ORGANIC LETTERS

2000
Vol. 2, No. 19
2975−2978

Catalytic Asymmetric Conjugate Addition of Nitroalkanes to Cycloalkenones

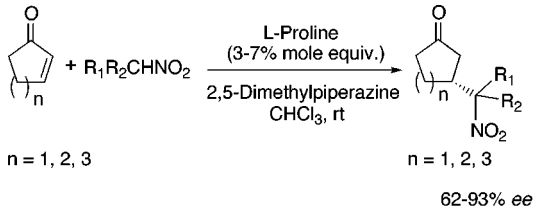
Stephen Hanessian* and Vinh Pham

Department of Chemistry, Université de Montréal, C.P. 6128, Succ. Centre-ville, Montréal, QC, H3C 3J7, Canada

hanessia@ere.umontreal.ca

Received June 29, 2000

ABSTRACT



Nitroalkanes add to cyclic and acyclic enones in an enantioselective manner in the presence of catalytic quantities of L-proline and *trans*-2,5-dimethylpiperazine as excess additive.

The formation of C−C bonds by conjugate addition of appropriate carbanionic reagents to α,β-unsaturated carbonyl compounds (Michael reaction) is one of the most useful methods of remote functionalization in organic synthesis.[1] In the case of nitroalkanes, the products of 1,4-addition to enones are also useful as precursors to aminoalkanes[2] through reduction and to other functionality that can be derived from the venerable nitro group.[3]

Efforts toward achieving asymmetric conjugate addition of nitroalkanes to α,β-unsaturated ketones in the presence of catalytic quantities of chiral bases have been the subject of several reports. For example, the reaction of nitroalkanes with chalcone catalyzed by chiral ammonium salts[4] (20% ee), Ni(II) or Co(II) complexes[5] (38% ee), quinine[6] (∼60% ee), azacrown ethers[7] (∼90% ee), and La−BINOL complex[8] (>95% ee) are known.

To the best of our knowledge, there is one definitive report describing catalytic asymmetric additions of nitroalkanes to cyclic enones. Yamaguchi and co-workers[9] found that rubidium prolinate was an effective catalyst in the addition of 2-nitropropane to cyclohexenone (59% ee) and cycloheptenone (79% ee). An attempt to use metal complexes of

(1) For recent reviews and monographs, see: (a) Leonard, J. *Contemp. Org. Synth.* **1994**, *1*, 387. (b) Perlmutter, P. *Conjugate Addition Reactions in Organic Synthesis;* Pergamon: Oxford, 1992. (c) Rossiter, B. E.; Swingle, N. M. *Chem. Rev.* **1992**, *92*, 771.

(2) For examples of conjugate addition of α-amino alkyl moieties to enones, see: (a) Dieter, R. K.; Alexander, C. W.; Nice, L. E. *Tetrahedron* **2000**, *56*, 2767. (b) Park, Y. S.; Weisenburger, G. A.; Beak, P. *J. Am. Chem. Soc.* **1997**, *119*, 10537. For α-aminoalkyl carbanions, see: (c) Shawe, T. T.; Meyers, A. I. *J. Org. Chem.* **1991**, *56*, 2751. (d) Beak, P.; Lee, W. K. *J. Org. Chem.* **1993**, *58*, 1109 and previous papers. For diastereoselective Michael additions of nitromethane to chiral nonracemic enoates, see: (e) Patrocinio, V. L.; Costa, P. R. R.; Correia, C. R. D. *Synthesis* **1994**, 474.

(3) For reviews, see: Tamura, R.; Kamimura, A.; Ono, N. *Synthesis* **1991**, 423. Rosini, G.; Ballini, R. *Synthesis* **1988**, 833.

(4) Colonna, S.; Hiemstra, H.; Wynberg, H. *J. Chem. Soc., Chem. Commun.* **1978**, 238; Colonna, S.; Re, A.; Wynberg, H. *J. Chem. Soc., Perkin Trans. 1* **1981**, 547.

(5) Botteghi, C.; Paganelli, S.; Shionato, A.; Boga, C.; Fava, A. *J. Mol. Catal.* **1991**, *66*, 7.

(6) Sera, A.; Takagi, K.; Katayama, H.; Yamada, H.; Matsumoto, K. *J. Org. Chem.* **1988**, *53*, 1157. See also ref 4.

(7) Bakó, P.; Töke, L. *Tetrahedron Lett.* **1997**, *38*, 7259. For related work, see: Bakó, P.; Novák, T.; Ludányi, K.; Pete, B.; Töke, L.; Keglevich, G. *Tetrahedron: Asymmetry* **1999**, *10*, 2373.

(8) Funabashi, K.; Saida, Y.; Kanai, M.; Arai, T.; Sasai, H.; Shibasaki, M. *Tetrahedron Lett.* **1998**, *39*, 7557.

(9) a. Yamaguchi, M.; Igarashi, Y.; Reddy, R. S.; Shiraishi, T.; Hirama, M. *Tetrahedron* **1997**, *53*, 11223. (b) Yamaguchi, M.; Shiraishi, T.; Igarashi, Y.; Hirama, M. *Tetrahedron Lett.* **1994**, *35*, 8233.

(10) Schionato, A.; Paganelli, S.; Botteghi, C.; Chelucci, G. *J. Mol. Catal.* **1989**, *50*, 11.

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

10.1021/ol000170g CCC: $19.00
Published on Web 08/19/2000

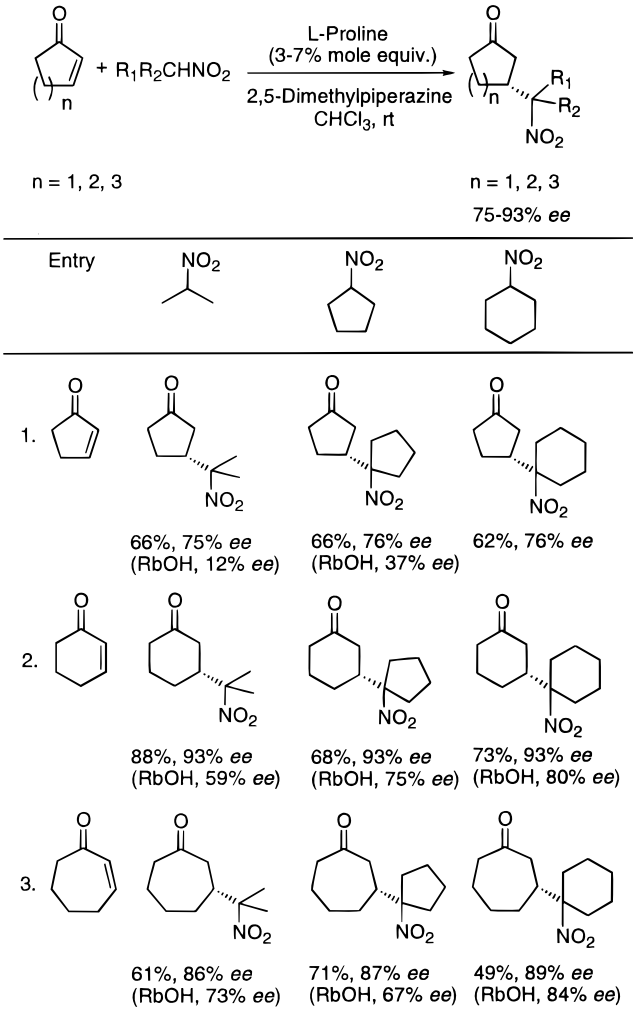
pyrrolidine derivatives as catalysts in the conjugate addition of nitromethane to cyclohexenone resulted in a product with 7% ee.[10]

We report herein on the catalytic asymmetric conjugate addition of various nitroalkanes to cyclic enones such as cyclopentenone, cyclohexenone, and cycloheptenone with hitherto unprecedented enantiomeric excesses. Promising results were also observed with some acyclic α,β-unsaturated ketones.

Utilizing L-proline as catalyst in the presence of *trans*-2,5-dimethylpiperazine as an additive[11] resulted in substantially improved enantioselectivities for the addition of 2-nitropropane, nitrocyclopentane, and nitrocyclohexane to cyclic enones compared to those of rubidium prolinate as shown in Table 1. Addition of 2-nitropropane to chalcone afforded the dextrorotary isomer with 68% ee, compared to rubidium prolinate (31% ee). Similar results were obtained in additions to (*E*)-3-nonen-2-one and (*E*)-3-phenyl-buten-2-one. Definitive confirmation of absolute or relative stereochemistry was obtained by spectroscopic and X-ray crystal structural analysis.[12]

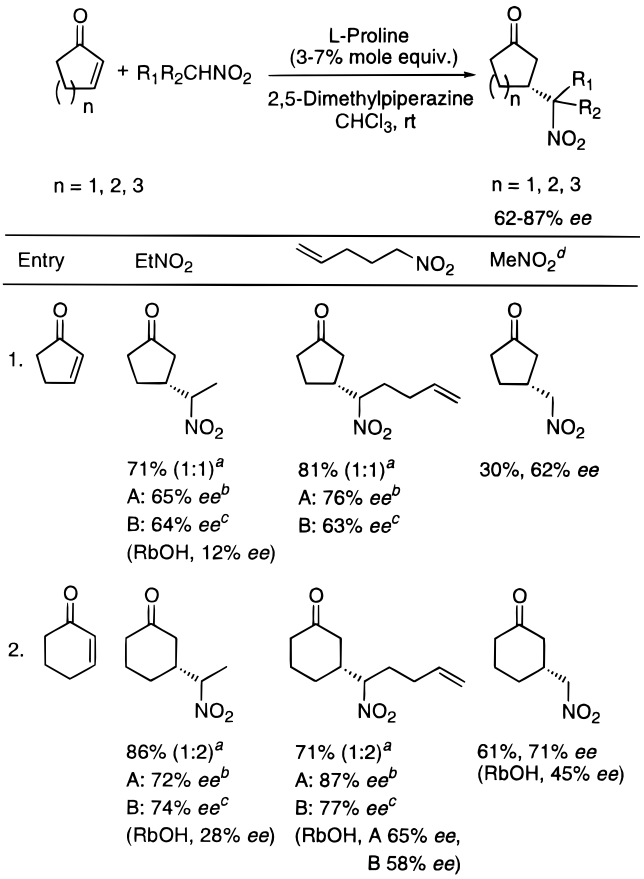
We then extended our studies to the addition of nitromethane, nitroethane, and 1-nitro-4-butene in the presence of L-proline as catalyst and *trans*-2,5-dimethylpiperazine as additive. Our results are shown in Table 2, where the enantioselectives are also compared to those of rubidium prolinate. Thus, with nitromethane in particular, significant enantioenrichment of the dextrorotatory isomer was observed in all cases (Table 2). When a 2-substituted nitroalkane was used, the high stereoselectivity at the β-position of the enone was maintained. However, the products were mixtures of diastereomers arising from the nitroalkyl side chain. Nevertheless, the isomers could be separated chromatographically and analyzed for their respective enantiopurities as shown in Table 2. In these cases, the ee values of each isomer were mediocre when using rubidium prolinate as catalyst. The

Table 1. Conjugate Addition with Nitroalkanes Catalyzed by L-Proline and *trans*-2,5-Dimethylpiperazine[a−c]



a. Yields (%) of chromatographically homogeneous product; *b.* RbOH % *ee* refers to rubidium prolinate catalyst as in reference 9; *c.* % *ee* measured by ^{13}C-NMR of corresponding ketal with 2*R*,3*R*-2,3-butane diol

Table 2. Conjugate Addition with Nitroalkanes Catalyzed by L-Proline and *trans*-2,5-Dimethylpiperazine[a−c]



a. ratio of isomer A to B; *b.* *ee* of less polar isomer A; *c.* *ee* of more polar isomer B; *d.* 53%, 72% *ee* (RbOH, 41% *ee*) for cycloheptenone substrate (n=3)

(12) Experimental conditions and pertinent details provided as Supporting Information.

(13) For an example of catalytic enantioselective conjugate additions of α-nitro esters, see: Keller, E.; Veldman, N.; Spek, A. L.; Feringa, B. L. *Tetrahedron: Asymmetry* **1997**, *8*, 3403.

adduct of methyl 3-nitro-1-propionate to cyclohexenone showed 29% ee after removal of the nitro group by elimination and catalytic hydrogenation. No asymmetric induction was observed with methyl 2-nitroacetate.[13]

It is evident from the above results that the highest levels of asymmetric induction in the addition of nitroalkanes are observed with cyclohexenone. Although somewhat lower, the enantioselectivities with cyclopentenone are encouraging in view of the conspicuous absence of related examples in the literature. Indeed, the majority of catalytic conjugate additions of nitroalkanes have utilized cyclohexenone as a model cyclic enone and chalcone as an acyclic analogue.

Yamaguchi and co-workers[9] had established strict steric and functional requirements for their amino acid catalyst. We investigated a variety of substituted and conformationally biased derivatives of proline and L-azetidine carboxylic acid in conjunction with various additives for the addition of 2-nitropropane to cyclohexenone.[12] Proline proved to be the best catalyst as observed by Yamaguchi also.[9]

We then launched a systematic search for a basic additive in order to find an optimal combination for the addition of 2-nitropropane to cyclohexenone.[14] While the relationship between the structure of the additive and the resulting ee values are not evident, it appears that the combination of basicity[15] and structure plays a stereodifferentiating role in the reaction. We also studied the possible effects of matched and mismatched pairs as in the case of the ephedrines, *N*,*N*-dimethyl-*trans*-1,2-diaminocyclohexanes, and α-methylbenzylamines. The results, however, were not particularly different within each pair. With the exception of quinine and quinidine, the need for a secondary amine became evident in comparing *N*,*N*-tetramethylethylenediamine (4% ee) with *N*,*N*-dimethylethylenediamine (75% ee) among other related examples.[14]

Consistently high ee values were observed within the group of piperazines studied, although piperidine itself proved to be beneficial as well. The choice of *trans*-2,5-dimethylpiperazine as the best additive in this study was based on its performance with the three enones with nitroalkanes, shown in Tables 1 and 2. The proportion of additive seemed to affect the time of the reaction but not the yield or enantiopurity of the product. Chloroform was the best solvent, although mixtures of chloroform and toluene were also acceptable except that reaction was incomplete after 66 h. The presence of alcohols (for example, $CHCl_3$: 2-PrOH 3:1) diminished the enantioselectively. Rigorous drying of the solvent resulted in recovery of the enone, emphasizing the intervention of a hydrolytic step in the catalytic cycle due to traces of water.

In view of the enhancing effect of the additives, it was interesting to study the nonlinear effect[16] as a mechanistic probe, particularly since Yamaguchi had observed a linear relationship of the ee of rubidium prolinate with the ee of the adduct of diisopropyl malonate to cycloheptenone in $CHCl_3$ containing 30 mol % of water (59% ee).[17]

We observed a linear effect for the reaction of 2-nitropropane with cyclohexenone catalyzed by rubidium prolinate,[9] or by L-proline in the presence of piperidine (Figure 1). However, in the presence of *trans*-2,5-dimethylpiperazine

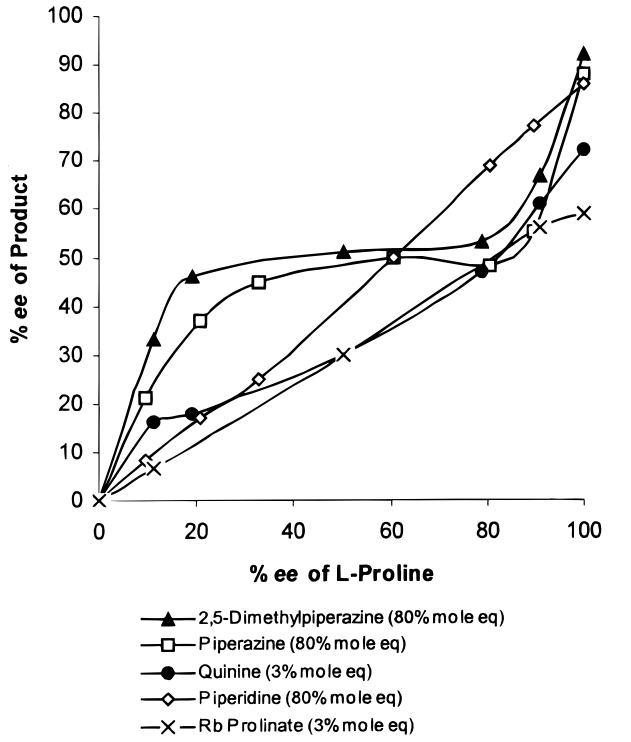


Figure 1. Nonlinear effects in the addition of 2-nitropropane to 2-cyclohexenone.

we observed a pronounced nonlinear effect. The ee of the product remained almost constant with increasing levels of ee of L-proline over the range 20−80% enantiopurity, only

(14) Effect of the bases in the Michael addition: **metals salts**, CsF, 66% ee; LiOH, 50% ee; RbOH, 59% ee; RbOH and crown 18-6, 9% ee (*S*); **secondary amines**, piperidine, 86% ee; pyrrolidine, 4% ee; morpholine, 85% ee; 2,2,6,6-tetramethylpiperidine, 76% ee; 3,5-dimethylpiperidine, 87% ee; 2,6-dimethylpiperidine, 72% ee; 4-(*N*-piperidinyl)piperidine, 80% ee; 2-(2-methylaminoethyl)pyridine, 66% ee; diethylamine (or triethylamine) and RbOH, 45% ee; (+)- or (−)-methylbenzylamine, 10−17% ee; **1,2-diamines**, (1*R*,2*R*)-(−)-diaminocyclohexane, 66% ee; (2*R*,3*R*)-(+)-diphenylethylenediamine and CsF, 58% ee; **1,2-dialkylamines**, *N*,*N*′-dimethylethylenediamine or *N*,*N*′-dimethylpropylenediamine, 70−75% ee; (*R*,*R*)- or (*S*,*S*)-*N*,*N*′-dimethyl-1,2-diaminocyclohexane, 48−58% ee; **tertiary amines**, DABCO, 15% ee; (−)-spartein, 12% ee (*S*); *N*,*N*′-tetramethylethylenediamine, 4% ee (with RbOH, 64% ee); DBU, 18% ee (*S*); DBN, 19% ee (*S*); 1,3,4,6,7,8-hexahydro-2*H*-pyrimido[1,2-*a*]pyrimidine, 27% ee in $CHCl_3$ (*S*), 19% ee (*R*) in benzene; **1,2-amino alcohols**, (1*R*,2*S*)- or (1*S*,2*R*)-ephedrine, 74% ee; *N*-methylethanolamine, 71% ee; L-prolinol, 16% ee (*S*); **quinine and quinidine**, quinine, 76% ee (in toluene, 63% ee); quinine and RbOH, 77% *ee*; quinine and alumina, 62% ee; quinidine, 62% ee; **piperazines**, *trans*-2,5-dimethylpiperazine, 93% ee; 2,6-dimethylpiperazine (*cis*), 86% ee; piperazine, 88% ee; piperazine and RbOH, 72% ee; *N*-methylpiperazine, 78% ee. (a) Percent enantioselectivity determined by conversion to the corresponding ketal with (2*R*,3*R*)-2,3-butanediol and recording ^{13}C NMR. (b) For ratios of additives and additional information, see Suppporting Information.

(15) For a discussion of basicities of piperazines and related secondary amines, see: Keyworth, D. A. *J. Org. Chem.* **1959**, *24*, 1355.

(16) For an excellent review, see: Girard, C.; Kagan, H. *Angew. Chem., Int. Ed.* **1998**, *37*, 2923.

(17) Yamaguchi, M.; Shiraishi, T.; Hirama, M. *J. Org. Chem.* **1996**, *61*, 3520.

to rise sharply to a maximum value of 93% ee for the final product. The effect of quinine was not as pronounced, although a deviation from linearity was also clear.

While it is not possible to derive clear mechanistic conclusions in a complex system that comprises a catalyst and an additive, in addition to the nitroalkane and the enone, the results are reminiscent of MLx systems where NLE curves show a similar trend.[16]

In conclusion, we have shown the first examples of catalytic asymmetric conjugate addition of nitroalkanes to cyclic enones in the presence of L-proline with high enantioselectivities and *trans*-2,5-dimethylpiperazine. The pronounced nonlinear effect indicates a complex multicomponent chiral catalytic system which reaches its maximum efficiency of 93% ee for (*S*)-3-(2-nitropropyl)cyclohexane.

Acknowledgment. We thank NSERCC and the Medicinal Chemistry Chair Program for generous financial assistance.

Supporting Information Available: Experimental procedures, X-ray structures, and ^{1}H and ^{13}C NMR spectra for compounds reported in Tables 1 and 2. This material is available free of charge via the Internet at http://pubs.acs.org.

OL000170G