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Efficient synthesis of optically active 4-nitro-cyclohexanones *via* bifunctional thiourea-base catalyzed double-Michael addition of nitromethane to dienones†

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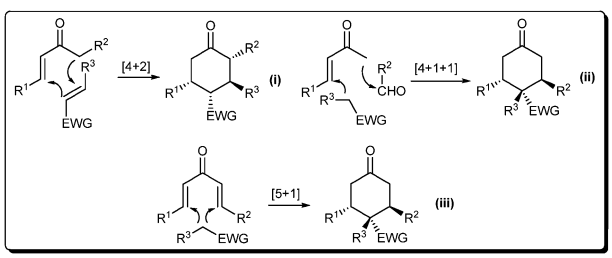
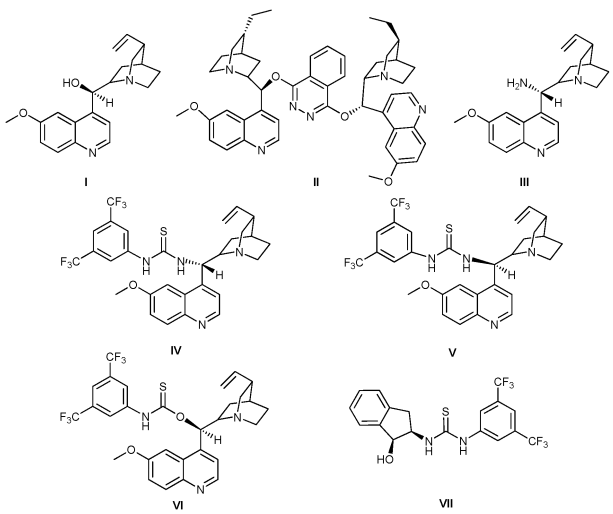
Thiourea-modified *cinchona* alkaloids as bifunctional catalysts and a base could catalyze a stepwise [5 + 1] cyclization of divinyl ketones with nitromethane *via* double Michael additions, furnishing optically active 4-nitro-cyclohexanones with good yields, excellent diastereoselectivities (> 20 : 1) and high enantiomeric ratios (up to 97 : 3).

The construction of suitably functionalized cyclohexane derivatives plays an important role in the synthesis of many natural products with significant biological and pharmaceutical activities.[1] Besides the classic Diels–Alder reaction,[2] some enantioselective organocatalytic domino routes[3] have been successfully developed in recent years, including Michael–Aldol, Michael–Mannich, Michael–Michael, *etc.*,[4] thus allowing facile access to a variety of functionalized cyclohexanes in optically enriched forms. Despite this remarkable progress, however, the organocatalytic preparation of enantiomerically enriched cyclohexanones *via* an intermolecular process still remains less explored. Three types of the organocatalytic cascade reactions have been employed for the construction of chiral cyclohexanone backbones, mostly with an intermolecular Michael addition as the key step (Scheme 1). Jørgensen,[5] Takemoto[6] and Melchiorre[7] groups have, respectively, disclosed that enantiomerically pure cyclohexanone derivatives can be synthesized *via* organocatalyzed [4 + 2] two-component tandem Michael–Michael or Michael–Aldol additions (eqn (i), Scheme 1). Alternatively, Ramachary group has recently reported a L-proline catalyzed one-pot [4 + 1 + 1] three-component cascade reaction for the synthesis of chiral cyclohexanone derivatives (eqn (ii), Scheme 1).[8] In contrast, considerably less attention has been paid to the investigation of a catalytic enantioselective synthesis of cyclohexanone derivatives with divinyl ketones as acceptors *via* [5 + 1] double Michael addition (eqn (iii), Scheme 1). This is somewhat surprising as an actually non-asymmetric version of the mode (iii) was reported as early as in 1924, when Kohler and Helmkamp found that cyclohexanone derivatives could be prepared by treatment of divinyl ketones with active methylene-containing pronucleophiles in the presence of an equivalent of sodium methylate or sodium hydroxide.[9] Following this work some other reagents such as KF/basic Al_2O_3,[10] phase transfer catalyst,[11] or DBU[12] have also been found to effectively promote the [5 + 1] double Michael addition of divinyl ketones with active methylene pronucleophiles for the synthesis of cyclohexanones. We envisioned that the dienone and an active methylene-containing Michael donor might be activated by



Scheme 1 The construction of functionalized cyclohexanones.



Scheme 2 Screened catalysts.

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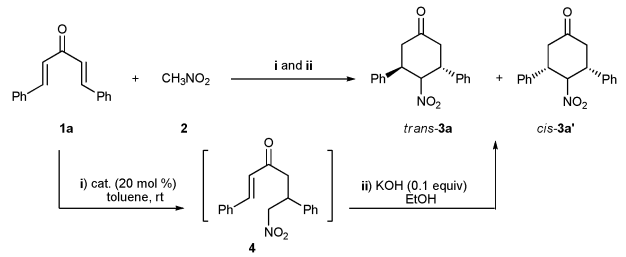
Table 1 Catalyst screening[a]



Entry	Catalyst	Time/h	Yield[b] (%)	dr[c] (**3a**/**3a**′)	er[d]
1	**I**	96	<5[e]	—	—
2	**II**	96	—	—	—
3	**III**	72	—	—	—
4	**IV**	48	58	>20 : 1	95 : 5
5[f]	**V**	48	38	>20 : 1	97 : 3
6	**VI**	48	—	—	—
7	**VII**	48	—	—	—

[a] Reactions were performed with (i) **1a** (0.25 mmol), **2** (0.30 mmol) and catalysts (20 mol%), in toluene (1.0 mL) at rt; (ii) KOH (0.025 mmol), EtOH (2.0 mL) at 0 °C for 2 hours. [b] Isolated yields. [c] Determined by chiral HPLC and ^{1}H NMR. [d] Determined by chiral HPLC. [e] Yield of **4**. [f] With **2** (5.0 mmol).

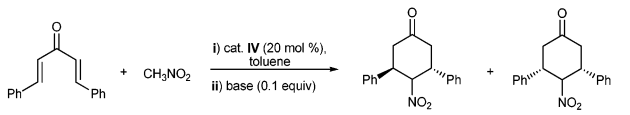
using a proper enantiopure organocatalyst, thus affording optically enriched cyclohexanone adducts *via* [5 + 1] double Michael addition. Herein we report our preliminary results on the facile synthesis of chiral 4-nitro-cyclohexanones *via* a bifunctional thiourea-base catalyzed double-Michael addition of nitromethane to dienones.

Initially, several common organocatalysts bearing a quinuclidine and/or a thiourea moiety[13] were examined for the catalysis of the Michael addition of 1,5-diphenylpenta-1,4-dien-3-one (**1a**) and nitromethane (**2**) in toluene at rt under a catalyst loading of 20 mol% (Scheme 2). As shown in Table 1, the *cinchona* alkaloids **I–III** were found to be ineffective for the reaction, affording essentially no or only trace amount of the intermediate **4** after prolonged reaction times (3–4 days, entries 1–3). To our delight, the reaction proceeded smoothly in the presence of 20 mol% bifunctional thiourea-modified (9-deoxy)-*epi*-*cinchona* alkaloid catalyst **IV**,[14] to afford the mono-Michael addition product **4** in good yield after 48 hours. Flash column chromatographic purification of **4** followed by subsequent KOH-promoted Michael addition–cyclization led to the formation of cyclohexanone **3a** in good overall yield (58% for two steps) with excellent diastereoselectivity (dr > 20 : 1 in favor of *trans*) and high enantioselectivity (95 : 5 er) (entry 4). Purification of **4** to homogeneity was found to be essential for this process, since otherwise the strong base potassium hydroxide would catalyze the non-asymmetric direct transformation of the residual **1a** and **2** to **3a** and thus degrade the enantioselectivity. Quinine-derived thiourea catalyst **V** as a pseudo-enantiomer of **IV** was also investigated for the reaction. Surprisingly, though the enantioselectivity (97 : 3 er) remains excellent in this case, a decrease in yield of **3a** was observed even when a large excess of nitromethane was used (entry 5), suggesting the subtle influence of the catalyst structure on its activity. Therefore, quinine derivative **VI** (an analogue of **IV**) and thiourea catalyst **VII** were subsequently tested for this transformation, but no reaction occurred after 48 h (entries 6–7). Thus, catalyst **IV** turns out to be the optimal catalyst in terms of both activity and selectivity for this transformation.

Further results on the optimization of the other parameters for **IV**-catalyzed reaction of **1a** and **2**, including the reactant's molar ratio and the base used for the cyclization step, are summarized in Table 2. Increasing the amount of nitromethane relative to that of dienone **1a** was found to considerably improve the yield of **3a**, with the best result (86% yield and 96 : 4 er) being obtained when a large excess of nitromethane (20 equiv.) was used in the reaction (entries 1–5). Under solvent-free conditions, the yield could be further improved to 90%, however accompanied by an appreciable loss in the enantioselectivity (92 : 8 er, entry 6). Furthermore, the yield of **3a** decreased sharply dramatically to <10% when the temperature was lowered to 0 °C (entry 7). With regard to the base for the cyclization step, organic bases such as DBU and TMG were also effective, albeit with er values somewhat inferior to that with KOH (entries 8 and 9). In addition, we also tested the direct addition of DBU or TMG into the mixture after 48 hours of reaction without isolation of **4**. Unfortunately, in these cases the enantiomeric ratios dropped significantly, though the yields were elevated to over 90% (entries 10 and 11).

Having established the optimal reaction conditions, we proceeded to explore the substrate scope and limitation of the present protocol. As shown in Table 3, all the reactions between divinyl ketones **1a–o** and nitromethane (**2**) proceed smoothly with the sequential catalytic actions of **IV** and potassium hydroxide, affording the corresponding cyclization products **3** in good yields with excellent enantioselectivities. For the divinyl ketones with identical arms (**1a–k**, **1n**), the different substituents on phenyl groups of the divinyl ketones demonstrated little effect on stereocontrol, albeit with a slight variation in the reactivity as evidenced by the yields of the corresponding cyclization products (entries 1–11, 14). Moreover, divinyl ketones **1l–m** containing heteroaromatic rings were

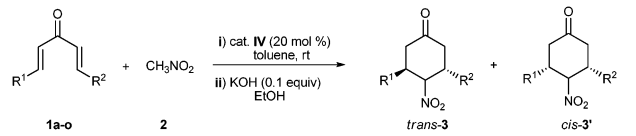
Table 2 Optimization of reaction conditions[a]



Entry	**1a**/**2**	Base	Yield[b] (%)	dr[c] (**3a**/**3a**′)	er[d]
1	1 : 1.2	KOH	58	>20 : 1	95 : 5
2	1 : 2	KOH	68	>20 : 1	94 : 6
3	1 : 5	KOH	78	>20 : 1	95 : 5
4	1 : 10	KOH	85	>20 : 1	95 : 5
5	1 : 20	KOH	86	>20 : 1	96 : 4
6[e]	—	KOH	90	>20 : 1	92 : 8
7[f]	1 : 20	KOH	<10	nd	nd
8	1 : 20	DBU	84	>20 : 1	93 : 7
9	1 : 20	TMG[h]	88	>20 : 1	94 : 6
10[g]	1 : 20	DBU	92	>20 : 1	93 : 7
11[g]	1 : 20	TMG	90	>20 : 1	90 : 10

[a] Reactions were performed with (i) **1a** (0.25 mmol), **IV** (20 mol%), in toluene (1.0 mL) at rt for 48 hours; (ii) base (0.025 mmol) in EtOH (2.0 mL) at 0 °C for 2 hours. [b] Isolated yields. [c] Determined by chiral HPLC and ^{1}H NMR. [d] Determined by chiral HPLC. [e] With **2** (2.0 mL). [f] 0 °C for 3 days. [g] One pot reaction. [h] TMG = 1,1,3,3-tetramethylguanidine.

Table 3 Substrate scope in the reaction[a]



Entry	Products (**3a–p**)	Time/h	Yield[b] (%)	dr[c] (**3**/**3′**)	er[d]
1	R^1, R^2 = Ph, **3a**	48	86	>20 : 1	95 : 5
2	R^1, R^2 = 3,5-$(OMe)_2C_6H_3$, **3b**	72	77	>20 : 1	96 : 4
3	R^1, R^2 = 4-MeC_6H_4, **3c**	72	54	>20 : 1	95 : 5
4	R^1, R^2 = 4-*i*-PrC_6H_4, **3d**	72	67	>20 : 1	95 : 5
5	R^1, R^2 = 4-FC_6H_4, **3e**	48	73	>20 : 1	96 : 4
6	R^1, R^2 = 2-ClC_6H_4, **3f**	48	65	>20 : 1	95 : 5
7	R^1, R^2 = 3-ClC_6H_4, **3g**	36	68	>20 : 1	92 : 8
8	R^1, R^2 = 4-ClC_6H_4, **3h**	24	82	>20 : 1	96 : 4
9	R^1, R^2 = 2-BrC_6H_4, **3i**	24	80	>20 : 1	95 : 5
10	R^1, R^2 = 4-BrC_6H_4, **3j**	48	66	>20 : 1	96 : 4
11	R^1,R^2 = 4-$CF_3C_6H_4$, **3k**	36	78	>20 : 1	97 : 3
12	R^1, R^2 = 2-furyl, **3l**	72	58	>20 : 1	93 : 7
13	R^1, R^2 = 2-thienyl, **3m**	48	74	>20 : 1	96 : 4
14	R^1, R^2 = 2,4-$(Cl)_2C_6H_3$, **3n**	48	71	>20 : 1	95 : 5
15	R^1 = Ph, R^2 = 4-ClC_6H_4, **3o**	36	84	1.25 : 1	82 : 18 96 : 4[e]
16	R^1, R^2 = cyclohexyl, **3p**	48	—	—	—

[a] Unless specified, see the experimental section in the ESI† for reaction conditions. [b] Isolated yields. [c] Determined by chiral HPLC and ^{1}H NMR. [d] Determined by chiral HPLC. [e] Minor diastereomer.

also suitable substrates for this reaction, with good yields and high stereoselectivities being attained under the optimized conditions (entries 12 and 13). Furthermore, non-symmetrical divinyl ketone **1o** provided the desired product in 84% yield, albeit with a somewhat inferior diastereoselectivity (1.25 : 1) and enantioselectivity (entry 15). We have examined the reactivity of dienones with aliphatic residues for this reaction, using a dicyclohexyl substituted divinyl ketone **1p** as the model substrate. Unfortunately, under our optimized conditions, catalyst **IV** was found to be ineffective for the transformation involving this compound (entry 16). Finally, we were fortunate to obtain single crystals of compound **3n**, which allows for an unambiguous assignation of the *trans* configuration of C2 and C6 stereocenters by X-ray crystallographic analysis (see ESI†).

The catalyst screening results discussed above provide some useful hints for the mechanism of this reaction. In contrast with the bifunctional catalysts **IV** and **V**, neither the basic *cinchona* alkaloids **I–III** (and **VI**) nor the acidic thiourea **VII** exhibited appreciable catalytic activity in the reaction, suggesting that a co-activation of both reaction partners by the bifunctional catalyst seems to be working for the first Michael addition to intermediate **4**. Catalyst **IV**, however, is not active enough for the second step of the reaction, which necessitates a stronger base such as KOH for the deprotonation and subsequent Michael addition–cyclization.

In summary, we have successfully developed a new route to synthesize the enantiomerically enriched 4-nitrocyclohexanones starting from divinyl ketones and nitromethane by sequential use of a thiourea-modified *cinchona* alkaloid as a bifunctional catalyst and a base, with good yields and excellent diastereoselectivities as well as high enantioselectivities being achieved for most symmetrical aryl- or heteroaryl divinyl ketones. Further extension of the present protocol by exploring other methylene pronucleophiles and the synthetic application studies are underway in our laboratory.

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