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Synthesis of prolinal dithioacetals as catalysts for the highly stereoselective Michael addition of ketones and aldehydes to β-nitrostyrenes

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Abstract—Catalytic highly enantioselective (up to >99% ee) and diastereoselective (up to 99% de) direct Michael addition of ketones and aldehydes to β-nitrostyrenes have been achieved with readily accessible and highly tunable prolinal dithioacetal catalysts.

Michael addition is one of the most important C–C bond formation reactions in organic synthesis[1] and, therefore, developing enantioselective Michael addition reactions has been the focus of organic chemists for decades.[2] Due to its environmentally friendly nature and its relevance to biocatalysis, organocatalysis is currently in vogue.[3] In this regard, many proline derivatives[4,5] have been proposed as the catalysts for the direct addition of ketones and/or aldehydes to β-nitrostyrenes via the enamine intermediate[6] in recent years, and excellent enantio- and/or diastereoselectivities have been obtained with some of these reported catalysts. In order to achieve the desired stereoselectivities, most of these proline-derived catalysts have a hydrogen-bonding moiety, such as hydroxy, amide, ammonium salt, and thiourea, in the side-chain to direct the substrate approach.[4]

As a tool of achieving stereocontrol, steric factors have been widely used in the asymmetric synthesis and catalysis. Surprisingly, the design and synthesis of highly efficient catalysts for this direct Michael reaction on the basis of pure steric interactions are much less studied.[5] The diphenylprolinol silyl ether catalyst **1** (Fig. 1)[5a,b] reported by Hayashi et al.[5a] represents the most successful example in this category. Nevertheless, the synthesis of this catalyst involves Grignard reagent.[7] Furthermore, no ketone substrates have been studied and, therefore, it is not certain whether this catalyst is limited for aldehyde substrates only.[5a,b]

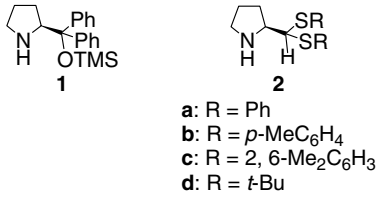

Figure 1. Catalysts utilized for the Michael addition.

The design and synthesis of highly stereoselective, readily accessible and tunable catalysts are always desirable for asymmetric catalysis. In the current Letter, we wish to disclose the synthesis of some prolinal dithioacetals (**2a**–**d**, Fig. 1) as the highly diastereoselective and enantioselective catalysts for the asymmetric Michael addition of both ketones and aldehydes to β-nitrostyrenes.

As shown in Figure 1, in our catalyst design, we replaced the normal C–C bonds in the side chain (such as those in **1**) with the C–S (thioacetal) bonds. Due to the ease of the thioacetal formation (vs the C–C bond formation) and the variety of available thiol structures, this design makes it much easier for the synthesis and fine-tuning of the catalyst structures. For example, these catalysts (**2a**–**d**) may be synthesized in high yields in just one step from commercially available *N*-Boc-prolinal and thiols.[8] Additionally, these catalysts are very stable under normal experimental conditions.

Keywords: Asymmetric; Dithioacetals; β-Nitrostyrene; *N*-Boc-prolinal; Proline; Enantioselective; Diastereoselective.
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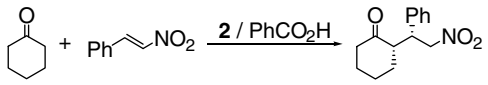
Table 1. Catalyst screening and reaction condition optimization[a]



3a **4a** **5a**

Entry	Cat.	Solvent	Time (h)	Yield[b] (%)	dr (*syn*/*anti*)[c]	ee[d] (%)
1	**2a**	CH_2Cl_2	29	81	97:3	97
2	**2b**	CH_2Cl_2	28	88	99:1	>99
3	**2c**	CH_2Cl_2	30	85	97:3	95
4	**2d**	CH_2Cl_2	40	75	95:5	80
5	**2b**	$CHCl_3$	30	80	98:2	95
6	**2b**	DMF	33	75	94:6	96
7	**2b**	Hexane	30	81	96:4	97
8	**2b**	Toluene	29	78	97:3	97
9[e]	**2b**	CH_2Cl_2	40	76	96:4	96

[a] Unless otherwise specified, all reactions were carried out with cyclohexanone (**3a**, 0.30 mmol), *trans*-β-nitrostyrene (**4a**, 0.10 mmol), the catalyst (**2**, 0.01 mmol, 10 mol %), and benzoic acid (0.01 mmol) in the specified solvent (0.5 mL) at rt.
[b] Yield of isolated product after chromatography.
[c] Determined by ^{1}H NMR analysis of the crude product.
[d] ee value of the major enantiomer was determined by HPLC analysis on a Chiralpak AD-H column. Absolute configuration was determined by comparison of the measured optical rotation with the reported data (Ref. 4t).
[e] Without benzoic acid.

By using cyclohexanone and *trans*-β-nitrostyrene as the model compounds, we first screened the catalysts (**2a**–**d**) for their ability in asymmetric inductions. The results are summarized in Table 1.

As shown in Table 1, in the presence of 10 mol % of benzoic acid and 10 mol % of the thiophenol acetal catalyst **2a**, the desired Michael product **5a** was obtained in 81% yield after reacting in CH_2Cl_2 at rt for 29 h (entry 1). Both excellent diastereoselectivity (97:3 dr) and enantioselectivity (97% ee) of the product were obtained. Catalyst **2b**, with a methyl group at the *para* position of the phenyl ring, generated even better results under these conditions: essentially a single enantiomer (>99% ee) of the *syn* diastereomer (99:1 dr; entry 2) was obtained. In contrast, the more hindered 2,6-dimethylthiophenol derivative **3b** gave slightly inferior results (97:3 dr, 95% ee; entry 3). Similarly, the *tert*-butyl mercaptan acetal **2d** also led to inferior results (entry 4). Thus, catalyst **2b** was identified as the best catalyst for the Michael addition, whereas catalysts **2a** and **2c** are also very good catalysts. By using **2b** as the catalyst, some common organic solvents were then screened, and CH_2Cl_2 was found to be the best solvent for this reaction (entry 2). $CHCl_3$ (entry 5), DMF (entry 6), hexane (entry 7), and toluene (entry 8) are all inferior solvents in terms of both enantioselectivity and diastereoselectivity, although the differences are not essential. It was also found that, even though benzoic acid does accelerate the reaction, it is not necessary for achieving the high enantioselectivity and diastereoselectivity in this reaction (entries 2 and 9). These results exclude the involvement of hydrogen-bond directing effects in the reaction and, therefore, the stereocontrol is achieved mainly through steric factors.

To understand the scope of this new catalytic system, we studied the reaction of various ketones and aldehydes and β-nitrostyrenes under the optimized conditions (0.3 mmol of carbonyl compounds, 0.1 mmol of β-nitrostyrene, 10 mol % of catalyst **2b**, and 10 mol % benzoic acid in 0.5 mL CH_2Cl_2 at rt). The results are collected in Table 2.

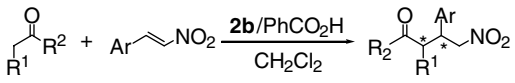
As is evident from Table 2, the reaction of cyclohexanone with various substituted β-nitrostyrenes gives the desired Michael products in excellent yields, diastereoselectivity (*syn*:*anti* ⩾ 97:3) and enantioselectivities (⩾95% ee, entries 1–8). The electronic nature and substitution pattern of the substituents on the phenyl ring have almost no influence on the stereoselectivities. Besides cyclohexanone, 4-oxacyclohexanone (entry 9) and 4-thiacyclohexanone (entry 10) produce similar results.

Cyclopentanone is an especially difficult substrate for this direct Michael reaction in terms of stereoselectivities: the best diastereoselectivity[4r] achieved so far was 77:23 and the highest ee value[4q] obtained for the major *syn* product was 83%. With our catalyst **2b**, the reaction generates the *syn* product in high diastereoselectivity (dr 90:10) and excellent enantioselectivity (98% ee, entry 11).

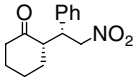
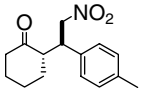
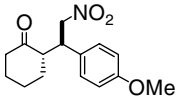
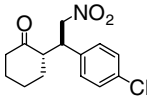
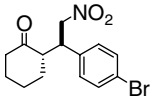
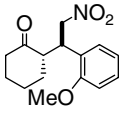
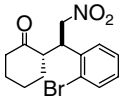
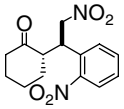
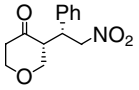
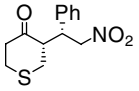
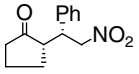
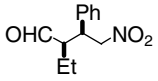
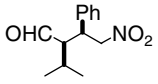
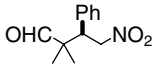
Besides ketones, our catalysts may also be applied to enolizable aldehyde substrates (entries 12–14). In the case of aldehydes, it was found that adding benzoic acid actually slows down the reaction (data not shown) and, therefore, these reactions were carried out without benzoic acid. Additionally, the reaction temperature was lowered to 0 °C to obtain optimum enantioselectivities of the products. Under these conditions, the reaction of butanal gives the desired *syn* product in perfect diastereoselectivity (dr 99:1) and enantioselectivity (99% ee, entry 12). The reactions of more hindered *iso*-valeraldehyde and 2-methylpropanal require more loading of **2b** (20 mol %). Also the enantioselectivities obtained for these products are lower. For example, with *iso*-valeraldehyde the Michael product was obtained in 92% de and 85% ee for the major *syn* diastereomer (entry 13). 2-Methylpropanal led to an even lower ee value of 76% of the Michael product (entry 14). Nonetheless, this result is not surprising: catalyst **1** leads to an ee value of 68% for the product of 2-methylpropanal.[5a] It should be pointed out the aldehyde substrates lead to the opposite enantiomer of the *syn* diastereomer as compared with cyclic ketones.

The stereoselectivity of this reaction may be explained by using the acyclic synclinal transition state proposed originally by Seebach and Golinski (Fig. 2).[9] The formation of opposite enantiomers of the *syn* adduct as the major products in the cases of cyclic ketones and aldehydes is due to the differences in the favored conformations of the enamine intermediates. As shown in Figure 2, for cyclohexanone (left structure), the enamine double bond is nearer to the thioacetal group, and attacking of the enamine onto *re* face of nitrostyrene leads to the observed major enantiomer. In contrast, for aldehyde

Table 2. Asymmetric Michael addition of ketones and aldehydes to β-nitrostyrenes[a]



3 **4** **5**

Entry	Product	Time (h)	Yield[b] (%)	dr[c] (*syn*/*anti*)	ee[d] (%)
1		28	88	99:1	>99
2		33	90	99:1	99
3		36	79	>99:1	97
4		20	86	99:1	99
5		20	90	99:1	99
6		38	77	>99:1	97[e]
7		25	81	99:1	97
8		30	85	97:3	95
9		27	79	99:1	96
10		29	76	98:2	95
11		26	80	90:10	98
12[f]		46	70	99:1	99
13[f,g]		59	70	96:4	85
14[f,g]		72	60	—	76

[a] Unless otherwise specified, all reactions were carried out with **3** (0.30 mmol), nitrostyrene **4** (0.10 mmol), catalyst **2b** (0.01 mmol, 10 mol %), and benzoic acid (0.01 mmol) in CH_2Cl_2 (0.5 mL) at rt.

[b] Yield of isolated product after chromatography.

[c] Determined by ^1H NMR analysis of the crude product.

[d] ee value of the major diastereomer; unless otherwise indicated, ee value was determined by HPLC analysis on a Chiralpak AD-H column. Absolute configuration was determined by comparison of the measured optical rotation with the reported data (Refs. 4t and 5c).

[e] On a chiralpak AS column.

[f] The reaction was carried out at 0 °C without adding benzoic acid.

[g] With 0.02 mmol (20 mol %) catalyst.

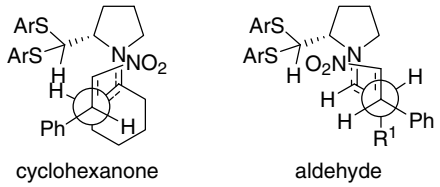


Figure 2. Proposed transition state models.

substrate (right structure), the *trans*-enamine[5a] double bond is away from the thioacetal group and the attack of this enamine onto the *si* face of the nitrostyrene leads to the formation of the observed opposite enantiomer of the *syn* diastereomer. Similar phenomena have been observed for other proline-derivatives, too.[5d]

In summary, we have synthesized some readily accessible and highly tunable prolinal dithioacetal catalysts for the direct Michael addition of both ketones and aldehydes to β-nitrostyrenes. Uniformly high diastereoselectivities and enantioselectivities have been obtained for both ketone and aldehyde substrates.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.06.085.

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