L-Prolinamide-catalyzed direct nitroso aldol reactions of α-branched aldehydes: a distinct regioselectivity from that with L-proline†

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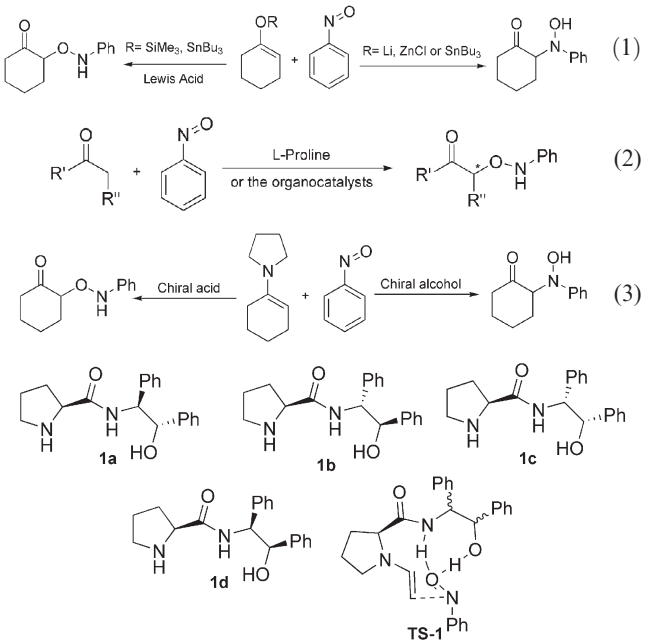
The first direct enantioselective *N*-nitroso aldol reaction of aldehyde with nitrosobenzene catalyzed by an L-prolinamide derivative is presented; the reactions proceed smoothly furnishing the α-hydroxyamino carbonyl compounds, the otherwise disfavored products, in good yields with up to 64% ee.

Nitrosobenzene and its analogues are important reagents since both the nitrogen and oxygen atoms in these compounds are highly reactive toward nucleophiles. Regioselectively controlling either the nitrogen or oxygen to preferentially react with the nucleophile is therefore a challenge and of fundamental importance. A number of studies of the reaction of nitrosobenzene with a silyl- or metal-enolate revealed that the *O versus N* selectivity is dependent on the nature of the enolate and presence or absence of a Lewis catalyst (eqn (1)).[1] Organocatalyzed reactions of nitrosobenzene in the presence of L-proline and its derivatives have also been actively investigated, exclusively giving α-oxygenated carbonyl compounds as the major products (eqn (2)).[2] Yamamoto and co-workers recently reported that stoichiometric amounts of enamine reacted with nitrosobenzene in the presence of chiral carboxylic acids to preferentially perform an amination reaction, while in the presence of chiral alcohol the oxygenated product was generated (eqn (3)).[3] To date, there is not a report on an organocatalyzed direct nitroso aldol reaction of nitrosobenzene with an aldehyde that preferentially takes place at the nitrogen.[1f,g]

In the L-proline-catalyzed α-aminoxylations of aldehydes and ketones (eqn (2)),[2] the high regioselectivity is possibly due to the higher basicity of nitrogen compared to that of oxygen, which leads to preferential protonation of the nitrogen, making the oxygen more electrophilic.[4] Our recent studies on organocatalyzed aldol reactions revealed that L-prolinamides **1a–d** are highly efficient at catalyzing the direct aldol reaction of aldehydes with simple ketones,[5] but totally inefficient in activating imines.[5b] These results, together with the TADDOL catalyzed nitroso aldol reaction of the enamine[3a] indicate that it is difficult to protonate the nitrogen with the proton of either the alcohol or the acylamide, and a hydrogen-bond between the oxygen of the nitroso group and the proton of either the amide or hydroxy group preferentially forms to make the nitrogen more electrophilic than oxygen. Thus, we reasoned that prolinamide derivatives **1a–b** would be able to catalyze the reaction of unmodified aldehydes and nitrosobenzene *via* a presumed transition state **TS-1**, regioselectively giving *N*-nitroso aldol adducts. To address this possibility, we herein report the first direct *N*-nitroso aldol reaction of nitrosobenzene with aldehyde catalyzed by L-prolinamide derivatives with high *N*-selectivity to give α-hydroamino aldehydes in good yields and with moderate enantioselectivity.



The reaction of 2-methyl-3-(3,4-methylenedioxyphenyl)propanal **2a** with nitrosobenzene **3a** in the presence of 10 mol% organocatalyst **1a** was first tested in toluene and at 0 °C. To our delight, the reaction proceeded as we anticipated, to give a *N*-selective nitroso aldol adduct **4aa** with a tertiary stereogenic center as the only product, which was reduced *in situ* with $NaBH_4$ to produce **5aa** in overall 68% yield (two steps), but the enantioselectivity (9% ee) is unsatisfactory (Table 1, entry 1). It is worth noting that the *O*-selective product was not observed. A catalyst survey demonstrated that both the reaction rate and enantioselectivity are dramatically dependent on the configuration of the stereogenic centers of the organocatalysts **1a–d** (Table 1). Of these catalysts, **1b** provided the best results in both catalytic activity and enantioselectivity. **1a** and **1b** show higher catalytic activity than **1c** and **1d**. Higher enantioselectivities were observed with **1b** and **1c** than with **1a** and **1d**. In terms of the reaction rate and enantioselectivity, the prolinamide derivative **1b** can be considered the best catalyst. The effects of the catalyst loading

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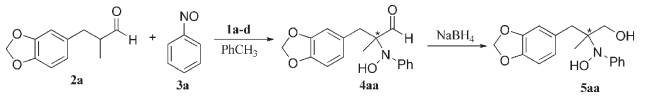
Table 1 Catalyst survey for the *N*-nitroso aldol reaction of 2-methyl-3-(3,4-methylenedioxyphenyl)propanal with nitrosobenzene[a]

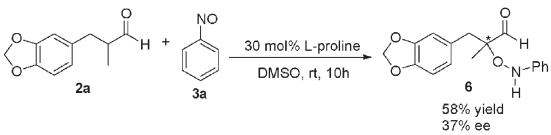


Entry	Cat (mol%)	Temp/°C	Time/h	Yield (%)[b]	Ee (%)[c]
1	**1a** (10)	0	5	68	9
2	**1b** (10)	0	5	68	45
3	**1c** (10)	0	25	45	44
4	**1d** (10)	0	25	42	13
5	**1b** (5)	0	8	65	43
6	**1b** (1)	0	24	41	45
7	**1b** (10)	−25	24	67	51
8	**1b** (10)	−40	48	68	60
9	**1b** (10)	−40	48	74	59[d]

[a] The reaction was conducted with 0.1 equiv. L-prolinamide derivative, 1.2 equiv. 2-methyl-3-(3,4-methylenedioxyphenyl)-propanal and 1.0 equiv. nitrosobenzene in toluene. [b] Isolated yields based on the alcohol (2 steps) and **2a**. [c] Determined by chiral HPLC (Supporting Information). [d] 3 equiv. 2-methyl-3-(3,4-methylenedioxyphenyl)propanal was used.

and temperature on the catalytic efficiency of **1b** were next evaluated (entries 5–8). Remarkably, as little as 1 mol% **1b** can be utilized without significant loss in the strereocontrol (entry 6). An improvement in the enantioselectivity was realized by performing the reaction at low temperature while the reaction time was prolonged (entries 7–8). A moderate enantioselectivity (60% ee) and good yield (68%) were given by **1b** at −40 °C (entry 8). The use of a large excess of aldehyde allows for a higher yield (entry 9).

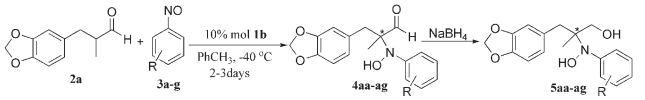
In comparison, the nitroso aldol reaction of nitrosobenzene with **2a** in the presence of 30 mol% L-proline gave rise to an α-oxygenated carbonyl compound **6** in a moderate yield with a low enantioselectivity in DMSO and at room temperature (eqn (4)). The divergence in the regioselectivity between L-prolinamides **1** and L-proline clearly demonstrates that the acidity of the proton of the L-proline-based organocatalysts exerts a determining influence on the regioselectivity, which was not noticed previously.[1–4]



(4)

To clarify the substituent-effect of nitrosobenzene on the reaction, various substituted nitrosobenzenes **3a–g** were examined as electrophiles to react with **2a** in the presence of 10 mol% **1b** under optimized reaction conditions (Table 2). All the reactions proceeded smoothly to exclusively generate *N*-selective nitroso aldol adducts **4aa–4ag**. Significant changes in the enantioselectivity were not observed by variation of the electron-nature of the substituent of nitrosobenzenes. However, a prolonged reaction time was required for a complete reaction of an electron-donating group substituted nitrosobenzene (entry 7). Higher yields were observed for the *ortho*-substituted nitrosobenzenes (entries 3 and 4) compared to those for the *para*- and *meta*-electron-withdrawing group substituted aromatic nitroso compounds (entries 2, 5–7).

Table 2 Effect of aromatic nitroso compounds on the asymmetric *N*-nitroso aldol reaction[a]

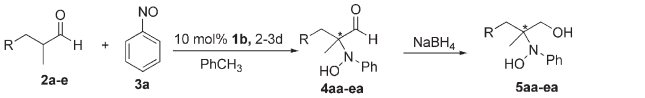


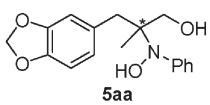
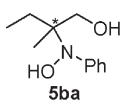
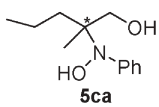
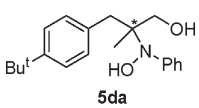
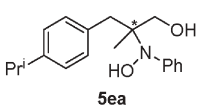
Entry	Product	R	Yield (%)[b]	Ee (%)[c]
1	**4aa**	H	74	59
2	**4ab**	*p*-Cl	63	63
3	**4ac**	*o*-Cl	71	59
4	**4ad**	*o*-Br	76	64
5	**4ae**	*m*-Br	60	55
6	**4af**	*p*-Br	61	61
7[d]	**4ag**	*p*-CH_3	66	59

[a] The reaction was conducted with 0.1 equiv. L-prolinamide derivative **1b**, 3 equiv. 2-methyl-3-(3,4-methylenedioxyphenyl)-propanal and 1.0 equiv. aromatic nitroso compound in toluene. [b] Isolated yield of the alcohol (2 steps). [c] Determined by HPLC (Supporting Information). [d] Reaction time was 4 days.

The generality of the reaction was also studied. Several commercially available α-branched aldehydes were examined to react with nitrosobenzene to give the *N*-selective products, which were *in situ* reduced with $NaBH_4$ to generate corresponding hydroxyamino alcohols **5aa–da** containing a tertiary stereogenic center with moderate enantioselectivities (46–59% ee) and good overall yields (53–71%, Table 3). Notably, no product from the aminooxylation was detected.

Table 3 Enantioselective *N*-nitroso aldol reaction: substrate scope[a]



Entry	Product	Yield (%)[b]	Ee (%)[c]
1	 **5aa**	74	59
2	 **5ba**	53	46
3	 **5ca**	55	46
4	 **5da**	69	59
5	 **5ea**	71	53

[a] The reaction was conducted with 0.1 equiv. L-prolinamide derivative **1b**, 3 equiv. 2-methyl-3-(3,4-methylenedioxyphenyl)-propanal and 1.0 equiv. nitrosobenzene in toluene. [b] Isolated yield of the alcohol (2 steps). [c] Determined by HPLC (Supporting Information).

The aggregate above-mentioned experimental results confirm that L-proline- and L-prolinamide-catalyzed nitroso aldol reactions occur *via* different transition states. In the former case, the oxygen is activated by the protonation of the nitrogen of nitrosobenzene with carboxylic acid.[4] In the latter case, in comparison, the nitrogen is activated by hydrogen-bonds formed between the oxygen and protons of both the amide and hydroxy, as shown in **TS-1**, which is a highly possible transition state to account for the observed experimental results in the current process.

In summary, we have described the first direct enantioselective α-hydroxyamination reaction of α-branched aldehydes with a variety of nitrosobenzenes catalyzed by an organocatalyst with good yields and moderate enantioselectivity. The high ability to control the regioselectivity of the L-prolinamide **1b** only allows for the formation of α-hydroxyamination products. Despite unsatisfactory enantioselectivities, our results are distinct from those reported previously[1–3] and thus, add new knowledge to the organocatalyzed nitroso aldol chemistry. Further efforts will be spent on evaluating the scope of this and related processes and the improvement of stereochemistry.

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Notes and references

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