** (entries 2 and 3); regioisomeric 2-indanone derivative **7** gave a slightly lower ee of 88% (entry 4). Cyclopentanone and cyclohexanone derivatives **8** and **9** were also found to be good substrates giving rise to the Michael adducts with high enantiocontrol, albeit with a prolonged reaction time in the latter case (entries 5 and 6). Notably, the hexafluoroisopropyl esters were found to be far superior to the *tert*-butyl ester analogues;[3a] cyclopentanone derivative **10**, bearing a *tert*-butyl ester moeity, gave only 67% ee after 18 h (entry 7) and its cyclohexyl analogue was found to be completely unreactive under the reaction conditions. Acyclic β-keto ester **11** was also found to react with **3c**, albeit more slowly and with a reduced enantioselectivity; product **18c** was obtained in 58% yield and 71% ee (entry 8).[11]

Next, the scope of the reaction with respect to the Michael acceptor was investigated. Comparable results were observed using thioacrylates **3d** and **3e** (entries 9 and 10); the reaction could also be extended to encompass the use of acrylate esters

Table 2 Scope of the Michael addition reaction[a]

Pro-nucleophiles:

2: X = Y = H
5: X = H, Y = Br
6: X = OMe, Y = H

7

8: n = 1, R = CH(CF₃)₂
9: n = 2, R = CH(CF₃)₂
10: n = 1, R = ᵗBu

11

Michael acceptors:

3c: Z = S, R⁴ = 1-naphthyl
3d: Z = S, R⁴ = 2-naphthyl
3e: Z = S, R⁴ = phenyl

3f: Z = O, R⁴ = 1-naphthyl
3g: Z = O, R⁴ = 2-naphthyl
3h: Z = O, R⁴ = phenyl
3i: Z-R⁴ = N-pyrrole

Entry	Pro-nucleophile	Michael acceptor	t/h	Yield (%)	ee[b] (%)	Product
1	**2**	**3c**	2	83	96	**4c**
2	**5**	**3c**	0.5	78	93	**12c**
3	**6**	**3c**	0.5	90	94	**13c**
4	**7**	**3c**	1	95	88	**14c**
5	**8**	**3c**	1	75	95	**15c**
6	**9**	**3c**	96	52	98	**16c**
7	**10**	**3c**	18	64	67	**17c**
8	**11**	**3c**	120	58	71	**18c**
9	**2**	**3d**	2	75	95	**4d**
10	**2**	**3e**	2	83	95	**4e**
11	**2**	**3f**	72	83	94	**4f**
12	**2**	**3g**	72	76	94	**4g**
13	**2**	**3h**	72	78	94	**4h**
14	**2**	**3i**	3	96	95	**4i**

[a] Reaction was carried out in CH₂Cl₂ at −20 °C using 3 equivalents of Michael acceptor and 10 mol% catalyst: see ESI† for full experimental details. [b] Determined by HPLC.
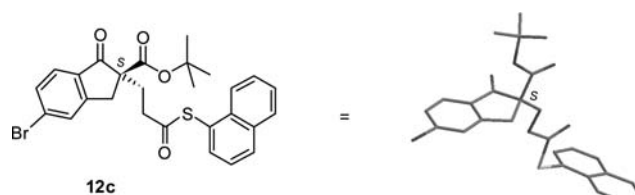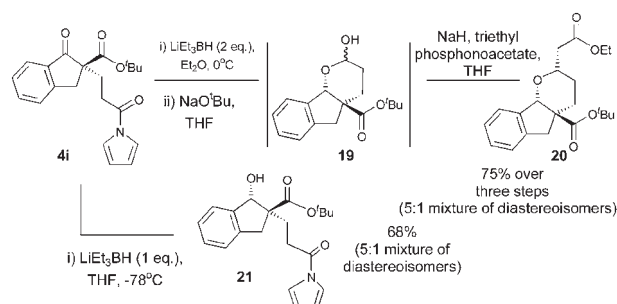
Fig. 2 Determination of absolute stereochemistry.

Scheme 1 Manipulation of *N*-acryloyl pyrrole Michael adduct **4i**.

such as **3f**, **3g** and **3h** (entries 11, 12 and 13). Recrystallisation of adduct **12c** to enantiopurity followed by single-crystal X-ray diffraction analysis allowed the *S* absolute stereochemical configuration of the major enantiomer to be assigned (Fig. 2). The absolute stereochemical configuration of all the other products was assigned by analogy.

The success of *N*-acryloyl pyrrole **3i** (entry 14) in this reaction is significant as *N*-acylpyrroles are valuable synthetic intermediates due to the unusual stability of the tetrahedral intermediate formed upon addition of a nucleophile.[12] To demonstrate this utility, adduct **4i** was treated sequentially with Super-hydride® followed by sodium *tert*-butoxide to generate lactol **19**; Wadsworth–Horner–Emmons olefination then afforded tetrahydropyran **20** (Scheme 1). The product was isolated as a 5 : 1 mixture of diastereoisomers; the stereochemistry of **20** as depicted in Scheme 1 was supported by NOE experiments on **20** itself and partially reduced indanol ester **21** (formed by treatment of **4i** with one equivalent of Super-hydride®).

To conclude, we have developed a highly enantioselective organocatalytic Michael addition of methine carbon acids to acrylic esters, thioesters and *N*-acryloyl pyrrole using a cinchona alkaloid-derived bifunctional organocatalyst. This reaction results in the formation of a quaternary stereogenic centre and generates adducts in high yields and up to excellent enantioselectivities. Further investigations in this field are ongoing and the results will be reported in due course.

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