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Optimization of the Catalytic Asymmetric Addition of Nitroalkanes to Cyclic Enones with *trans*-4,5-Methano-L-proline

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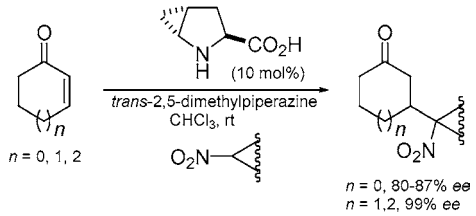
ABSTRACT



The conjugate addition of symmetrical 2-nitroalkanes to 2-cycloalkenones catalyzed by *trans*-4,5-methano-L-proline proceeds with >99% ee and excellent chemical yields. 1-Nitroalkanes afford diastereomeric *syn*/*anti* products that can be separated with good individual enantioselectivities. Proline hydroxamic acid and its *trans*-4,5-methano -L-proline hydroxamic acid are also effective organocatalysts in the addition of 2-nitropropane to 2-cyclohexenone (75% and 81% ee, respectively).

The base-catalyzed addition of nitroalkanes to cyclic enones is a fundamentally important preparative route to β-substituted cycloalkanones.[1] Formally grouped under Michael addition reactions, the resulting nitroalkyl appendages in these compounds can be chemically transformed into a variety of functionally useful compounds, which can also benefit from the rich chemistry of the resident carbonyl group.[2]

The first example of a preparatively useful metal-free catalytic asymmetric addition of 2-nitropropane to 2-cyclohexenone was achieved in the presence of rubidium L-prolinate by Yamaguchi and co-workers in 1994.[3] Thus, 3-(2-nitropropan-2-yl)cyclohexanone and the corresponding cycloheptanone were obtained in 59% and 79% ee, respectively. Enantioselectivities were substantially lower with nitromethane and 2-cyclohexenone (45% ee).

Subsequent studies in our laboratory revealed that the use of 3−7 mol % equiv of L-proline (**1**) in the presence of achiral *trans*-2,5-dimethylpiperazine as an additive led to the 3*R*-nitroalkyl cyclohexanone adduct in 93% ee with 2-nitropropane, 1-nitrocyclopentane, and 1-nitrocyclohexane as nucleophiles.[4] Contrary to the case of Rb prolinate, this reaction exhibited a very unusual nonlinear effect,[5] especially with *trans*-2,5-dimethylpiperazine as the additive,[4,6] Since then, the catalytic asymmetric Michael addition of 2-nitropropane to 2-cyclohexenone has been reported in the

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(5) For a review, see: Girard, C.; Kagan, H. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 2923

(6) For a review on additives and cocatalysts in asymmetric reactions, see: Vogel, E. M.; Gröger, H.; Shibasaki, M. *Angew. Chem., Int. Ed. Engl.* **1999**, *38*, 1570.

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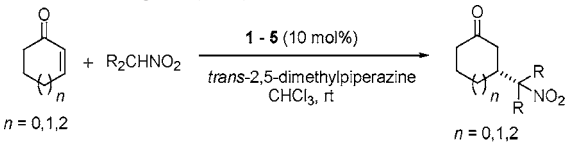
presence of a peptide catalyst and *trans*-2,5-dimethylpiperazine as additive (80% yield, 77% ee).[7] Using an optimized *N*-spiro C_2-symmetrical chiral quaternary ammonium bromide catalyst, Maruoka and co-workers[8] reported the conjugate addition of various 1-nitroalkanes with good to excellent *syn*/*anti* selectivities and 82−93% ee for the *syn*-isomers depending on the enone and the nature of the nucleophile. The *anti*-diastereomers, usually obtained as minor components, exhibited poor to modest enantioselectivities (37−57% ee for 1-nitropropane). The rationale for the selectivity was attributed to transition-state models favoring *syn*-addition of a *N*-spiro ammonium alkyl nitronate salt to 2-cyclohexenone.[9]

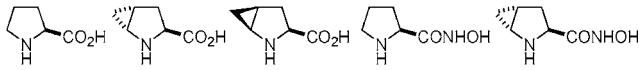
In a recent paper we showed that the high stereodifferentiation in the catalytic asymmetric addition of 2-nitropropane to 2-cyclohexenone in the presence of 5−10 mol % L-proline was not subject to variations in the chirality of the added 2,5-dialkylpiperazine.[10] We also reported the first use of L-proline hydroxamic **4**[11] as an effective catalyst to achieve 75% ee of adduct.

Herein we report on the use of *trans*-4,5-methano-L-proline **2**[12]as an optimized, metal-free organocatalyst[13] for the asymmetric conjugate addition of symmetrical and nonsymmetrical nitroalkanes to 2-cycloalkenones (reaction scheme in Table 1). The results of reactions catalyzed by L-proline (**1**), *trans*-4,5-methano-L-proline (**2**), and *cis*-4,5-methano-L-proline (**3**) for 2-nitropropane, 1-nitrocyclopentane, and 1-nitrocyclohexane with 2-cyclopentenone, 2-cyclohexenone, and 2-cycloheptenone, respectively, reveal a preference for higher enantioselectivities when using the *trans*-isomer **2** as a catalyst in all cases. Thus, with 2-cyclohexenone and 2-cycloheptenone, only the 3*R*-adduct is formed with **2** (Table 1, entries 2, 22, 25, and 28). Unprecedented enantioselectivity is shown in the case of 2-cyclopentenone at 80−87% ee with 2-nitropropane, 1-nitrocyclopentane, and 1-nitrocyclohexane (Table 1, entries 13, 16, and 19, respectively). It should be noted that none of the previous reports[3,7,8] include 2-cyclopentenone as a substrate. Using Yamaguchi's Rb prolinate as a catalyst for the addition of 2-nitropropane to 2-cyclopentenone gave the adduct with 12% ee.

With *trans*-4,5-methano-L-proline hydroxamic acid **5** as a catalyst, the addition product of 2-nitropropane to 2-cyclohexenone showed an ee of 81% compared to 75% with L-proline hydroxamic acid **4**[10] (Table 1, entry 5). Extension of the addition reactions to nitromethane and 2-cyclohexenone or 2-cyclopentenone under the same conditions gave the corresponding 3*R*-nitromethyl adducts as major isomers (74% and 61% ee, respectively) (Table 2, entries 2 and 6). The highest reported ee for 2-cyclohexenone and nitromethane was 58% ee in the presence of a peptide catalyst and *trans*-2,5-dimethylpiperazine as an additive.[7] In the case of 1-nitropent-4-ene, the diastereomeric addition products with catalyst **2** (Table 2, entry 4) were separable by column chromatography. The less polar compound corresponds to the *anti*-(*R*,*R*) diastereomer (87% ee) while the more polar compound corresponds to the *syn*-(*R*,*S*)-isomer (77% ee). A notable difference in comparison with Maruoka's results is

Table 1. Catalytic Enantioselective Addition of Nitroalkanes to Cyclic α,β-Unsaturated Ketones Catalyzed by Proline (**1**) and Proline Analogues (**2**−**5**)





1 2 3 4 5

entry	*n*	(R)	catalyst	time (h)	yield[a] (%)	ee[b] (%)
1	1	CH_3	**1**	72	83	89[c]
2			**2**	140	**92**	**99**
3			**3**	146	52	75
4			**4**	162	78	75
5			**5**	216	65	81
6	1	$(CH_2)_4$	**1**	72	79	90
7			**2**	141	**93**	**99**
8			**3**	149	50	76
9	1	$(CH_2)_5$	**1**	78	83	92
10			**2**	140	**91**	**99**
11			**3**	157	40	74
12	0	CH_3	**1**	71	72	69
13			**2**	96	**87**	**80**
14			**3**	146	40	66
15	0	$(CH_2)_4$	**1**	72	74	76
16			**2**	98	**90**	**87**
17			**3**	144	47	73
18	0	$(CH_2)_5$	**1**	71	59	77
19			**2**	96	**84**	**83**
20			**3**	144	23	76
21	2	CH_3	**1**	80	60	84
22			**2**	144	**57**	**99**
23			**3**	144	15	60
24	2	$(CH_2)_4$	**1**	76	65	86
25			**2**	144	**56**	**99**
26			**3**	144	22	59
27	2	$(CH_2)_5$	**1**	84	49	85
28			**2**	144	**50**	**99**
29			**3**	144	8	61

[a] Isolated yield. [b] By ^{13}C NMR analysis of the corresponding ketal with (2*R*,3*R*)-2,3-butanediol (average of three runs). See the Supporting Information. [c] ee values of 89−92% were obtained on average of three runs.

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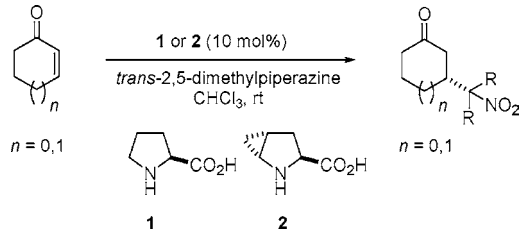
Table 2. Diastereoselective Addition of 1-Nitroalkanes to Cyclic α,β-Unsaturated Ketones Catalyzed by **1** and **2**



entry	n	2 (R)	catalyst	reaction time (h)	yield[a] (%)	ee (%)
1	1	H	**1**	72	69	71
2	1	H	**2**	142	**80**	**74**
3	1	$CH_2CH(CH_2)_2$	**1**	86	77 (2:3)[b]	84[c]
						70[d]
4	1	$CH_2CH(CH_2)_2$	**2**	144	**94** (2:3)[b]	**87**
						77[d]
5	0	H	**1**	71	40	57
6	0	H	**2**	143	**50**	**61**
7	0	$CH_2CH(CH_2)_2$	**1**	82	84	70[c]
						50[d]
8	0	$CH_2CH(CH_2)_2$	**2**	144	**91**	**76**[c]
						60[d]
9	1	CH_3CH_2	**1**	72	80 (1:2)[b]	85[c]
						72[d]
10	1	CH_3CH_2	**2**	144	**89** (1:2)[b]	**91**[c]
						74[d]

[a] Isolated yield. [b] Diastereomeric ratio. [c] Less polar isomer (*anti-R,R*-isomer). [d] More polar isomer (*syn-R,S*-isomer).

the relatively high ee of the *anti*-diastereomer in the addition to 2-cyclohexenone catalyzed by **2**. In the case of 2-cyclopentenone (Table 2, entry 8), the ratios were 76% and 60% ee for *anti*- and *syn*-isomers, respectively. Although enantioselectivies of individual products are still modest, these are the first examples of additions of unsymmetrical 1-nitroalkanes to cyclopentenone. Compared to Maruoka's results with 1-nitropropane and 2-cyclohexenone (*syn*-major, 91% ee; *anti*-minor 57% ee), catalysis with **2** gave *anti*/*syn* enantioselectivities of 91% and 74% ee, respectively, and a 1:2 diastereomeric ratio of separable 3-nitropropyl adducts (Table 2, entry 10). The preponderance of higher enantioselectivity for *anti*-isomers in all cases is also noteworthy.

A plausible catalytic cycle representing the prototypical addition of 2-nitropropane to 2-cyclohexenone in the presence of **2** as a catalyst is shown in Figure 1. Thus, iminium carboxylate intermediate **A** undergoes face selective addition of the piperazinium nitronate anion in an *anti*-trajectory relative to the carboxylate group, to give the enamine adduct **B**. The cycle continues with the formation of a second iminium carboxylate **C**, which leads to the hemiaminal **D**. Release of the amino acid into the medium together with the adduct allows for the catalytic cycle to continue. An analogous mechanism can be suggested for **1** and **3** resulting in products having 89−92% ee and 75% ee, respectively. The reaction time with L-proline is roughly half compared to that of **2** and **3**. There is considerable unreacted material

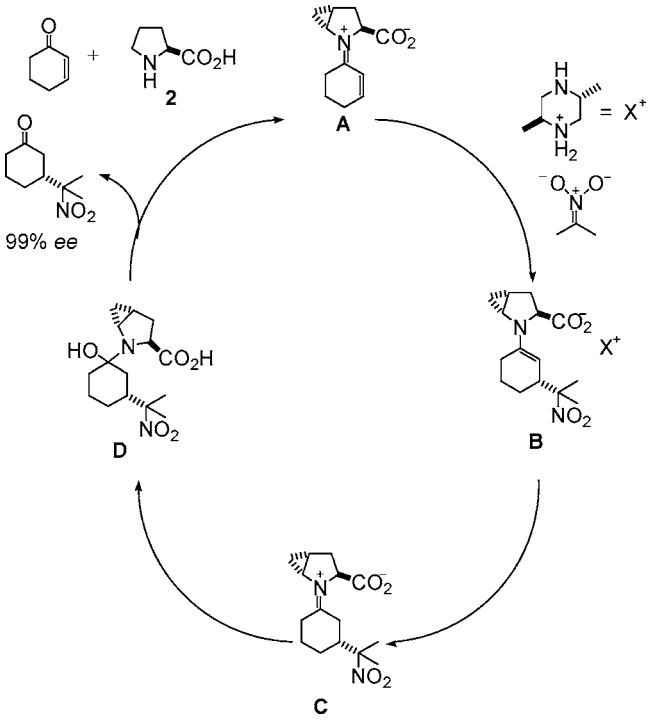


Figure 1. Possible catalytic cycle for *trans*-4,5-methano-L-proline, 2-cyclohexenone, and 2-nitropropane.

left in the case of the *cis*-isomer **3**. No reaction was observed with L-proline alone, and only trace amounts of racemic product were seen in the presence of the piperazine without L-proline as controls.

It is not immediately obvious why catalyst **2** should surpass **1** and its *cis*-isomer counterpart **3** in its ability to significantly bias the enantioselectivities of the conjugate addition reactions products. A priori, based on steric arguments, the results are counterintuitive, since the *pro-R* face of the 2-cyclohexenone should be more accessible to attack by the 2-nitropropane anion with its associated bulky base in the case of the *cis*-isomer **3**. In comparison to L-proline (**1**) as a catalyst, there must be an intrinsic bias in favor of **2** that leads to the exclusive formation of the enantiopure *R*-adduct with symmetrical 1-nitroalkanes and 2-nitrocycloalkanes.

The solid-state crystal structure of **3** reveals a boatlike conformation with the carboxylate out-of-plane (Figure 2).[14] Torsional effects involving the cyclopropane ring in **3** will favor a boat conformation.[15,16] However, a pseudoaxial carboxyl[17] group that is normally favored due to minimization of $A^{1,3}$ strain[18] (as in **Ia** compared to **Ib**, Figure 2) will not be favored due to a steric interaction with the cyclopropane ring. The combination of these two effects may account for

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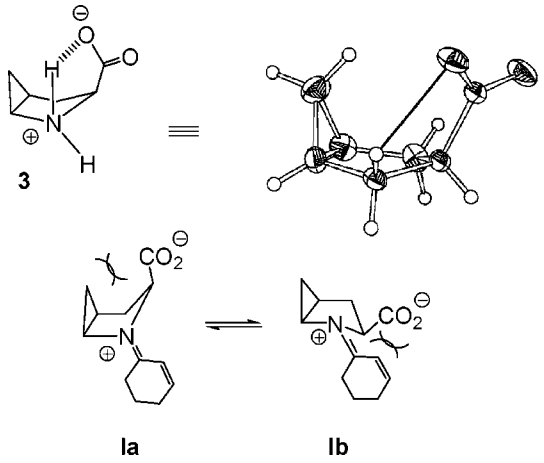

Figure 2. (Top) X-ray structure of **3**;. (Bottom) Torsional (**Ia**) and **A**[1,3] strain (**Ib**) effects in iminium ion derived from **3**.

the sluggish progress of the reaction and the lower enantioselectivity in the case of **3**. We have previously shown that in the solid state, *N*-Boc-4,5-*trans*-methano-L-proline is considerably flatter compared to the *cis*-isomer (rms 0.003 and 0.013 Å, respectively).[12,19] It is therefore possible that formation of the iminium ion **A** from **2** (Figure 1) requires less geometrical reorganization compared to **3** (**Ia**, Figure 2).[20]

In conclusion, we have shown that *trans*-4,5-methano-L-proline **2** is an optimal catalyst for the asymmetric conjugate addition of symmetrical 2-nitroalkanes to 2-cycloalkenones. Hitherto unreported additions to 2-cyclopentenone afford products with enantioselectivities surpassing 80% ee. While the ratios of the two *syn*- and *anti*-isomers in the case of 1-nitroalkanes are low, the products can be easily separated, and each exhibits good enantioenrichment favoring the *anti*-isomer, contrary to when quaternary bases are used.[8] These results are of interest, since efforts to extend such conjugate additions of nitroalkanes to ring-substituted analogues of proline have not been successful in the past.[3,21]

In addition to their recent versatile applications as proline analogues in prototypical enzyme inhibitors,[22−24] 4,5-methanoprolines are also useful organocatalysts that can surpass the venerable proline in conjugate additions of nitroalkanes to cyclic enones in many cases. *Trans*-4,5-methano-L-proline hydroxamic acid **5** is also an effective catalyst albeit with modest enantioselectivity in a model reaction.

Acknowledgment. We thank NSERC for generous financial assistance.

Supporting Information Available: Representative experimental procedures, ^{13}C NMR spectra, and X-ray data of compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(19) The cyclopropane C−C bonds toward its apex extending from C-4 and C-5 are significantly longer in *N*-Boc **2** compared to *N*-Boc **3**, indicating a relatively less rigid ring (ref 12).

(20) The iminium ion **A** may also benefit from a through space interaction with the electron-rich cyclopropane ring.

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