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Organocatalytic Asymmetric Michael/Acyl Transfer Reaction between *α*-Nitroketones and 4-Arylidene-pyrrolidine-2,3-diones

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Abstract

An organocatalytic asymmetric Michael/acyl transfer reaction between *α*-nitroketones and 4-arylidene-pyrrolidine-2,3-diones was reported. Bifunctional thiourea catalyst was found to be effective for this reaction. With 10 mol% of the catalyst, good results were attained for a variety of 1,5-dihydro-2*H*-pyrrol-2-ones under mild reaction conditions.

Key Words

organocatalysis, acyl transfer, Michael reaction, pyrrolidine-2,3-dione, enantioselectivity

Introduction

The Micahel reaction of carbon nucleophiles to *α*,*β*-unsaturated carbonyl compounds is one of the most important C-C bond-forming reactions in organic synthesis [1-2]. Over the last two decades, organocatalytic asymmetric conjugate addition has been proven to be a powerful method for the synthesis of enantiopure organic compounds [3-5]. The conjugate addition of nitroalkanes and their derivatives to enones is a popular reaction in organic chemistry because the corresponding products can be chemoselectively converted to a variety of valuable structures such as amino alkanes, amino carbonyls etc [6]. As a consequence, considerable efforts have been put forward for the asymmetric version of this reaction in the recent years [7-9]. One of the challenges is to employ highly substituted enones in the reaction. Indeed, additional substituents, especially at the *α*-position of enones/activated olefins, decreases the reactivity significantly because of unfavourable steric interactions. To overcome this problem, reactive Michael donors must be used to get good conversion in the reaction. In recent years, *α*-nitroketones have emerged as active nucleophiles in Michael reactions and a range of substrates have been explored [10]. Also, *α*-nitroketones have been found to be a popular nucleophilic acyl transfer reagent. In 2011, three research groups namely Wang, Yan and Kwong independently revealed organocatalytic asymmetric conjugate addition of *α*-nitroketones to *β*,*γ*-unsaturated *α*-keto esters with concomitant acyl transfer reaction to the keto group [11-13]. Consequently, our group developed organocatalytic asymmetric Michael-acyl transfer reaction of *α*-nitroketones with unsaturated pyrazolones, 2-hydroxycinnamaldehydes, *γ/δ*-hydroxyenones, *otrho*-quinone methides etc [14-18]. Other groups also contributed contemporarily [19-21].

In recent years 4 arylidene-pyrrolidine-2,3-diones have been explored mainly for the preparation of bicyclic dihydropyrane derivatives through catalytic inverse-electron-demand hetero-Diels Alder reaction [22-24]. We postulated that 4 arylidene-

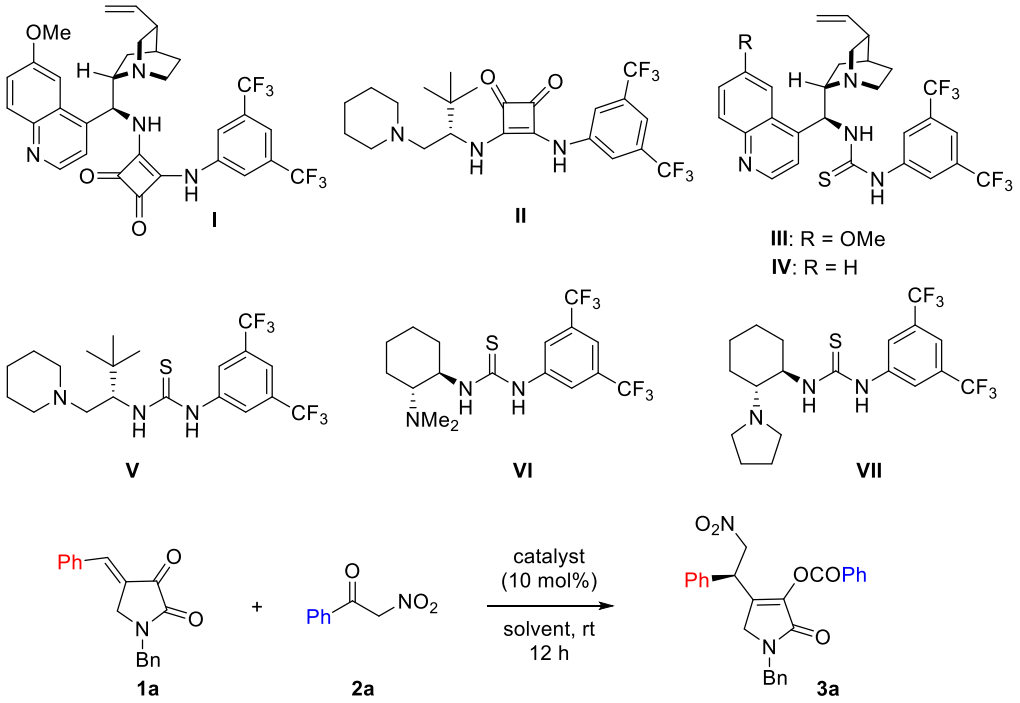
pyrrolidine-2,3-diones could also be suitable reaction partner of *α*-nitroketones. However, during the progress of our work, Bonne, Bugaut and co-workers have shown one example of the reaction of 2-nitro acetophenone with 4-benzylidine pyrrolidine-2,3-dione and only moderate enantioselectivity (50% ee) was achieved [25]. Here in, we develop a better enantioselective version of the reaction between *α*-nitroketones and 4 arylidene-pyrrolidine-2,3-diones.

Results and Discussion

Initially a model reaction was examined between *N*-benzyl 4-benzylidene-pyrrolidine-2,3-dione (**1a**) and 2-nitro-1-phenylethanone (**2a**) with quinine derived bifunctional squaramide catalyst **I** in dichloromethane at room temperature (Table 1). Delightfully, after stirring for 12 hours, a product was isolated in 70% yield and it was characterized as **3a** that was supposed to be formed *via* conjugate addition followed by benzoyl transfer reaction. However only 20% enantiomeric excess was achieved. Then tertiary leucine derived squaramide catalyst **II** was employed and here both yield and ee got slightly improved. Then we turned our attention to employ bifunctional thiourea catalysts [26-27] and it proved to be fruitful. Thus, quinine and cinchonidine derived bifunctional thiourea catalysts **III** and **IV** were employed in the reaction and moderate enantiomeric excesses were achieved. The yield and enantioselectivity got further improved with *t*-leucine derived thiourea catalyst **V.** Takemoto catalyst **VI** [28] was also suitable for the reaction though moderate enatiomeric excess was detected. Finally, the best catalyst turned to be pyrrolidine containing bifunctional thiourea catalyst **VII** and the desired product was isolated in 80% yield with 80% ee. Then solvent optimization was carried out to obtain better

enantioselectivity. Similar enantioselectivity was attained in α,α,α-trifluoro toluene and tetrahydrofuran. The enantioselectivity got improved to 86% ee in chloroform. Finally, the best solvent was found to be 1,2-dichloroethane and the product 3a was obtained in 82% yield with 90% ee.

Table 1: Catalyst Screening and Optimization of Reaction Conditions



entry[a]	catalyst	solvent	yield[b]	ee[c]
1	**I**	CH_2Cl_2	70	20
2	**II**	CH_2Cl_2	73	34
3	**III**	CH_2Cl_2	76	55
4	**IV**	CH_2Cl_2	78	52
5	**V**	CH_2Cl_2	80	74
6	**VI**	CH_2Cl_2	75	50
7	**VII**	CH_2Cl_2	80	80
8	**VII**	$PhCF_3$	78	78
9	**VII**	THF	80	80

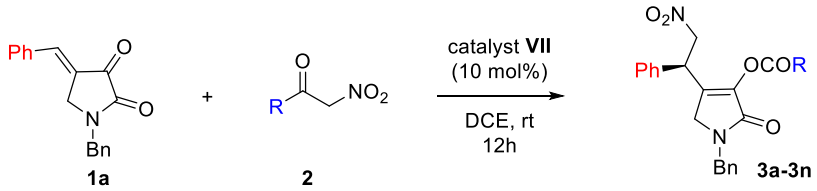
10	**VII**	$CHCl_3$	80	86
11	**VII**	$(CH_2Cl)_2$	80	90

[a]Reactions were carried out with 0.1 mmol of **1a** and 0.1 mmol of **2a** in 0.6 mL solvent at rt for 12 hours; [b]Isolated yield after silica gel column chromatography; [c]Determined by HPLC.

After finding the best optimized conditions we ventured in the scope and generality of the reaction. Initially a variety of α-nitroketones **1** having different aryl substitutents were tested (Table 2). Infact, different *ortho*-, *meta*- and *para*-substitutions on the phenyl group could be incorporated and satisfactory results were obtained (entries 2-11). For example, *p*-tolyl containing nitroketone **2b** delivered product **3b** in 80% yield with 88% ee (entry 2). Similar enantioselectivity was obtained for product **3c** with *p*-anisyl group (entry 3). Interestingly, the enantioselectivity dropped slightly after replacing *p*-methoxy substituent with *p*-ethoxy group and product **3d** was isolated in 78% yield with 80% ee (entry 4). Biphenyl group can also be tolerated and good result was achieved (entry 5). Then 4-fluoro and 4-bromo containing nitroketones **2f** and **2g** were employed in the reaction and gratifyingly the same 90% ee were obtained for both products **3f** and **3g** (entrie 6-7). *meta*-Substitutions were also tolerated in the reactions though lesser enantioselectivities were detected for products **3h** and **3i** (entries 8-9). Then *ortho*-substituted nitroketones **2j** nd **2k** were employed in the reaction. To our delight, the reactions progressed well to provide products **3j** and **3k** in moderate enantioselectivities (entries 10-11). 2-Naphthyl group containing nitroketone **2l** also participated in the reaction to deliver **3l** in 80% ee (entry 12). Moreover, hydrocinnamyl group containing nitroketone **2m** also took part in the reaction and product **3m** was isolated in 65% yield with 64% ee (entry 13).

Finally, nitroketone **2n** with cyclohexyl group was engaged in the reaction and moderate enantioselectivity was detected for product **3n** (entry 14).

Table 2: Scope of *α*-Nitroketones in the Reaction.

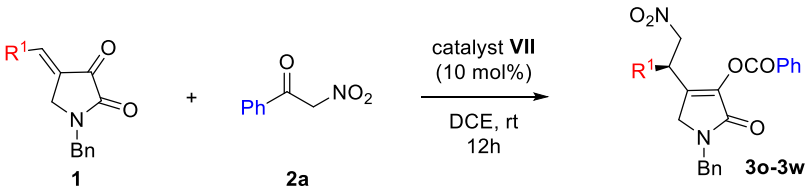


entry[a]	R	**3**	yield[b]	ee[c]
1	Ph	**3a**	80	90
2	4-MeC_6H_4	**3b**	80	88
3	4-OMeC_6H_4	**3c**	82	88
4	4-OEtC_6H_4	**3d**	78	80
5	4-PhC_6H_4	**3e**	82	82
6	4-FC_6H_4	**3f**	79	90
7	4-BrC_6H_4	**3g**	78	90
8	3-MeC_6H_4	**3h**	70	72
9	3-OMeC_6H_4	**3i**	72	66
10	2-MeC_6H_4	**3j**	65	68
11	2-OMeC_6H_4	**3k**	68	70
12	2-naphthyl	**3l**	75	80
13	$PhCH_2CH_2$	**3m**	65	64
14	cyclohexyl	**3n**	70	72

[a]Reactions were carried out with 0.1 mmol of **1a** and 0.1 mmol of **2** in 0.6 mL 1,2-dichloroethane at rt for 12 hours; [b]Isolated yield after silica gel column chromatography; [c]Determined by HPLC.

In the next phase, screening of a variety of pyrrolidine-2,3-diones **1** having different benzylidene substitutents were investigated with catalyst **VII** (Table 3). It turned out that a range of substitutions were tolerated and good results were attained. Initially, different *para*-substitutions were checked and gratifyingly smooth conversions were detected (Table 3, entries 1-5). For example, pyrrolidine-2,3-dione **1b** with 4-tolyl substituent provided product **3o** in 83% yield with 72% ee (entry 1). Similar enantioselectivity was obtained with 4-tertbutylphenyl substituted pyrrolidine-2,3-dione **1c** (entry 2). Then different 4-halo substituted pyrrolidine-2,3-diones **1c-1f** were employed in the reaction and mixed results were obtained. Though product **3q** having 4-fluorophenyl substitution was isolated in 80% yield with 84% ee, slight less enantioselectivities were obtained for products **3r** and **3s** (entries 3-5). These products could be useful for further elaboration via cross-coupling reactions. *ortho*-Substituted pyrrolidine-2,3-dione **1g** also participated in the reaction to deliver product **3t** in 86% ee (entry 6). 2,4-Disubstitutions was also tolerated in the reaction and moderate enantioselectivity was observed for product **3u** (entry 7). Then 3,5-disbstituted aryl group containing pyrrolidine-2,3-dione **1i** was prepared and engaged in the reaction. To our delight, smooth conversion was detected and product **3v** was isolated in 80% yield with 72% ee (entry 8). Finally, 2-thienyl group containing pyrrolidine-2,3-dione **1j** was screened and acceptable enantioselectivity for product **3w** was witnessed (entry 9).

Table 3: Scope of Pyrrolidine-2,3-diones.



entry[a]	R^1	**1**	**3**	yield[b]	ee[c]
1	4-MeC_6H_4	**1b**	**3o**	83	72
2	4-^{t}BuC_6H_4	**1c**	**3p**	80	72
3	4-FC_6H_4	**1d**	**3q**	80	84
4	4-ClC_6H_4	**1e**	**3r**	79	70
5	4-BrC_6H_4	**1f**	**3s**	82	76
6	2-FC_6H_4	**1g**	**3t**	79	86
7	2,4-$F_2C_6H_3$	**1h**	**3u**	78	72
8	3,5-$(OMe)_2C_6H_3$	**1i**	**3v**	80	72
9	2-thienyl	**1j**	**3w**	81	82

[a]Reactions were carried out with 0.1 mmol of **1** and 0.1 mmol of **2a** in 0.6 mL 1,2-dichloroethane at rt for 12 hours; [b]Isolated yield after silica gel column chromatography; [c]Determined by HPLC.

From the literature study, the optical rotation of the compound (*S*) **3a** is $[\alpha]_D^{20}$ = 30.69 (c 1.03, $CHCl_3$, 25.1 ^oC).[25] Our value was $[\alpha]_D^{20}$ = -35.00 (c 1.03, $CHCl_3$, 27.5 ^oC). Thus the absolute configuration of compound **3a** was determined to be (*R*).

Conclusion

In summary, this paper reports an organocatalytic asymmetric Michael/acyl transfer reaction between *α*-nitroketones and 4 arylidene-pyrrolidine-2,3-diones. The products

were obtained in good yields with moderate to high enantioselectivities. Easily available bifunctional thiourea catalyst was employed in the methodology.

References

1. Krause, N.; Hoffman-Roder, A. *Synthesis* **2001**, 2, 171-196

2. Sibi, M. P.; Manyem, S. *Tetrahedron* **2000**, *56*, 8033-8061.

3. Alonso, D. A.; Baeza, A.; Chinchilla, R.; Gómez, C.; Guillena, G.; Pastor, I. M.; Ramón, D. J. *Molecules* **2017**, *22*, 895.

4. Tsogoeva, S. B. *Eur. J. Org. Chem*. **2007**, 2007, 1701-1716.

5. Vicario, J. L.; Badía, D.; Carrillo, L. *Synthesis* **2007**, 14, 2065-2092.

6. Ballini, R.; Bosica, G.; Fiorini, D.; Palmieri, A.; Petrini, M. *Chem. Rev*. **2005**, *105*, 933-972.

7. Yang, W.; Du, D.-M. *Org. Lett*. **2010**, *12*, 5450-5453.

8. Kwiatkowski, P.; Cholewiak, A.; Kasztelan, A. *Org. Lett.* **2014**, *16*, 5930-5933.

9. Bera, K.; Namboothiri, I. N. N. *J. Org. Chem*. **2015**, *80*, 1402-1413.

10. Gharui, C.; Pan, S. C. *Org. Biomol. Chem.* **2019**, *17*, 5190–5211.

11. Gao, Y.; Ren, Q.; Siau, W.-Y.; Wang, J. *Chem. Commun*. **2011**, *47*, 5819-5821.

12. Lu, R.-J.; Yan, J.-Y.; Wang, J.-J.; Du, Q.-S.; Nie, S.-Z.; Yan, M. *J. Org. Chem*. **2011**, *76*, 6230-6239.

13. Li, P.; Chan, S. H.; Chan, A. S. C.; Kwong, F. Y. *Org. Biomol. Chem.* **2011**, *9*, 7997-7999.

14. Maity, R.; Gharui, C.; Sil, A. K.; Pan, S. C. *Org. Lett*. **2017**, *19*, 662-665.

15. Maity, R.; Pan, S. C. *Org. Biomol. Chem*. **2018**, *16*, 1598-1608.

16. Mondal, K.; Pan, S. C. *J. Org. Chem.* **2018**, *83*, 5301–5312.

17. Gharui, C.; Behera, D.; Pan, S. C. *Adv. Synth. Catal.* **2018**, *360*, 4502–4508.

18. Maity, R.; Sahoo, S. C.; Pan, S. C. *Eur. J. Org. Chem.* **2019**, 2297–2304.

19. Liu, Y. Y.; Mo, Y. R.; Dong, X. D.; Chen, L.; Ye, L.; Li, X. Y.; Zhao Z. G., Li, X. F. *Tetrahedron* **2019**, *75*, 2466–2471.

20. Song, Y.-X.; Du, D.-M. *Adv. Synth. Catal.* **2019**, *361*, 5042-5049.

21. Zhou, J.; Bai, L.-J.; Liang, G.-J.; Xu, Q.-G.; Zhou, L.-P.; Zhou, H. *Org. Biomol. Chem.* **2020**, *18*, 2641-2645.

22. Li, J.-L.; Fu, L.; Wu, J.; Yang, K.-C.; Li, Q.-Z.; Gou, X.-J.; Peng, C.; Han, B.; Shen, X.-D. *Chem. Commun.* **2017**, *53*, 6875−6878.

23. Hu, X.; Zhou, Y.; Lu, Y.; Zou, S.; Lin, L.; Liu, X.; Feng, X. *J. Org. Chem*. **2018**, *83*, 8679−8687.

24. Wang, Y.; Chen, Y.; Li, X.; Mao, Y.; Chen, W.; Zhan, R.; Huang, H. *Org. Biomol. Chem*. **2019**, *17*, 3945−3950.

25. Fofana, M.; Dudognon, Y.; Bertrand, L.; Constantieux, T.; Rodriguez, J.; Ndiaye, I.; Bonne, D.; Bugaut, X. *Eur. J. Org. Chem.* **2020**, 3486-3490.

26. Connon, S. J. *Chem. Commun.* **2008**, 2499-2510.

27. Siau, W.-Y.; Wang, J. *Catal. Sci. Technol.* **2011**, *1*, 1298-1310.

28. Okino, T.; Hoashi, Y.; Takemoto, Y. *J. Am. Chem. Soc*. **2003**, *125*, 12672-12673.