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Organocatalytic enantioselective conjugate addition of ketones to isatylidine malononitriles†

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An enantioselective Michael addition of ketones to alkylidene-malononitriles catalyzed by chiral primary amine I with (*R*)-5c as a co-catalyst in good yields (>90%) and with good enantioselectivities (85–96% ee) has been developed. The strategy has also been extended to a three-component version through a domino Knoevenagel/Michael sequence with similar or better outcomes.

The 'privileged' status of 3,3′-disubstituted oxindoles bearing functional diversity and complex molecular architectures[1] while possessing a wide array of intriguing biological properties has trigged considerable synthetic interest.[2] Impressively, significant progress has been made in the development of organocatalytic enantioselective reactions.[2,3] Among them, organocatalytic asymmetric conjugate additions to oxindole derived Michael receptors have been demonstrated as a viable approach to the 3,3′-disubstituted oxindole framework.[4,5] 1,3-Diketones,[4e,f] aldehydes,[4g] and nitroalkenes[4h] have been employed as nucleophiles in these processes. While simple ketones could be used to generate structurally diverse oxindoles, implementing it faces the daunting challenge of creating a quaternary stereogenic center *via* conjugate addition of chiral enamines derived from ketones to β,β′-disubstituted unsaturated systems. The lower reactivity of ketones than aldehydes and active carbon nucleophiles and difficulty in governing the enantiofacial discrimination and regioselectivity of formed enamines are important factors. Furthermore, organocatalytic enantioselective conjugate additions of ketones to highly functionalized Michael acceptors in biologically important molecular architectures are a largely untapped field. Successful realization of the process affords a highly valuable tool for the construction of structurally diverse molecules.

Toward this end, in this communication, we would like to disclose an organocatalytic highly enantioselective conjugate addition of ketones to isatylidine malononitriles. The process is efficiently promoted by a quinidine derived primary amine and (*R*)-binol-phosphoric acid as a co-catalyst in high yields (90–97%) and with high enantioselectivities (85–95% ee). Notably, unsymmetrical ketones proceed exclusively at a less substituted site. Moreover, significantly, the strategy has been extended in a highly efficient 3-component version using readily available malononitrile, isatins and ketones.

Inspired by the capacity[6] and our experience[7] in cinchona alkaloid derived primary amines **I–III** in enamine catalysis with ketones, we decided to explore them in the studies (Table 1). A model reaction between isatylidine malononitrile **1a** and acetone **2a** under a neat condition was carried out in initial investigations. It was found that the process took place in good yields, but low enantioselectivities (entries 1–3). Catalyst **I** gave a slightly lower yield while the ee value was much higher than **II** and **III**. To further improve the enantioselectivity, we performed the reaction with **I** in a solvent accordingly (entries 4–9). The best results (85% yield, 49% ee) were obtained in THF (entries 4). We also examined other factors such as reaction temperature and catalyst loadings, but disappointingly no significant improvement in enantioselectivity was seen (entries 10 and 11). Then acidic additives as co-catalysts were investigated in combination with catalyst **I** (entries 12–15). Achiral 4-nitrobenzoic acid **5a** led to a drop in enantioselectivity (entry 12), while chiral phosphoric acid **5b** was beneficial (entry 13). Gratifyingly, the use of binaphthyl derived phosphoric acids (*R*)-**5c** and (*S*)-**5c** gave significant enhancement in enantioselectivities without diminishing the yield and reaction time (entries 14 and 15). Interestingly, the (*S*)-enantiomer gave a relatively low ee value (entry 15), while 92% ee was achieved with the (*R*)-**5c** enantiomer, but with an opposite configuration (entry 14). This indicates that the chiral counter anions play an important role in governing both the level of enantioselectivity and the identity of the major enantiomer.[8,9]

Having established the optimal reaction parameters, we then examined the generality of the conjugate addition process (Table 2). It is shown that structurally varied isatylidene malononitrile derivatives **1** can efficiently engage in the reaction (entries 1–10). High enantioselectivities (85–96% ee) and high yields (90–97%) were obtained, irrespective of the alternations in electronic and steric properties of the substituents appending to the aromatic rings of the oxindole framework. It appears that the free "*N*" in the oxindole is critical for achieving high enantioselectivity. Masking of the "*N*" (*e.g.*, Bn, entry 11) led

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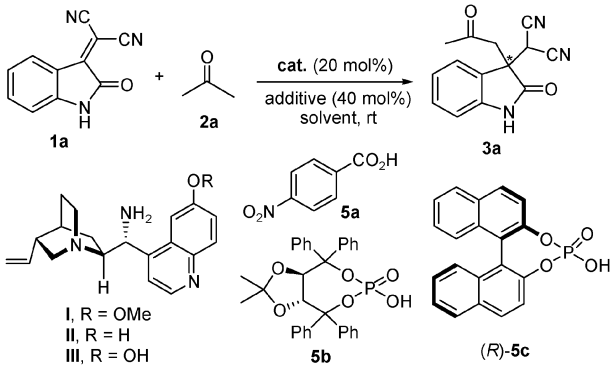
Table 1 Optimization of the reaction conditions[a]

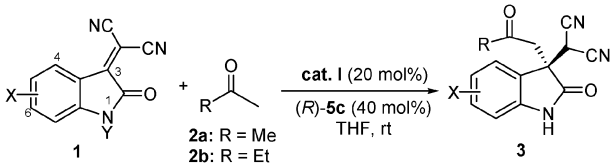


Entry	Cat.	Solvent	Additive	t/h	Yield[b] (%)	ee[c] (%)
1	**I**	Neat	None	2	65	35
2	**II**	Neat	None	9	77	8
3	**III**	Neat	None	12	85	6
4	**I**	THF	None	6	85	49
5	**I**	MeCN	None	4	77	37
6	**I**	DMF	None	5	77	23
7	**I**	Dioxane	None	7	64	49
8	**I**	$CHCl_3$	None	72	77	31
9	**I**	Toluene	None	96	64	42
10[d]	**I**	THF	None	18	85	49
11[e]	**I**	THF	None	20	80	52
12	**I**	THF	**5a**	22	95	37
13	**I**	THF	**5b**	5	70	59
14	**I**	THF	(*R*)-**5c**	9	95	−92
15	**I**	THF	(*S*)-**5c**	9	95	78

[a] Unless specified otherwise, the reaction was carried out with **1a** (0.03 mmol), **2a** (0.3 mmol, 10.0 equiv.), additive (0.012 mmol, 0.4 equiv.) and cat (0.006 mmol, 0.2 equiv.) in 0.3 mL of solvent at rt. [b] Isolated yield. [c] Determined by HPLC analysis (Chiralpak AD-H). [d] 15 mol% cat. used. [e] Reaction run at −15 °C.

to dramatic decrease of the ee value (46%). The reaction proceeded exclusively at a less substituted site for unsymmetrical ketone 2-butanone with high enantioselectivity (92% ee)

Table 2 Scope for **I** and (*R*)-**5c** co-catalyzed asymmetric Michael addition reaction[a]



Entry	X, Y, R	**3**	t/h	Yield[b] (%)	ee[c] (%)
1	H, H, Me	**3a**	9	95	92
2	4-Cl, H, Me	**3b**	6	91	96
3	5-F, H, Me	**3c**	5	95	95
4	5-Cl, H, Me	**3d**	4.5	90	91
5	5-Br, H, Me	**3e**	6	93	94
6	5-NO_2, H, Me	**3f**	6	92	93
7	5-Me, H, Me	**3g**	8	95	94
8	5-OMe, H, Me	**3h**	6	95	95
9	6-Cl, H, Me	**3i**	8	91	85
10	7-Cl, H, Me	**3j**	9	91	86
11	H, Bn, Me	**3k**	7	92	46
12	H, H, Et	**3l**	168	97	92

[a] Unless stated otherwise, see ESI. [b] Isolated yield. [c] Determined by HPLC analysis (Chiralpak AD-H or AS-H).

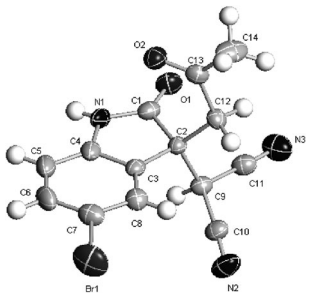
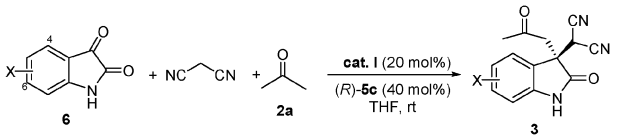


Fig. 1 X-Ray structure of **3e**.

Table 3 Scope for **I** and (*R*)-**5c** co-catalyzed asymmetric three component Michael addition reactions[a]



Entry	X	**3**	t/h	Yield[b] (%)	ee[c] (%)
1	H	**3a**	10	92	95
2	4-Cl	**3b**	6	92	97
3	5-F	**3c**	5	94	96
4	5-Cl	**3d**	5	92	95
5	5-Br	**3e**	6	93	94
6	5-NO_2	**3f**	6	94	93
7	5-Me	**3g**	8	95	95
8	5-OMe	**3h**	6	96	95
9	6-Cl	**3i**	8	93	96
10	7-Cl	**3j**	9	91	86
11	5,7-Me_2	**3m**	48	85	93
12	4-Br	**3n**	8	90	>99
13	4-F	**3o**	9	97	88

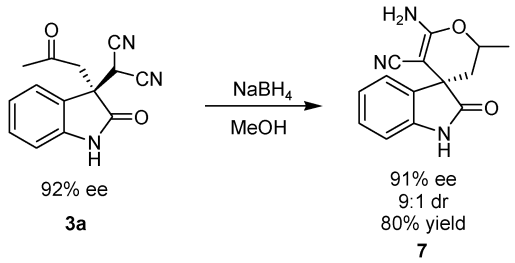
[a] Unless stated otherwise, see ESI. [b] Isolated yield. [c] Determined by HPLC analysis (Chiralpak AD-H or AS-H).

and in high yield (97%) despite long reaction time (entry 12). The absolute configuration of the Michael adducts is determined based on single X-ray structural analysis of compound **3e** (Fig. 1).[10]

Trigged by the possibility of *in situ* formation of isatylidene malononitriles **1** from corresponding isatins **6** and malononitrile, we explored a more atom-economical, three component process under the same reaction conditions (Table 3). To our delight, the Knoevenagel–Michael cascade process proceeded smoothly to afford desired adducts **3** using only 1.0 equiv. of malononitrile. Notably, even slightly higher efficiencies in terms of reaction yields (85–97%) and enantioselectivities (86–>99% ee) were observed with significant tolerance of structural demand of isatins **6**.

We also demonstrated that the Michael adducts **3** can be conveniently transformed into spirooxindole derivatives (Scheme 1). The reduction of **3a** with $NaBH_4$ in MeOH at room temperature[11] was followed by spontaneous cyclization to afford the spirooxindole product **7** in 80% yield and with 91% ee and 9 : 1 dr.

In conclusion, we have developed a new highly enantioselective asymmetric Michael reaction of ketones with alkylidenemalononitriles. The processes are efficiently catalyzed by primary aminocatalyst **I** in the presence of (*R*)-**5c** as a



Scheme 1 Transformation of 3,3′-disubstituted oxindole **3a** to spiro-oxindole **7**.

co-catalyst under mild reaction conditions. Furthermore, more atom-economical three-component processes through a domino Knoevenagel/Michael sequence have been realized while achieving similar or better efficiencies. The products bearing dense functionalities can be conveniently elaborated to generate structurally diverse molecular architectures for biological studies; further efforts along this line are being pursued in this laboratory.

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