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Prolinal dithioacetals: Highly efficient organocatalysts for the direct nitro-Michael additions in both organic and aqueous media

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ABSTRACT

Some novel prolinal dithioacetal derivatives have been synthesized and applied as the organocatalysts for the direct Michael addition of ketones and aldehydes to nitroalkenes. High enantioselectivities and diastereoselectivities have been obtained in both organic and aqueous media (dichloromethane, water, or brine).

1. Introduction

The Michael addition reaction is arguably one of the most convenient and powerful methods for building new carbon-carbon bonds.[1] Since List[2] and Barbas[3] reported the first examples of the amine-catalyzed intermolecular Michael addition of ketones and aldehydes to nitroalkenes (the nitro-Michael reaction), numerous organocatalysts have been reported in the last sixteen years for the enantioselective nitro-Michael reactions and excellent stereoselectivities have been achieved in many cases.[4,5] In recent years, conducting traditional organic reactions in aqueous media has been an important topic in organic research due to the green nature of water as a solvent and its dramatic solvent effects on organic reactions.[6] Not surprisingly, some organocatalytic reactions have also been realized either in water or on water.[6c,e] Nevertheless, despite the fact that numerous organocatalysts have been developed for the asymmetric nitro-Michael reaction between aldehydes and ketones to nitroalkenes, catalytic systems that can operate in aqueous media are relatively few.[7,8] Apparently, finding novel catalysts that can operate in aqueous media is still warranted. Our group is interested in developing novel catalysts for the nitro-Michael reaction.[9] In this regard, a few years ago we briefly reported that prolinal dithioacetal derivatives[10] are highly stereoselective catalysts for the nitro-Michael reaction of aldehydes and ketones in organic solvents.[9a] Recently we found that these catalysts could also catalyze the nitro-Michael reaction in water and brine with high enantio- and diastereoselectivities. Herein we wish to report a detailed study of the nitro-Michael reaction using these derivatives as the catalysts in both organic and aqueous media.

2. Results and discussion

We are interested in using prolinal dithioacetals (**3**, Scheme 1) as potential organocatalysts for the direct nitro-Michael reaction because the formation of the dithioacetal functional group is much easier than that of C–C bonds and there are many different thiol structures available.[11] These features make the modification and fine-tuning the catalyst structure much easier. Indeed, most of the prolinal dithioacetal catalysts used in the current study were easily synthesized in high yields using a one-pot two-step reaction between the commercially available (*S*)–*N*-Boc-prolinal (**1**) and the corresponding thiols (**2**) using indium(III) chloride as the catalyst (Scheme 1).[9a,10] Nonetheless, catalyst **3d** derived from 4-chlorobenzenethiol (**2d**) needed boron trifluoride diethyl etherate as an additional catalyst for the synthesis, and it was obtained also in a much lower yield (68%, Scheme 1). All of these catalysts were

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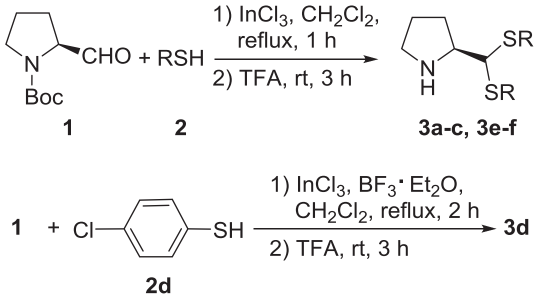


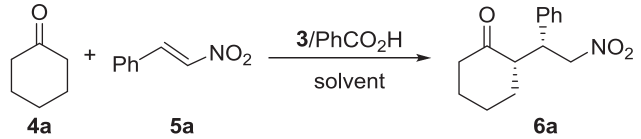
3a: R = C_6H_5-, yield = 94%;
3b: R = 4-MeC_6H_4-, yield = 93%;
3c: R = 4-$MeOC_6H_4$-, yield = 82%;
3d: R = 4-ClC_6H_4- ; yield = 68%
3e: R = 2,6-$Me_2C_6H_3$-; yield = 91%;
3f: R = *t*-Bu; yield = 88%.

Scheme 1. Synthesis of the prolinal dithioacetal catalysts.

found to be very stable under our reaction conditions.

With these catalysts in hand, we initially screened them in the direct nitro-Michael reaction in CH_2Cl_2 at rt with benzoic acid as the cocatalyst, using cyclohexanone (**4a**) and *trans*-β-nitrostyrene (**5a**) as the model substrates. The results are collected in Table 1. As the results in Table 1 show, with a 10 mol % loading of the benzenethiol-derived catalyst **3a**, the desired *syn* nitro-Michael adduct **6a** was obtained in 81% yield, 97:3 dr, and 97% ee in 29 h (entry 1). With the 4-methylbenzenethiol-derived catalyst **3b**, a slightly improved yield (88%), dr (99:1), and ee value (>99%) of **6a** was obtained (entry 2). Excellent results were also obtained with catalysts **3c** and **3d**, derived from 4-methoxybenzenethiol, and 4-chlorobenzenethiol, respectively (entries 3 and 4). When the thioacetal moiety in the catalyst contains two sterically demanding 2,6-dimethylphenyl groups (**3e**), the stereoselectivities of the reaction dropped slightly (entry 5). In contrast, an alkylthiol-derived catalyst **3f** gave a much lower ee value of the product (80%), although the diastereoselectivity was only slightly lower than the other arylthiol derivatives (entry 6). With the best catalyst **3b** (entry 2), we found that slightly lower yield, dr, and ee value of **6a** were obtained without adding benzoic acid as the cocatalyst (entry 7 vs. entry 2). Thus, benzoic acid has some beneficial effects on both the reactivity and stereoselectivity of the reaction, but it is not essential. Next, using the best catalyst **3b**, some common organic solvents were screened, and it were found slightly worse results were obtained in $CHCl_3$ (entry 8), DMF (entry 9), hexane (entry 10), and toluene (entry 11). Therefore, CH_2Cl_2 was identified as the best organic solvent for this reaction.

Table 1
Catalyst screening and reaction condition optimizations.[a]



Entry	Catalyst	Solvent	Time (h)	Yield (%)[b]	dr[c] (*syn*/*anti*)	ee (%)[d]
1	**3a**	CH_2Cl_2	29	81	97:3	97
2	**3b**	CH_2Cl_2	28	88	99:1	>99
3	**3c**	CH_2Cl_2	28	81	98:2	97
4	**3d**	CH_2Cl_2	30	82	98:2	98
5	**3e**	CH_2Cl_2	30	85	97:3	95
6	**3f**	CH_2Cl_2	40	75	95:5	80
7[e]	**3b**	CH_2Cl_2	40	76	96:4	96
8	**3b**	$CHCl_3$	30	80	98:2	95
9	**3b**	DMF	33	75	94:6	96
10	**3b**	hexane	30	81	96:4	97
11	**3b**	toluene	29	78	97:3	97
12[f]	**3b**	brine	31	79	98:2	98
13[f,g]	**3b**	water	26	90	97:3	98

[a] Unless otherwise specified, all the reactions were carried out with cyclohexanone (**4a**, 0.30 mmol), *trans*-β-nitrostyrene (**5a**, 0.10 mmol), catalyst **3** (0.01 mmol, 10 mol %), and benzoic acid (0.01 mmol, 10 mol %) in the specified solvent (0.5 mL) at room temperature.
[b] Yield of the isolated product after column chromatography.
[c] Determined by ^1H NMR analysis of the crude product.
[d] Value of the major diastereomer 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.[12]
[e] Without benzoic acid.
[f] Reaction was conducted in 1.0 mL of solvent.
[g] Reaction was carried out at 5 °C.

Recently there has been substantial interest in conducting the direct nitro-Michael reactions in water and brine,[7,8] since these two solvents are both cheap, green, and renewable.[6] We also evaluated catalyst **3b** in these two solvents. As the results in Table 1 show, when the reaction of **4a** and **5a** was conducted in brine (saturated NaCl solution in water) at rt, the desired product **6a** was obtained in 79% yield with an ee value of 98% and a dr of 98:2 (entry 12). A slightly lower ee value (92% ee) of **6a** was obtained when water was used as the solvent under similar conditions; Nonetheless, when the reaction was carried out at 5 °C, **6a** was obtained in 90% yield with an ee value of 98% and a dr of 97:3 (entry 13). We speculate that these observations are due to the slight differences of the catalyst conformation in these two solvents. Thus, both water and brine are almost equally good solvents as CH_2Cl_2 for this reaction, except that the reaction using water as solvent has to be carried out at subambient temperature.

The scope of this reaction were initially studied in the best organic solvent (CH_2Cl_2). The results are presented in Table 2. As the data in Table 2 show, besides *trans*-β-nitrostyrene (**5a**, entry 1), substituted *trans*-β-nitrostyrenes also reacted with cyclohexanone under the optimized conditions to yield the desired *syn* nitro-Michael adducts in high yields and excellent diastereo- and enantioselectivities (**6b-h**, entries 2–8). Neither the electronic nature of the *para*-substituent (entries 1–5) nor the position of the substituent on the phenyl ring (entries 6–8) has any meaningful effects on the reactivity or the stereoselectivities of the reaction. Nevertheless, our attempt to react an aliphatic nitroalkene (*trans*-1-nitroprop-1-ene) with cyclohexanone failed to produce any desired product under the optimized conditions (data not shown). Good product yields and high stereoselectivities were obtained for the products of other cyclic ketones, such as 4-oxacyclohexanone (**6i**, entry 9), 4-thiacyclohexanone (**6j**, entry 10), and cyclopentanone (**6k**, entry 11). In contrast, acetone appears to be a more challenging substrate for this reaction in terms of stereoselectivity. After careful optimizations, an ee value of only 50% was obtained for the product **6l** at −25 °C (entry 12). In addition to ketones, aldehydes may also be applied in this reaction. Nonetheless, in the case of aldehyde substrates, it was found that adding benzoic acid actually slowed down the reaction and, therefore, these reactions were carried out without benzoic acid. Under these new conditions, the Michael addition product of butanal could be obtained in 99% ee with a dr of 99:1 for the major *syn* product **6m** (entry 13). However, with the increase of the steric hindrance next to the aldehyde group, the product ee value decreases. For examples, the best results of the Michael addition of 3-methylbutanal and 2-methylpropanal to *trans*-β-nitrostyrene were achieved only when the reactions were carried out 0 °C. Under these optimized conditions, the ee value of the Michael adduct of 3-