Letter

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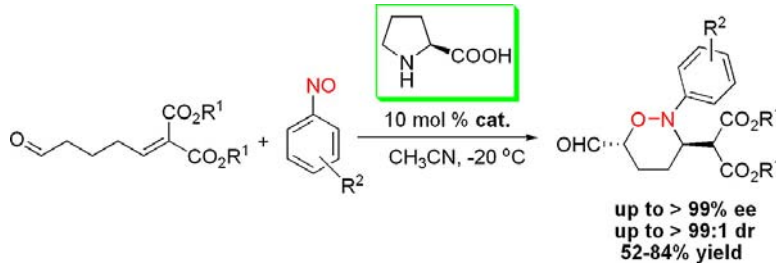

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A Highly Stereoselective Organocatalytic Tandem Aminoxylation/Aza-Michael Reaction for the Synthesis of Tetrahydro-1,2-Oxazines

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ABSTRACT

A facile stereoselective synthesis of multifunctionalized tetrahydro-1,2-oxazines (THOs) has been achieved by the organocatalyzed asymmetric tandem α-aminoxylation/aza-Michael reaction for the C−O/C−N bond formations in moderate to good yields with excellent diastereo- (>99:1 dr) and enantioselectivities (92% to >99% ee).

One of the most intensely studied areas in chemical synthesis at present is the development of new catalytic and highly enantioselective processes, particularly to generate useful structural components present in biologically active natural product.[1] Asymmetric organocatalyses, especially with L-proline and its derivatives, have witnessed marked progress in a variety of reactions such as aldol,[2] Mannich,[3] Michael,[4] Diels−Alder,[5] α-amination,[6] and α-aminoxylation reactions.[7] Although much research has been devoted to the field of carbon−carbon bond formation, the search for new methods to stereoselectively generate the C−O and C−N bonds for preparation of certain heterocyclic systems is still a significant challenge in organic chemistry. Tetrahydro-1,2-oxazine

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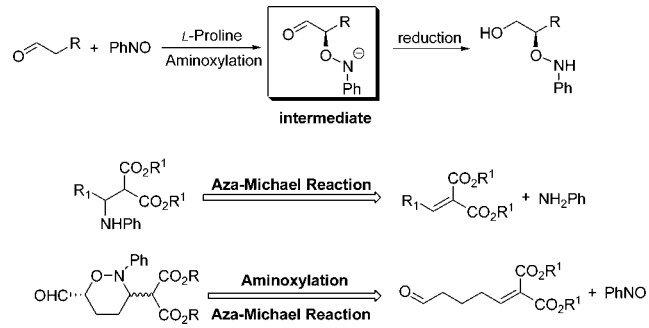
derivatives occur frequently in biologically active compounds[8] and are valuable synthetic intermediates.[9] Not only do they have the potential to act as therapeutic agents and chiral building blocks, they also possess synthetic utility through reductive N−O bond cleavage to form highly functionalized 1,4-amino alcohols which can be found in a number of bioactive natural products.

The nitroso function is recognized as a unique source to prepare nitrogen- and oxygen-containing molecules. Various catalytic asymmetric reactions exploiting the unique properties of nitroso compounds,[10] such as aminoxylation,[7] oxyamination,[11] and nitroso Diels−Alder reactions,[12] have recently been developed.

In 2003, our group first reported the L-proline catalyzed asymmetric α-aminoxylation of aldehydes with excellent enantioselectivity.[7a] This methodology provides an easy access to the enantioselective installation of a C−O bond. Conjugate addition of amines or their synthetic equivalents to α,β-unsaturated compounds constitutes one of the most interesting methods for the C−N bond formation due to the resulting β-amino adducts being privileged structures found in natural products and used in the pharmaceutical industry.[13] Despite the importance of this methodology, catalytic enantioselective aza-Michael reactions remain elusive and can thus be considered a challenging task.[14]

In 2004, Yamamoto et al. reported an enantioselective tandem *O*-nitroso aldol/Michael reaction with cyclic α,β-unsaturated ketones to produce nitroso Diels−Alder adducts with complete control of both regio- and stereochemistry.[1b] However, a direct tandem α-aminoxylation/aza-Michael reaction of aldehydes has not been reported yet. Herein, we describe a highly diastereo- and enantioselective tandem aminoxylation /aza-Michael reaction of aldehydes bearing a remote enemalonate as Michael acceptor at the δ-position for the synthesis of functionalized tetrahydro-1,2-oxazines (THOs) (Scheme 1), among which both C−O and C−N bonds were formed in excellent stereoselectivity.

Scheme 1. Synthetic Strategy



We started our investigation using our previously established conditions: nitrosobenzene (0.1 mmol, 1.0 equiv) and dimethyl 2-(5-oxopentylidene)malonate (0.12 mmol, 1.2 equiv) were added to 20 mol % L-proline in 1.0 mL of DMSO. To our delight, the proposed organocatalytic tandem aminoxylation/aza-Michael reaction was indeed facile at room temperature and can be accomplished within 30 min. The reaction progress can be easily monitored by observation of its color change from green to orange. After workup, the desired cyclic product was isolated in 37% yield with excellent enantioselectivity (98% ee) and diastereoselectivity (>99:1 dr) (Table 1, entry 1). Furthermore, various catalysts and solvents were surveyed and summarized in Table 1. The reaction proceeded smoothly in the presence of pyrrolidinyl tetrazole **II** or thiazolidine-4-carboxylic acid **III** to afford the cycloadduct in a slightly lower yield and without any loss in the ee and dr values (Table 1, entries 2 and 3). Unfortunately, Jørgenson's catalyst **IV** cannot be employed in this reaction to afford the corresponding α-aminoxylation/aza-Michael product. L-Proline was chosen as the catalyst not only because it is abundant and cheap, but more importantly because of its efficiency among all the other investigated catalysts. The screening

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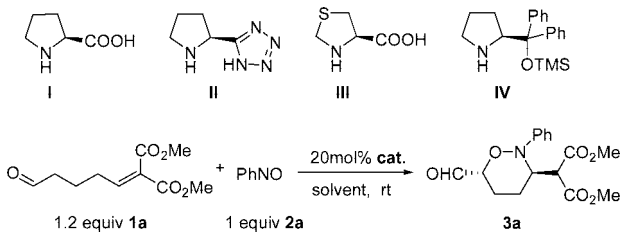
Table 1. Catalyst and Solvent Screening in Tandem Aminoxylation/Aza-Michael Reaction[a]



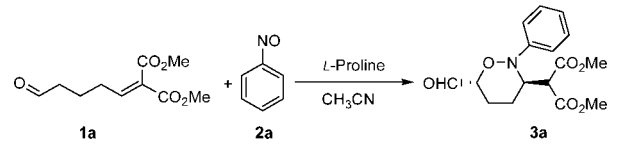
entry	cat.	solvent	time	yield (%)[b]	dr[c]	ee (%)[c]
1	**I**	DMSO	20 min	37	>99:1	98
2	**II**	CH_3CN	60 min	34	>99:1	97
3	**III**	DMSO	45 min	32	>99:1	98
4	**IV**	$CHCl_3$	60 min	<10	nd	nd
5	**I**	CH_3CN	60 min	52	>99:1	98
6	**I**	$CHCl_3$	60 min	46	>99:1	98
7	**I**	DMF	45 min	41	>99:1	98
8	**I**	NMP	45 min	45	>99:1	98
9	**I**	THF	3 h	<20	nd	nd
10	**I**	DCM	60 min	31	>99:1	98
11[d]	**I**	H_2O	24 h	<10	nd	nd

[a] In all cases, 0.2 equiv of catalyst was used in 0.1 M of nitrosobenzene solution. [b] Isolated yields. [c] Ee and dr determined by HPLC employing a Daicel Chiracel AS-H column. [d] 2 equiv of PTC added, PTC = tetraethylammonium bromide.

of various solvents revealed that CH_3CN is the best solvent as it gave the highest yield (52%) and without any loss of enantio- or diastereoselectivities (Table 1, entry 5). Halogenated solvent $CHCl_3$ (Table 1, entry 6) and highly polar and protophilic solvents, such as DMF and NMP (Table 1, entries 7 and 8), gave relatively lower yields (41−46%) whereas a less polar ethereal solvent, such as THF (Table 1, entry 9), and the most polar solvent water showed a deleterious effect on reactivity even after addition of tetraethyl ammonium bromide as PTC and stirring for 24 h (Table 1, entry 11).

Having established the choice of catalyst, we moved on to screen the reaction temperatures. We observed that when the reaction temperature decreased from room temperature to −20 °C (Table 2, entries 1−3), the supression of both side reaction and homodimer formation led to an increase in yield (from 52% to 65%) and without any loss in the ee and dr values. Increasing the equivalence of aldehyde to nitrosobenzene from 1.2 to 3 equiv increased the yield from 65% to 79% and at the same time decreased the reaction time from 24 h to 13 h. (Table 2, entries 3−6). Lastly, when we decreased the catalyst loadings from 20 to 5 mol %, the highest yield was found when 10 mol % of L-proline was used (Table 2, entries 6−8). In terms of operational convenience, 10 mol % of L-proline ensured high levels of reaction efficiency and enantioselectivity and was thus used in the next reaction. It is also noteworthy that after in situ reduction, the dr of corresponding alcohol product dropped significantly to 1:1 (Table 2, entry 9).

Table 2. Optimized Conditions for the Tandem Aminoxylation/Aza-Michael Reaction[a]



entry	equiv[b]	temp (°C)	cat. (%)[c]	time	yield (%)[d]	dr[e]	ee (%)[e]
1	1.2	23	20	1 h	52	>99:1	98
2	1.2	0	20	3 h	61	>99:1	98
3	1.2	−20	20	24 h	65	>99:1	98
4	1.5	−20	20	18 h	69	>99:1	98
5	2	−20	20	16 h	73	>99:1	98
6	3	−20	20	13 h	79	>99:1	98
7	3	−20	10	18 h	84	>99:1	98
8	3	−20	5	24 h	72	>99:1	98
9[f]	3	−20	10	24 h	73	1:1	nd

[a] Conditions: nitrosobenzene (0.1 mmol) was added to the solution of aldehyde and catalyst in 1 mL of CH_3CN at −78 °C, then stirred at various temperatures. [b] Equiv is mol ratio of aldehyde/nitrosobenzene. [c] Catalyst loading = proline/nitrobenzene. [d] Isolated yields. [e] Ee and dr determined by HPLC employing a Daicel Chiracel AS-H column. [f] Reduction in situ was performed to provide the corresponding alcohol. Dr was determined by ^1H NMR.

We further explored the generality of the reaction. The optimized reaction condition was applicable for reactions of various aromatic nitroso compounds **2a**−**h** and some 2-(5-oxopentylidene) malonate derivatives **1a**−**g**, to give moderate to good yields (52−84%) in excellent ee values (92−99%) and dr values (>99:1). The 2-methyl substituent in nitrosotoluene introduced more steric hindrance in the Michael addition step and this may account for the decrease in ee values (from 98% to 94% ee) when compared to the other nitrosobenzene derivatives. We observed that the substitutents in malonate also affected the yield of the Michael adducts. Isopropyl substituent, being more sterically hindered than propyl groups, generally gave low yields when compared with that of propyl substituents (Table 3, entries 10−11, 16−17, and 20−21). The reason why dipentyl 2-(5-oxopentylidene) malonate gave the worst result remains unknown (Table 3, entry 13).

To determine the stereochemistry of the tandem aminoxylation/aza-Michael reaction, a (2,4-dinitrophenyl) hydrazine derivative **4i** of the aldehyde product **3i** was synthesized (Scheme 2). The relative configuration of the

Scheme 2. Synthesis of Hydrazine Derivative

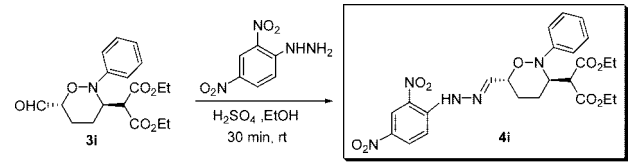
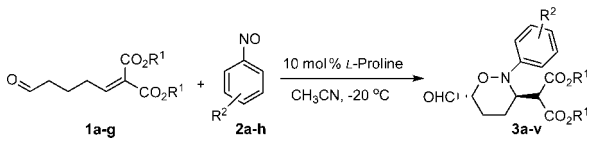


Table 3. Reaction Scope of the Tandem Aminoxylation/ Aza-Michael Addition[a]



entry	R^1	R^2	product	yield (%)[b]	dr[c]	ee (%)[c]
1	Me	H	**3a**	84	>99:1	98
2	Me	2-Me	**3b**	70	>99:1	94
3	Me	3-Me	**3c**	63	>99:1	98
4	Me	4-Me	**3d**	73	>99:1	99
5	Me	3-Cl	**3e**	65	>99:1	98
6	Me	4-Cl	**3f**	62	>99:1	99
7	Me	4-Br	**3g**	72	>99:1	99
8	Me	4-OPh	**3h**	52	>99:1	99
9	Et	H	**3i**	73	>99:1	99
10	Pr	H	**3j**	81	>99:1	99
11	*i*-Pr	H	**3k**	69	>99:1	99
12	Bu	H	**3*l***	79	>99:1	99
13	Pen	H	**3m**	67	>99:1	92
14	Hex	H	**3n**	71	>99:1	99
15	Et	2-Me	**3o**	73	>99:1	95
16	Pr	2-Me	**3p**	72	>99:1	98
17	*i*-Pr	2-Me	**3q**	69	>99:1	96
18	Bu	2-Me	**3r**	71	>99:1	96
19	Et	4-Br	**3s**	67	>99:1	99
20	Pr	4-Br	**3t**	74	>99:1	99
21	*i*-Pr	4-Br	**3u**	67	>99:1	99
22	Bu	4-Br	**3v**	71	>99:1	99

[a] Conditions: Nitrosobenzene (0.1 mmol) and L-proline (0.01 mmol) were added to the solution of aldehyde (0.3 mmol) in 1 mL of CH_3CN at −78 °C, then stirred at −20 °C. [b] Isolated yields. [c] Ee and dr determined by HPLC employing a Daicel Chiracel AS-H or AD-H column (see the Supporting Information).

(2,4-dinitrophenyl) hydrazone **4i** was then determined by X-ray crystallography (Figure 1). The R configuration of the chiral center created by the Michael addition was established by comparing it with the sterogenic center generated by the aminoxylation step based on the relative configuration of **4i** and the known chemistry[7] of the aminoxylation.

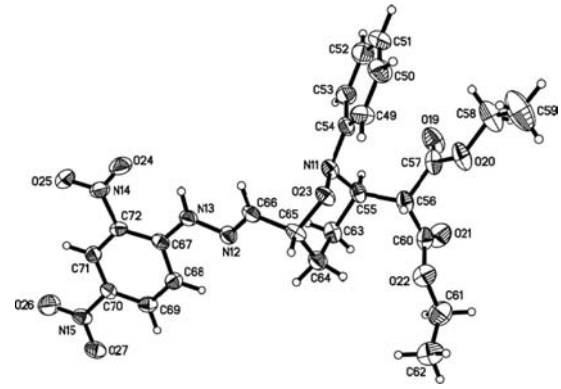


Figure 1. X-ray crystal structure of **4i**.

In summary, we have reported the first highly diastereo- and enantioselective approach for the synthesis of these functionalized tetrahydro-1,2-oxazines via an organocatalyzed asymmetric tandem aminoxylation/aza-Michael reaction. Further applications of this functionalized THOs to other synthetically useful transformations are underway.

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Supporting Information Available: Experimental procedures, characterization, spectra, chiral HPLC conditions and X-ray crystallographic data (CIF file). This material is available free of charge via the Internet at http://pubs.acs.org.

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