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Asymmetric Michael Addition Reactions of Nitroalkanes to 2-Furanones Catalyzed by Bifunctional Thiourea catalysts†

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The first bifunctional thiourea catalyzed asymmetric Michael addition reactions of nitroalkanes to 2-furanones are described. The high functionalized *γ*-lactones with two or three consecutive stereogenic carbons were gave in high yields (up to 99%), high diastereoselectivities (up to >20:1 dr) and enantioselectivities (up to >99% ee).

The γ-butyrolactone skeleton widely presents in many synthetic and natural products with biological activities.[1] Functionalized chiral γ-butyrolactones are useful building blocks for the synthesis of γ-butyrolactone derivatives.[2] As a consequence, more attentions have focused on the construction of functionalized chiral γ-butyrolactones in recent years. One of the most important approaches is the asymmetric Michael addition of γ-butenolides with various carbanion nucleophiles.[3] Nitroalkanes have been demonstrated to be a valuable stabilized carbanion for the conjugate addition due to the strong electron-withdrawing nature of the nitro group and its potent transformation to a variety of important functional groups.[4] However, to the best of our knowledge, there is still no previous report on asymmetric Michael additions of nitroalkanes to γ-butenolides.

In the previous papers, we have successfully carried out the chiral 1,2-primary catalyzed asymmetric Michael additions of γ-butenolides to chalcones and aryl methyl ketones to γ-butenolides.[5] As a continuation of our work, we now disclose the first asymmetric Michael addition of nitroalkanes with γ-butenolides catalyzed by bifunctional thiourea catalysts in good yields, excellent diastereoselectivities and enatioselectivities.

Initially, reaction of 2-furanone **1a** and nitromethane **2a** was investigated using chiral 1, 2-primary diamines **I** as catalysts.[6] Unfortunately, although the product **3a** was obtained in 92% yield with >20:1 dr, no any enantioselectivity was observed. In order to improve the enantioselectivity, various bifunctional catalysts derived from cinchona alkaloids (**II-VII**) were then screened due to their excellent catalytic activity for the asymmetric Michael reactions.[7] As shown in Table 1, except catalyst **VII**, all the catalysts were able to catalyze the formation of product **3a** in high yield (74-98%) and excellent diastereoselectity (dr>20:1). To our delight, the catalyst **III** gave the product **3a** not only in excellent yield (98%) and diastereoselectivity (>20:1dr), but also good enantioselectivity (76% ee) (Table 1, Entry 3). Therefore, catalyst **III** was selected for the further optimization of the solvents (Table 1, Entries 8-17). It appeared that the properties of solvent greatly effected on the reaction. Both high polar and nonpolar solvents are unfavorable for the reaction (Table 1, Entries 10-11, 14-16). However, EtOAc as solvent could greatly improve the stereoselectivity from 76 % ee to 97% ee (Table 1, Entry 9); Subsequently, the influence of the catalyst loading on the reaction was tested in EtOAc (Table 1, Entries 17-19). It is glad to find that the yield and the enantioselectivity are without any loss reducing the catalyst loading from 20 mol% to 10 mol% (Table 1, entry 17). Thus, 10 mol% of catalyst (**III**) in EtOAc at room temperature were found to be the most suitable reaction conditions.

Having identified the optimal reaction conditions, the substrate scope of the reaction was then explored. The reactions of furanone **1a** with different nitroalkanes were firstly investigated under the optimized reaction conditions. As showed in Table 2, the nitroethane (**2b**) and nitropropane (**2c**) were excellent substrates for this reaction and the products (**3b** and **3c**) with three stereogenic centers were formed in high yields with excellent diastereoselectivity and enantioselectivity (Entries 2-3). It should be noted that there are few researches using substituted nitromethanes as Michael donators and the mixture of epimers at $C_{1'}$, often in ratios close to 1:1, were generally obtained.[4e, 7a, 7c, 7d, 8] However, for the phenyl nitromethane (**2d**), the yield (42%), diastereoselectivity (dr = 2:3) and enantioselectivity (72/41% ee) obviously decreased possibly due to the influence of steric

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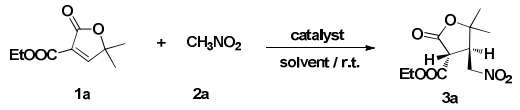
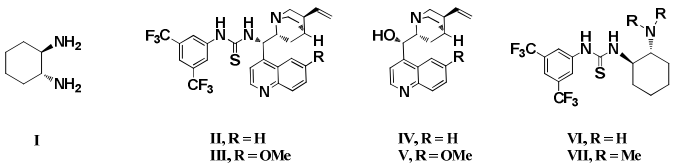
hindrance. Fortunately, benzyl substituted nitromethanes (**2e-g**) afforded the desired addition products (**3e-g**) in good yields (78%-89%) and excellent enantioselectivities (89%-93%), though the diastereoselectivities were still low. The possible reason for the decrease of diastereomeric ratioes (dr) is the long reaction time (120h) which might lead to the epimerization of products.[4f] Subsequently, γ-position higher sterically hindered 2-furanones **1b** and **1c** were investigated because the 2-furanone with quaternary carbon frameworks at γ-position are typical structural features in many diterpenoid natural products and pharmaceutical drugs. Similarly to **1a**, **1b** and **1c** showed favorable reactivity with nitromethane and rendered the products **3h-i** in over 95% yields with 91% ee (Entries 8-9). However, when using nitroethane as Michael donator to **1b** and **1c**，,the yields and enatioselectivities decreased owing to the effect of steric hindrance (**3j**, **3k**).

Table 1 Optimization of the reaction conditions for the addition of nitromethane **2a** to 2-furanone **1a** promoted by bifunctional organocatalysts[a]

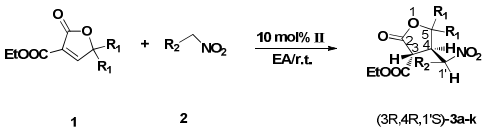




Entry	Catalyst	Solvent	t(h)	Yield (%)[b]	dr[c]	ee(%)[d,e]
1	I[f]	Neat	12h	92	>20:1	-
2	II[f]	Neat	12	98	>20:1	-63
3	III[f]	Neat	12	98	>20:1	76
4	IV [f]	Neat	12	86	>20:1	31
5	V[f]	Neat	12	74	>20:1	-12
6	VI[f]	Neat	12	94	>20:1	-67
7	VII[f]	Neat	12	44	>20:1	-44[h]
8	II[f]	Toluene	12	96	>20:1	87
9	II[f]	EtOAc	12	98	>20:1	97
10	II[f]	*n*-hexane	12	9	>20:1	50
11	II[f]	THF	12	40	>20:1	87
12	II[f]	CH_2Cl_2	12	91	>20:1	86
13	II[f]	CH_3CN	12	93	>20:1	74
14	II[f]	MeOH	12	94	>20:1	54
15	II[f]	DMSO	12	9	>20:1	10
16	II[f]	H_2O	12	-	-	-
17	II(10%)	EtOAc	12	98	>20:1	97
18	II(5%)	EtOAc	24	95	>20:1	93
19	II(2%)	EtOAc	30	82	>20:1	88

[a]Reaction conditions: unless specified, **1a** (0.25 mmol) and catalyst (0.05 mmol) in nitromethane (2 mL) was stirred at rt for 12h. After concentration in vacuo, the residue was purified by silica gel chromatography, eluting with EtOAc and petroleum (1/10 v/v ratio). [b]Isolated yield. [c]Determined by ^{1}H NMR of the crude mixture. [d]Determined by chiral HPLC(Chiral AD-H or AS-H) of the products. [e]Negative ee indicates the formation of the opposite enantiomer. [f]20 mol% of catalyst used.

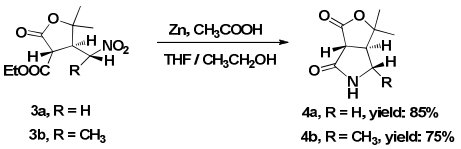
Table 2 The addition of nitroalkanes to 2-furanones **1a-c** promoted by based bifunctional thiourea catalyst **II**[a]



Entry	R_1	R_2	t(h)	Yield[b] (%)	dr[c]	ee(%)[d]
1	Me	H,**2a**	12	**3a**(98)		97
2	Me	Me,**2b**	24	**3b**(97)	>20:1	96
3	Me	Et,**2c**	24	**3c**(89)	>20:1	>99
4	Me	 ,**2d**	120	**3d**(42)	3:2	72/41
5	Me	 ,**2e**	120	**3e**(78)	1:1	89/53
6	Me	 ,**2f**	120	**3f**(89)	2:3	93/46
7	Me	 , **2g**	120	**3g**(79)	1:1	92/49
8	Et,**1b**	H,**2a**	12	**3h**(99)		91
9	 ,**1c**	H,**2a**	12	**3i**(95)		91
10	Et,**1b**	Me,**2b**	72	**3j**(50)	>20:1	87
11	 , **1c**	Me,**2b**	72	**3k**(85)	7:1	77/64

[a]Reaction conditions: unless specified, **1a** (0.25 mmol), **2a**（0.75 mmol）and catalyst (0.025 mmol) in EtOAc (2 mL) was stirred at rt for 12h. After concentration in vacuo, the residue was purified by silica gel chromatography, eluting with EtOAc and petroleum (1/10 v/v ratio). [b]Isolated yield. [c]Determined by ^{1}H NMR of the crude mixture. [d]Determined by chiral HPLC (Chiral AD-H or AS-H) of the products.

The synthetic versatility of the Michael addition adduct **3** was also illustrated by a further transformation. For example, the nitro groups of compound **3a** and **3b** were selectively reduced to



Scheme 1 Synthetic transformations involving **3a-b**

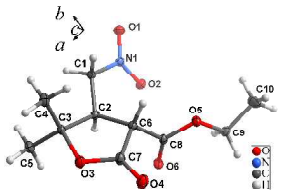


Figure 1 X-ray structure of **3a**

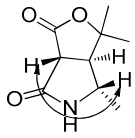
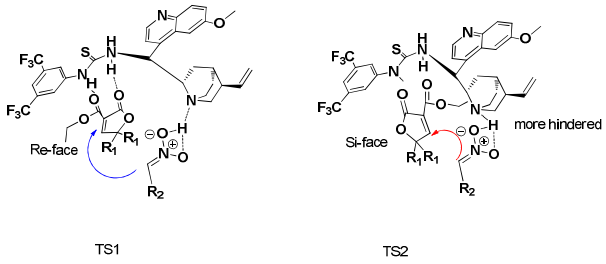


Figure 2 NOESY for compound **4b**



Scheme 2 Proposed transitional state

amines by Zn/CH_3COOH, followed by lactamization to afford the furo[3,4-c]pyrrole derivatives **4a** and **4b** in 75% and 85% yield, respectively.

The absolute configuration of **3a** with two stereogenic centers was confirmed to be (3R, 4R) by the X-ray structure (Fig. 1). The structure of **3b** with three stereogenic centers was deduced to be (3R, 4R, 1'S) by the analysis of the 2D-NOESY of its derivative **4b** (Fig. 2; see ESI, Fig S3).

According to dual hydrogen-bonding activation model proposed by Takemoto and Deng,[9] we deduced that 2-furanone **1** was activated by bifunctional thiourea catalyst via the dual hydrogen-bonding activated transition state as shown in Scheme 2. This dual hydrogen-bonding activated transition state led to the formation of the products **3** with (3R, 4R) configuration, which is consistent with the X-ray crystal structure of **3a**.

In summary, we have developed the first example for the asymmetric Michael addition of nitroalkanes to 2-furanones catalyzed by bifunctional thiourea catalyst. This reaction provides an efficient approach to synthetically and biologically interesting highly functionalized chiral γ-lactones with two or three consecutive stereogenic carbons in good to excellent yields and high stereoselectivities. The Michael addition adducts have been successfully transformed into a chiral furo[*3,4-c*]pyrrole-1,6-diones. We fully expect that this new method could be further applied to a broader substrate scope, which may contributes to the diversity of biologically interesting molecules in medicinal chemistry.

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Notes and references

‡ Crystal data for **3a**: $C_{10}H_{15}NO_6$, M = 245.23, monoclinic, a = 8.772(6) Å, b = 7.482(4) Å, c = 9.640(6) Å, α = 90.00°, β = 113.568(15)°, γ = 90.00°, V= 579.9(6) Å^3, T = 150(2) K, space group $P2_1$, Z = 2, μ(Cu Kα) = 1.002 mm^{-1}, 4173 reflections measured, 1877 independent reflections (R_{int} = 0.0434). The final R_1 values were 0.0394 (I>2σ(I)). Thefinal wR(F^2) values were 0.1053 (I>2σ(I)). The final R_1 values were 0.0424 (all data). The final wR(F^2) values were 0.1075 (all data). Flackparameter = -0.3(3).

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