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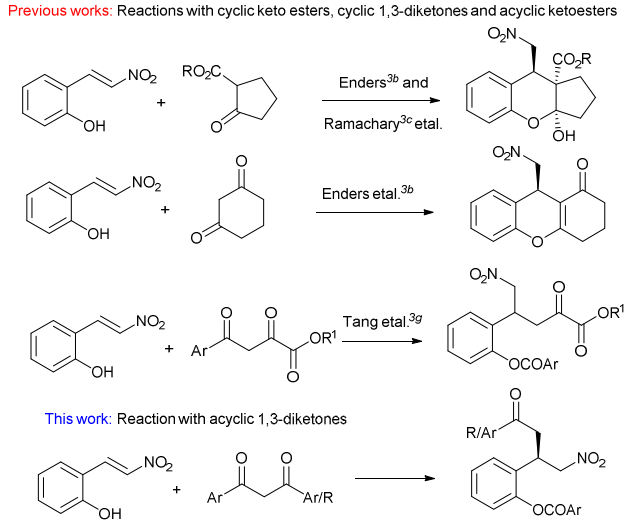
Organocatalytic Asymmetric Michael/Hemiketalization/Acyl Transfer Reaction of 1,3-Propanediones with (*E*)-2-(2-nitrovinyl)phenols

Nimisha Bania and Subhas Chandra Pan*

An organocatalytic asymmetric cascade Michael/ hemiketalization /acyl transfer reaction between (*E*)-2-(2-nitrovinyl)phenols and 1,3-propanediones is disclosed. Cinchona alkaloid derived bifunctional thiourea catalyst was found to be the most effective for this reaction and provided the desired products in moderate to good yields with good to high enantioselectivities.

The Michael reaction of carbon-centered nucleophiles to nitro olefins represents one of the direct and fascinating routes to nitroalkanes, which are important synthetic intermediates in organic chemistry as diverse transformations of the nitro group into other functional groups could be possible. The organocatalytic asymmetric versions of such processes have been studied extensively in recent years by a large number of synthetic organic chemistry groups.[1] Also, Michael addition reaction-triggered cascade reactions have drawn significant attention because of the ultimate formation of different structural frameworks having multiple stereocentres.[2] Thus the development of new organocatalytic asymmetric Michael based cascade reactions is an important arena of research.

In this regard, (*E*)-2-(2-nitrovinyl)phenols have been broadly utilized as bidentate substrate and a range of asymmetric organocatalytic one-pot double Michael or Michael-cyclization reactions has been developed with the induction of neighboring *ortho* hydroxyl group.[3] The conjugate addition of 1,3-dicarbonyl compounds to these substrates could potentially lead to different types of products. For example, in 2012 Enders disclosed domino Michael–hemiacetalization/lactonization and dehydration sequences for the generation of tricyclic chroman scaffolds by employing cyclic β-ketoesters and cyclic 1,3-diketones (Scheme 1).[3b] In the same year Ramachary and co-workers reported a related Michael–lactonization reaction between (*E*)-2-(2-nitrovinyl)phenols and cyclic β-ketoesters (Scheme 1).[3c] In 2013, Tang and co-workers developed an organocatalytic Michael-acyl transfer reaction between 2,4-dioxo-4-arylbutanoates and (*E*)-2-(2-nitrovinyl)phenols (Scheme 1).[3g] However, acyclic 1,3-diketones have not been investigated in the asymmetric reaction with (*E*)-2-(2-nitrovinyl)phenols though an achiral method was developed by Wang and co-workers.[4] Realizing the potential of γ-nitrocarbonyl compounds, we envisaged in developing an asymmetric Michael/hemiacetalization/retro-aldol reaction[5] between linear 1,3-diketones and (*E*)-2-(2-nitrovinyl)phenols (Scheme 1).



Scheme 1 Organocatalytic asymmetric reaction between 1,3-dicarbonyl compounds and (*E*)-2-(2-nitrovinyl)phenols.

Initially, the reaction between (*E*)-2-(2-nitrovinyl)phenol (**1a**) and 1,3-diphenyl-1,3-propane-1,3-dione (**2a**) was examined with cinchona alkaloid derived bifunctional thiourea catalysts (**I-III**)[6] in dichloromethane solvent at room temperature (Table 1, entry 1). To our delight, the reaction progressed well in 3 days with quinidine derived thiourea **I** to deliver the Michael-acyl transfer product **3a** in 70% yield, however the enantioselectivity was moderate (47% ee, Table 1, entry 1).

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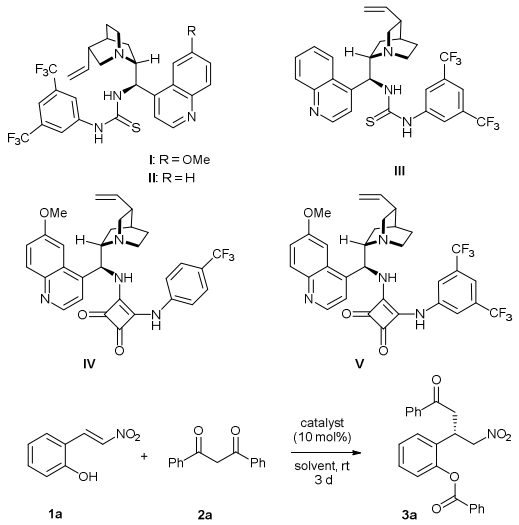
The enantioselectivity did not improve with cinchonine derived thiourea catalyst **II** (entry 2). Then cinhonidine derived catalyst **III** was employed in the reaction and gratifyingly a big jump to 92% ee was observed (entry 3). Bifunctional squaramide catalysts **IV**-**V** were also screened but lower enantioselectivities were detected (entries 4-5). Then we turned our attention on the solvent optimization and this proved to be rewarding. For example, the enantiomeric excess got enhanced to 94% ee in toluene and similar conversion was observed (entry 6). Xylene as a solvent also afforded similar enantioselectivity (entry 7). Finally the best solvent was found to be mesitylene which provided the product in 73% yield with 96% ee (entry 8).

Table 1 Catalyst screening and optimization of reaction conditions

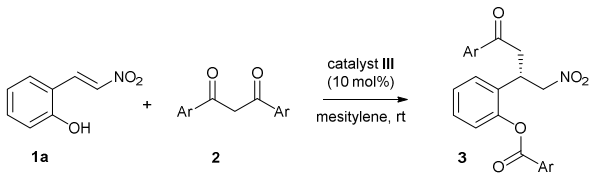


entry[a]	catalyst	solvent	yield[b]	ee[c]
1	**I**	CH_2Cl_2	70	(-) 47
2	**II**	CH_2Cl_2	67	(-) 47
3	**III**	CH_2Cl_2	71	92
4	**IV**	CH_2Cl_2	70	64
5	**V**	CH_2Cl_2	69	82
6	**III**	toluene	73	94
7	**III**	xylene	72	95
8	**III**	mesitylene	73	96

[a]Reactions were carried out with 0.05 mmol of **1a** with 0.055 mmol of **2a** in 0.2 mL solvent using 10 mol% catalyst at room temperature. [b]Isolated yield after silica gel column chromatography. [c]Determined by chiral HPLC.

After the identification of suitable conditions, the scope and generality of the reaction was investigated. Initially a range of 1,3-propanediones **2** having different aryl groups were tested and the results are shown in Table 2. Gratifyingly quite a number of substituents can be incorporated in the *ortho-*, *meta-* and *para*-position of the aryl group and good results were achieved (entries 2-9). At first, different *meta*-substituted di-aryl propanediones **2b**-**e** were screened and the products **3b-e** were isolated in good yields with high enantioselectivities (entries 2-5). For example, 3-methoxy substituted diarylpropanedione **2b** reacted smoothly to provide product **3b** in 75% yield with 95% ee (entry 2). Inspired by this result, other 3-alkoxy propanediones **2c** and **2d** were employed and high enantioselectivities were detected for the products **3c** and **3d** respectively (entries 3-4). 3-Bromo substituted propanedione **2e** also participated in the reaction delivering the product **3e** in 78% yield with 95% ee (entry 5). Then different *para*-substituted

Table 2 Scope of 1,3-propanediones



entry[a]	Ar	Time (d)	3	yield[b]	ee[c]
1	Ph	3	**3a**	73	96
2	3-$OMeC_6H_4$	3	**3b**	75	95
3	3-$OEtC_6H_4$	3	**3c**	68	94
4	3-$O^nPrC_6H_4$	3	**3d**	66	90
5	3-BrC_6H_4	3	**3e**	78	95
6	4-MeC_6H_4	3	**3f**	77	81
7[d]	4-$OMeC_6H_4$	4	**3g**	65	74
8	4-FC_6H_4	3	**3h**	73	77
9	4-BrC_6H_4	3	**3i**	76	86

[a]Unless otherwise mentioned, reactions were carried out with 0.1 mmol of **1a** and 0.11 mmol of **2** with 10 mol% catalyst **III** in mesitylene at room temperature. [b]Isolated yield after silica gel column chromatography. [c]Determined by HPLC. [d]Reaction was run at 0 °C.

propane diones **2f**-**2i** were prepared and engaged in the reaction (entries 6-9). Propanedione **2f** having tolyl groups afforded the corresponding product **3f** in 77% yield with 81% ee (entry 6). The enantiomeric excess for product **3g** having anisyl substituents was less at room temperature, thus the reaction was studied at 0 °C to obtain acceptable enantioselectivity (entry 7). Further lowering of the reaction temperature could not improve the enantioselectivity. 4-Halo substitutions were also tolerated in the reaction and the products **3h**-**3i** were obtained in similar yields. Though the enantiomeric excess for product **3h** was moderate (entry 8), product **3i** was isolated in high enantioselectivity (entry 9). These halo substituted products could be further elaborated via cross-coupling reactions.

Then the scope of (*E*)-2-(2-nitrovinyl)phenol was studied and here also good results were achieved with different

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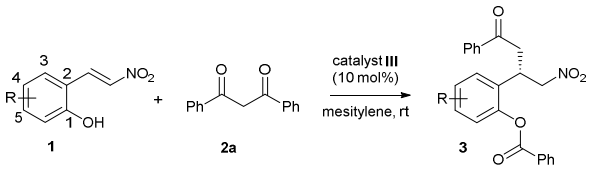
substitutions (Table 3). Initially different 4-substituted nitrovinylphenols were employed in the reaction and acceptable yields were detected. Though 4-methyl substitution lowered the enantioselectivity a little, high



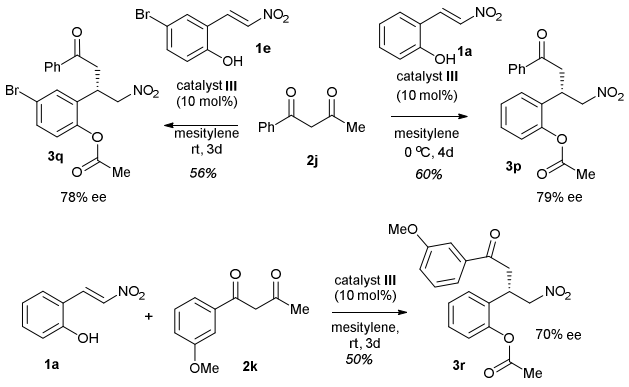
1 2a 3

Table 3 Scope of (*E*)-2-(2-nitrovinyl)phenols

entry[a]	R	1	Time (d)	3	yield[b]	ee[c]
1	4-Me	**1b**	3	**3j**	75	83
2	4-OMe	**1c**	3	**3k**	75	86
3	4-Cl	**1d**	3	**3l**	78	81
4	4-Br	**1e**	3	**3m**	72	81
5[d]	5-OMe	**1f**	4	**3n**	70	92
6	6-Me	**1g**	3	**3o**	73	97

[a]Unless otherwise mentioned, reactions were carried out with 0.1 mmol of **1** and 0.11 mmol of **2a** with 10 mol% catalyst **III** in mesitylene at room temperature. [b]Isolated yield after silica gel column chromatography. [c]Determined by HPLC. [d]Reaction was run at -20 °C.

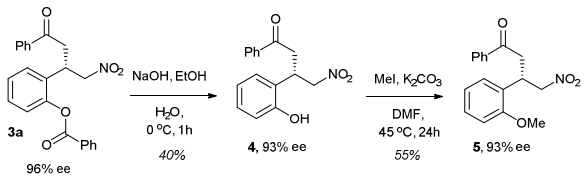
enantioselectivity was obtained for product **3k** having 4-methoxy substitution (entries 1-2). 4-chloro and 4-bromo gave similar enantioselectivities (entry 3-4). The reaction was also found to be smooth with 5-methoxy substituted nitrophenol **1f** however less enantioselectivity was obtained at room temperature**.** Gratifyingly lowering the temperature to -20 °C could improve the enantioselectivity to 92% ee (entry 5). Finally, 6-substitutions were also tolerated in the reaction and 6-methyl substituted nitrovinylphenol **1g** emerged as the best substrate for the reaction providing product **3o** in 73% yield with 96% ee (entry 6).



Scheme 2 Employment of unsymmetrical 1,3-diketones **2j** and **2k**

The scope of the reaction was then further extended by incorporating unsymmetrical 1,3-diketones in the reaction. Thus initially 4-phenyl,1,4-butanedione **2j** was prepared and reacted with (*E*)-2-(2-nitrovinyl)phenols **1a** and **1e** (Scheme 2). Pleasingly the reactions progressed smoothly to deliver major *O*-acetyl containing products **3p** and **3q** in good yields. The enantioselectivity of **3p** was moderate at room temperature and thus the reaction was performed at 0 °C to improve the ee (79%). Another unsymmetrical diketone **2k** having methoxy substituent was also prepared and engaged in the reaction. This resulted in the formation of 3r in 70% ee.

To strengthen our methodology few derivatizations were performed on **3a** (Scheme 3). At first, the ester moiety of **3a** was hydrolyzed with sodium hydroxide to provide phenol **4** in 40% yield and enantioselectivity was almost retained. Then methoxy protection with iodomethane delivered **5** with retention in enantioselectivity. (Scheme 3). Based on the HPLC chromatogram of **5** as reported by Kwiatkowski and co-workers,[7] the absolute configuration of product **3a** was assigned to be (*S*).



Scheme 3 Synthetic transformations of **3a**.

A plausible mechanism[8] has been shown in Scheme 4 to explain the stereochemistry of the product. It is believed that the nitro functionality of (*E*)-2-(2-nitrovinyl)phenol **1a** will co-ordinate with the thiourea motif of the catalyst **III**. Since the *Re* face of the nitroolefin is blocked by the catalyst, the addition of enol **2a'** occurs only from the *Si* face to provide intermediate **A**. Intramolecular hemiketalization then generates **B**. Finally retro-aldol reaction of **B** delivers product **3a**.

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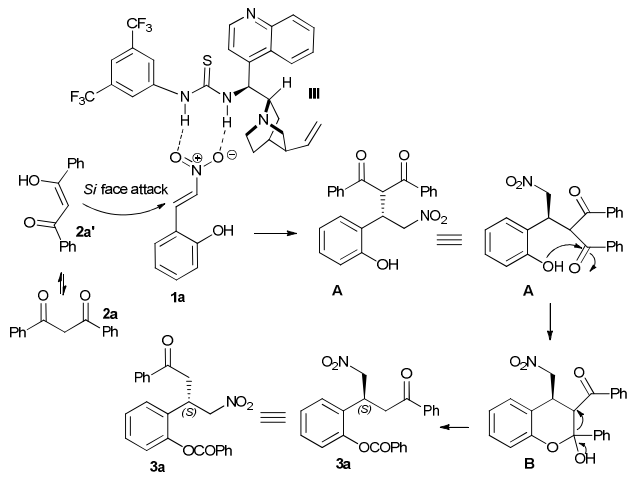

Scheme 4 Proposed mechanism.

In summary, this report has shown the development of an efficient Michael-hemiketalization-acyl transfer reaction between 1,3-propanediones and (*E*)-2-(2-nitrovinyl)phenols. The products having nitro, keto and ester functionalities were obtained in moderate to good yields with good to high enantioselectivities. Also selective acetyl transfer was observed from unsymmetrical 1,3-diketones. Given the high importance of chiral nitroalkanes in synthetic organic chemistry our method might be useful to prepare these compounds in a convenient way.

Acknowledgements

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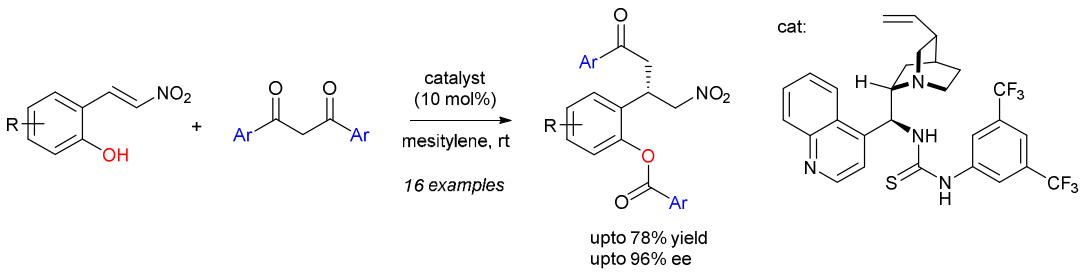

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