The highly enantioselective Michael addition of ketones to nitrodienes catalyzed by the efficient organocatalyst system of pyrrolidinyl-thioimidazole and chiral thioureido acid†

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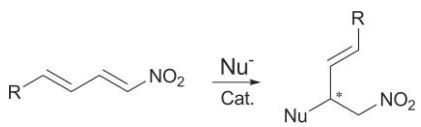
The highly enantioselective Michael addition reaction of ketones to nitrodienes was promoted efficiently by the accessible and fine-tunable organocatalytic system of pyrrolidinyl-thioimidazole and chiral thioureido acid. The corresponding adducts were afforded in good yields with high diastereoselectivities (up to 99 : 1) and excellent enantioselectivities (up to 99% ee).

Introduction

As one of the most important chiral carbon–carbon bond-forming processes in modern organic chemistry, the asymmetric catalytic Michael addition employing chiral organocatalysts has gained more and more attention.[1,2] Among them, the asymmetric conjugate additions of aldehydes or ketones to Michael accepters, such as α,β-unsaturated carbonyl compounds, nitroolefins, phosphonates, vinylic sulfones and acrylonitriles have been developed through enamine activation mode.[2] In particular, as one of the most efficient, atom-economical and powerful methods, the direct Michael reaction of carbonyl compounds to nitroolefins has stimulated extensive interest because the enantioenriched adducts (γ-nitrocarbonyl compounds) serve as versatile intermediates for the preparation of complex organic targets and thus considerable attention has been given to developing efficient catalytic systems for a wide variety of carbonyl compounds as carbon nucleophiles.[3] In contrast, only β-nitrostyrenes were most widely used and little progress has been made in the development of nitrodienes as Michael acceptors. Recently Alexakis group succeeded in developing the asymmetric organocatalyzed Michael addition of aldehydes to nitrodienes.[4] Whereas, the development of efficient organocatalysts for the Michael addition of ketones to nitrodienes is still challenging (Scheme 1).



Scheme 1 The Michael addition of nitrodienes.

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Pyrrolidinyl-thioimidazole **1** (Fig. 1) and its analogs were designed in our previous work and successfully applied to catalyze some asymmetric reactions[5] including the Michael addition of ketones to nitroolefins. Moreover we developed the chiral thioureido acids **2a–7b** used as novel chiral functional acidic additives for the organocatalyst **1**, and the readily available and fine-tunable organocatalytic system display well catalytic activity and excellent enantioselectivity.[5c] To explore further application of the pyrrolidinyl-thioimidazole and chiral thioureido acid organocatalytic system, the asymmetric Michael addition of ketones to nitrodienes was investigated.

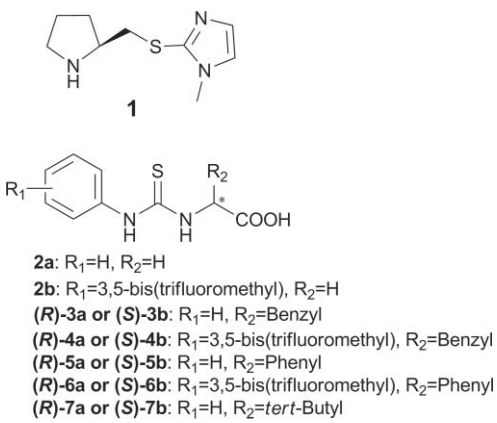
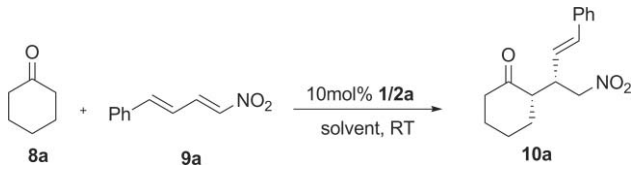


Fig. 1 Pyrrolidinyl-thioimidazole and chiral thioureido acids.

Results and discussion

Preliminary experiments were carried out in order to examine the reactivity in the direct Michael addition. Cyclohexanone **8a** and ((1*E*,3*E*)-4-nitrobuta-1,3-dienyl)benzene **9a** were used as model substrates in the presence of pyrrolidinyl-thioimidazole **1** and the thioureido acid **2a**. The desired 1,4-addition adduct was obtained and significant solvent effects were noted. As the results summarized in Table 1, polar solvents and protonic solvents seemed to suppress the reaction and only medium yields, low diastereo- and enantioselectivities were obtained (entries 1–5). This indicated that polar solvents may interact with **2a** through hydrogen bonding to weaken the activation ability of **2a** towards the reaction. Aliphatic ethers were not good solvents for this reaction either because of the poor solubility of the catalyst system (entries 9 and 10). While in halohydrocarbon solvents, such as dichloroethane, chloroform, and 1,2-dichloroethane (DCE) both

Table 1 Solvent screen for the direct Michael addition of **8a** to **9a**[a]

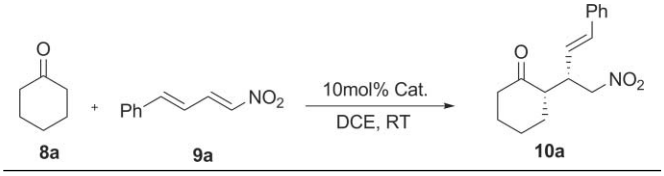


8a **9a** **10a**

Entry	Solvent	Time (d)	Conv. [b](%)	dr [c](*syn*/*anti*)	ee [d](%)
1	DMSO	3	68	68 : 32	58
2	DMF	3	69	61 : 39	53
3	CH_3OH	3	53	63 : 37	32
4	*i*-PrOH	3	50	59 : 41	–14
5	*n*-BuOH	3	55	64 : 36	16
6	CH_2Cl_2	2	97	79 : 21	70
7	$CHCl_3$	2	98	78 : 22	70
8	**$ClCH_2CH_2Cl$**	**2**	**99**	**78 : 22**	**74**
9	$C_2H_5OC_2H_5$	3	69	62 : 38	48
10	$Me_2CHOCHMe_2$	3	36	67 : 33	57

[a] A mixture of cyclohexanone (0.25 mmol), phenylnitrodiene (0.25 mmol) and catalyst system **1/2a** (10 mol% each) in different solvents was stirred at room temperature for the time given in tables. [b] Determined by GC. [c] Determined by GC-MS. [d] Determined by chiral HPLC analysis (Daicel Chiralpak AD-H, hexane/*i*-PrOH = 90 : 10, flow rate 1.0 mL min^{-1}, λ = 264 nm).

Table 2 The effect of different thioureido acids on the Michael reaction of **8a** to **9a** catalyzed by **1**[a]



8a **9a** **10a**

Entry	Additive acid	Time (d)	Conv. [b](%)	dr [c](*syn*/*anti*)	ee [d](%)
1	—	3	53	75 : 25	51
2	PhCOOH	3	60	73 : 27	68
3	**2a**	2	99	78 : 22	74
4	**2b**	2	97	79 : 21	75
5	**3a**	2	99	92 : 8	88
6	**3b**	2	97	90 : 10	81
7	**4a**	2	99	95 : 5	90
8	**4b**	2	99	90 : 10	85
9	**5a**	2	98	95 : 5	89
10	**5b**	2	99	91 : 9	81
11	**6a**	2	99	98 : 2	99
12	**6b**	2	99	93 : 7	83
13	**7a**	2	97	89 : 11	87
14	**7b**	2	98	85 : 15	84
15[e]	**6a**	**1**	**96**	**98 : 2**	**99**
16[f]	**6a**	3	80	98 : 2	99

[a] A mixture of cyclohexanone (0.25 mmol), phenylnitrodiene (0.25 mmol) and catalyst system (10 mol% each) in DCE was stirred at room temperature for the time given in tables. [b] Determined by GC. [c] Determined by GC-MS. [d] Determined by chiral HPLC analysis (Daicel Chiralpak AD-H, hexane/*i*-PrOH = 90 : 10, flow rate 1.0 mL min^{-1}, λ = 264 nm). [e] 5 mol% catalyst system was loaded. [f] 3 mol% catalyst system was loaded.

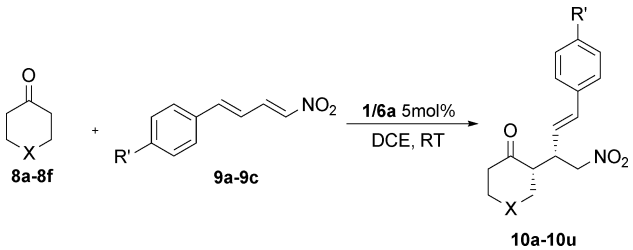
yields and enantioselectivities were good (entries 6–8). DCE was found to be the best solvent, which afforded **10a** with high yield of 99%, with moderate diastereo- and enantioselectivity of 78 : 22 and 74% respectively within two days.

Next, in order to accomplish higher enantioselectivity, we carefully fine-tuned the structure of chiral thioreido acids according to its synergistical effects[6] and steric effects of the chiral thioureido acids. As shown in Table 2, without acidic addictive (entry 1) or used the benzoic acid (entry 2), the pyrrolidinyl-thioimidazole **1** failed to generate the desired product in good yields and ee values. In contrast, all Michael reactions catalyzed by **1** and thioureido acids proceeded well and the product were obtained with the yields higher than 96%, with the ee values ranging from 74% to 99% (entries 3–15). Moreover, R_2 groups of chiral thioureido acids was benzyl, phenyl or *tert*-butyl group (entries 5–15) showed better steric efficiency than **2a** and **2b** (entries 3 and 4). As the phenomena found in the Michael reaction of ketones to nitroolefins,[5c] the configuration of the chiral thioureido acids had important influence on the reaction performance, especially on the enantioselectivity of the product. The chiral thioureido acids **3a**, **4a**, **5a**, **6a** and **7a**, all having an ***R*** configuration (entries 5, 7, 9, 11 and 13), showed better efficiency than **3b**, **4b**, **5b**, **6b** and **7b** which have an ***S*** configuration (entries 6, 8, 10, 12 and 14). All these results indicated that the chiral thioureido acids could act in a dual role, not only activating pyrrolidinyl-thioimidazole **1** presumably by providing a proton, but also activating and chirally inducing the phenylnitrodiene **9a** by hydrogen bonding and steric effects. To our delight, no significant decrease of both yield and ee value was detected even when the amount of the catalyst system of **1/6a** was reduced to 5 mol% (entries 15 and 16).

With the optimal reaction conditions established, the Michael addition reactions with a variety of *cyclo*-ketones, aliphatic ketone and aldehydes to nitrodienes were explored. As the results in Table 3 showed, cyclohexanone, tetrahydrothiopyran-4-one and tetrahydropyran-4-one were very suitable substrates, giving the products with the isolated yields of 82% to 93% and ee values of 85% to 99% (entries 1, 3, 4, 7, 9, 10, 13, 15 and 16). When cyclopentanone and 1-methylpiperidin-4-one were as Michael donor substrates, the enantioselectivities of corresponding products were decreased. Although the diastereoselectivity was mild decline, 4-*tert*-butyl cyclohexanone was also a suitable substrate for the Michael addition reaction, leading to the products with the ee values of up to 96% (entries 5, 11 and 17). Aliphatic ketone and aldehydes were also tested and moderate to good results were obtained (entries 19–21).

To explain the origin of the high enantioselectivity performance of the synergistic co-catalytic system **1/6a** for the Michael addition reactions, a transition state model is proposed and the absolute configuration of adduct **10m** was confirmed by an X-ray crystallographic analysis (Fig. 2). Because of the ionic interaction of the pyrrolidinyl-thioimidazole and the carboxylate of the chiral thioureido acid, the stable ammonium catalyst ionic pair is formed; therein the chiral thioureido acids with the ***R*** configuration can synergistically cover the up-side of the phenylnitrodiene **9a** with **1** more efficiently than those chiral thioureido acids with the ***S*** configuration. Because of the combined steric effects of the thioimidazole group of **1** and the chiral phenyl group of **6a**, the *Si* face of phenylnitrodiene **9a** was shielded efficiently and the enamine which was activated by the pyrrolidine motif of **1** is favored to attack the phenylnitrodiene **9a** which was activated by **6a** through hydrogen bonding from the *Re* face to afford the desired (*S*,*S*) adduct.

Table 3 Michael addition reactions of *cyclo*-ketones, aliphatic ketone and aldehydes to nitrodienes[a]



Entry	8/X	9/R′	Time/h	Product	Yield [b](%)	dr [c](*syn*/*anti*)	ee [d](%)
1	**8a**/CH_2	**9a**/H	24	**10a**	92	98 : 2	99
2	**8b**/$(CH_2)_0$	**9a**/H	24	**10b**	87	95 : 5	95
3	**8c**/O	**9a**/H	24	**10c**	84	89 : 11	97
4	**8d**/S	**9a**/H	24	**10d**	85	99 : 1	96
5	**8e**/CH *t*-Bu	**9a**/H	24	**10e**	92	83 : 17[e]	96
6	**8f**/NCH_3	**9a**/H	24	**10f**	91	98 : 2	72
7	**8a**/CH_2	**9b**/OMe	36	**10g**	90	99 : 1	85
8	**8b**/$(CH_2)_0$	**9b**/OMe	36	**10h**	84	90 : 10	93
9	**8c**/O	**9b**/OMe	36	**10i**	82	89 : 11	93
10	**8d**/S	**9b**/OMe	36	**10j**	84	91 : 9	95
11	**8e**/CH *t*-Bu	**9b**/OMe	36	**10k**	89	89 : 11[e]	93
12	**8f**/NCH_3	**9b**/OMe	36	**10l**	89	98 : 2	77
13	**8a**/CH_2	**9c**/Cl	18	**10m**	93	99 : 1	87
14	**8b**/$(CH_2)_0$	**9c**/Cl	18	**10n**	91	97 : 3	91
15	**8c**/O	**9c**/Cl	18	**10o**	89	88 : 12	93
16	**8d**/S	**9c**/Cl	18	**10p**	89	93 : 7	94
17	**8e**/CH *t*-Bu	**9c**/Cl	18	**10q**	93	88 : 12[e]	93
18	**8f**/NCH_3	**9c**/Cl	18	**10r**	93	72 : 28	73
19	3-Pentanone	**9a**/H	48	**10s**	82	97 : 3	80
20	Isovaleraldehyde	**9a**/H	20	**10t**	76	59 : 41	83
21	Isobutyraldehyde	**9a**/H	20	**10u**	77	64 : 36	68

[a] A mixture of *cyclo*-ketones or aliphatic ketone and aldehydes (0.25 mmol), nitrodienes (0.25 mmol) and catalyst system **1/6a** (5 mol% each) in DCE was stirred at room temperature for the time given in tables. [b] Isolated yield. [c] Determined by GC-MS. [d] Determined by chiral HPLC analysis (Daicel Chiralpak AD-H, hexane/*i*-PrOH = 90 : 10, flow rate 1.0 mL min^{-1}). The configurations of **10a–10s** were assumed by analogy to **10m** and the configurations of **10t–10u** were assumed by analogy to corresponding products in Ref.4 [e] This ratio referred to two *syn*-products with ***S*** configuration to those with ***R*** configuration in the 4-position of cyclohexanone (See ESI and Ref.7).

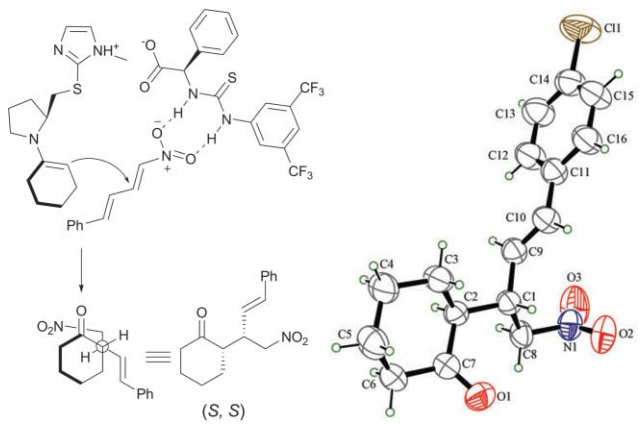


Fig. 2 Proposed transition state model and the X-ray Structure of **10m**.

Conclusions

In summary, the organocatalytic asymmetric Michael addition which involved ketones and nitrodienes as the Michael donors and acceptors was first systematically reported. The pyrrolidinyl-thioimidazole **1** and chiral thioureido acid **6a** organocatalyst system showed efficient synergistic co-catalytic ability in the asymmetric Michael addition reactions. The Michael adducts were afforded with good isolated yields (up to 93%), high diastereoselectivities (up to 99 : 1) and excellent enantioselectivities (up to 99% ee). Further applications of this organocatalytic system were ongoing in our laboratory.

Acknowledgements

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