J|A|C|S
COMMUNICATIONS

Published on Web 05/08/2002

The First Direct and Enantioselective Cross-Aldol Reaction of Aldehydes

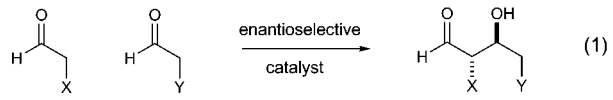
Alan B. Northrup and David W. C. MacMillan*

Division of Chemistry and Chemical Engineering, California Institute of Technology, Pasadena, California 91125

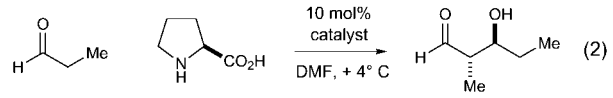
Received March 19, 2002

Over the last three decades, seminal research from the laboratories of Evans,[1] Heathcock,[2] Masamune,[3] and Mukaiyama[4] has established the aldol reaction as the principal chemical reaction for the stereoselective construction of complex polyol architecture. Recently, studies by Barbas,[5] List,[6] Shibasaki,[7] and Trost[8] have outlined the first examples of enantioselective direct aldol reactions, an important class of metal- or proline-catalyzed transformations that do not require the pregeneration of enolates or enolate equivalents. With these remarkable advances in place, a new goal for asymmetric aldol technology has become the development of catalytic methods that allow the direct coupling of aldehyde substrates[9] (eq 1), a powerful yet elusive aldol variant that has only been accomplished within the realm of enzymatic catalysis.[10,11]

Enantioselective Aldehyde Aldol: Elusive Transformation



Proline Catalyzed Aldehyde Aldol Dimerization



2 equiv. catalyst L-Proline 80% yield, 4:1 *anti*:*syn*, 99% ee

Traditionally, the enantioselective aldol coupling of nonequivalent aldehydes has been viewed as a formidable synthetic challenge on account of (i) the propensity of aldehydes to polymerize under metal-catalyzed conditions and (ii) the mechanistic requirement that nonequivalent aldehydes must selectively partition into two discrete components, a nucleophilic donor and an electrophilic acceptor. In this communication, we demonstrate that this elusive aldol sequence can be accomplished using enamine catalysis to allow the first highly enantioselective coupling of aldehyde substrates. We expect this new variant of the Hajos−Parrish−Barbas−List reaction[5,6,12] will provide a powerful yet operationally simple protocol for the rapid production of enantioenriched aldolate architecture.

As part of an ongoing program to develop small organic catalysts that have broad utility for asymmetric synthesis, we have recently initiated studies toward the identification of chiral amines that function as aldolase enzyme mimics. On the basis of preliminary studies,[13] we were inspired to investigate whether enantioselective aldehyde−aldehyde couplings might also be accomplished using proline catalysis, a mechanistic hypothesis based on the documented utility of this amino acid in ketone based aldol reactions.[5,6] To our delight, exposure of propionaldehyde to catalytic quantities of proline in DMF provided the desired aldol adduct with both *anti*-aldol selectivity and excellent levels of enantiocontrol (eq 2, 80% yield, 4:1 *anti*:*syn*, 99% ee). Despite the use of proline in previous aldol reactions, to our knowledge, this is the first example of a direct enantioselective aldehyde−aldehyde dimerization.[14]

As revealed in Table 1, this enantioselective aldehyde coupling is readily accomplished in a wide variety of solvents (entries 1−9, ≥96% ee) including low dielectric media such as benzene (entry 1, >99% ee) as well as highly polarized solvents such as dimethyl sulfoxide (entry 7, >99% ee). It is important to note that byproducts arising from dehydration of the initial β-hydroxy aldehyde adduct were not isolated in significant quantities (≤4% yield). The superior levels of reaction efficiency observed with proline in DMF at +4 °C (entry 9, 91% conversion, 3:1 *anti*:*syn*, 99% ee), prompted us to select these reaction conditions for further exploration.

The capacity of proline to catalyze asymmetric cross-aldol reactions between nonequivalent aldehydes was next examined. As highlighted in Table 2, syringe pump addition of propionaldehyde (aldehyde donor) to a series of aldehyde acceptors in the presence of the amine catalyst effectively suppressed homodimerization of the donor aldehyde[15] while providing excellent yields of the desired cross-aldol product (Table 2, entries 1−5, 80−88% yield). Indeed, propionaldehyde can be used as an aldol nucleophile with a broad range of aldehyde acceptors—including both alkyl (entries 1−3, 5, 80−88% yield, 97−99% ee) and aromatic substituted aldehydes (entry 4, 81% yield, 99% ee). Of particular note is the addition of propionaldehyde to isovaleraldehyde to provide the cross-aldol product in 88% yield and 97% ee. The principal issue in this reaction is that both the aldol donor and acceptor bear enolizable α-methylene protons; however, only a single regioisomer of the cross-aldol product is obtained (as determined by ^{1}H NMR analysis). Structural variation in the aldehyde donor component has also been examined. As revealed in entries 5−7, this cross-aldol reaction can tolerate a range of substituted nucleophiles (R_1 = Me, *n*-Bu, Bn, 19:1 to 24:1 *anti*:*syn*, 91 to >99% ee).

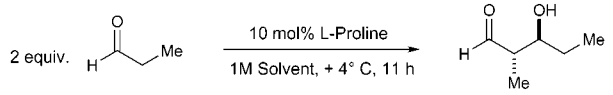
It is important to note that the absolute and the relative configurations of the aldol products obtained in this survey are in complete accord with the previously proposed models for proline-catalyzed aldol reactions.[5a] In contrast to proline-mediated ketone additions, lower catalyst loadings (10 mol %) and shorter reaction times (11 to 26 h) were possible without loss in reaction efficiency.[12] Last, to illustrate the preparative utility of this new cross-aldol process, the addition of propionaldehyde to isobutyraldehyde (Table 2, entry 5) was performed on a 25 mmol scale to afford 2.65 g (82% yield) of (2*S*,3*S*)-3-hydroxy-2,4-dimethylpentanal in >99% ee and with 24:1 *anti*-diastereoselectivity.

In summary, we have documented the first direct enantioselective catalytic aldol reaction using aldehydes as both the aldol donor and the aldol acceptor. Significantly, this method allows enantioselective access to β-hydroxy aldehydes, important synthons in

* To whom correspondence should be addressed. E-mail: dmacmill@caltech.edu.

10.1021/ja0262378 CCC: $22.00

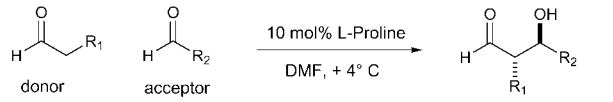
Table 1. Effect of Solvent on the Propionaldehyde Dimerization

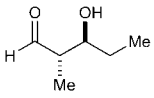
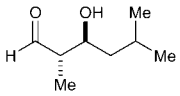
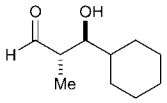
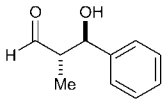
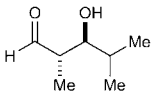
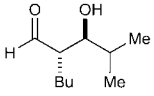
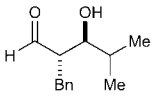


entry	solvent	conversion[a]	*anti*:*syn*[b]	% ee[c] (*anti*)
1	Ph-H	32	5:1	>99
2	$CHCl_3$	29	4:1	98
3	EtOAc	41	5:1	99
4	THF	36	4:1	98
5	dioxane	41	4:1	98
6	CH_3CN	42	3:1	96
7	DMSO	38	3:1	>99
8	NMP	62	3:1	98
9	DMF	91	3:1	99

[a] Relative conversion at an arbitrary 11 h time point. [b] Relative and absolute stereochemistry assigned by correlation. [c] GLC analysis of the 2,2-dimethyl-propane-1,3-diol derived acetal.

Table 2. Enantioselective Direct Aldehyde Cross-Aldol Reaction



entry	R_1	R_2	Product	% yield[a]	*anti*:*syn*[b]	% ee[c,d]
1	Me	Et		80	4:1	99
2	Me	*i*-Bu		88	3:1	97
3	Me	*c*-C_6H_{11}		87	14:1	99
4	Me	Ph		81	3:1	99
5	Me	*i*-Pr		82	24:1	>99
6[e]	*n*-Bu	*i*-Pr		80	24:1	98
7[e]	Bn	*i*-Pr		75	19:1	91

[a] Yield represents the combined yield of diastereomers. [b] Relative stereochemistry assigned by literature correlation. [c] Determined by GLC or HPLC. [d] Absolute stereochemistry assigned by chemical correlation or by analogy. [e] Conducted at 23 °C.

polypropionate and polyacetate natural product synthesis. A full account of these studies will be presented in due course.

Acknowledgment. We thank S. P. Brown, N. C. Goodwin, and I. K. Mangion for early contributions to this work. Financial support was provided by AstraZeneca, GlaxoSmithKline, Johnson and Johnson, Lilly, Merck Research Laboratories, and Pfizer. A.B.N. is grateful for an NSF predoctoral fellowship.

Supporting Information Available: Experimental procedures, and spectral data for all new compounds (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) (a) Evans, D. A.; Nelson, J. V.; Taber, T. In *Topics in Stereochemistry*; John Wiley and Sons: New York, 1982; Vol. 13, p 1. (b) Evans, D. A.; Vogel, E.; Nelson, J. V. *J. Am. Chem. Soc.* **1979**, *101*, 6120. (c) Evans, D. A.; Nelson, J. V.; Vogel, E.; Taber, T. R. *J. Am. Chem. Soc.* **1981**, *103*, 3099. (d) Evans, D. A.; Bartroli, J.; Shih, T. L. *J. Am. Chem. Soc.* **1981**, *103*, 2127.

(2) (a) Heathcock, C. H. *Asymmetric Synthesis*; Morrion, J. D., Ed.; Academic Press: New York, 1984; Vol. 3, part B, p 111. (b) Kleschick, W. A.; Buse, C. T.; Heathcock, C. H. *J. Am. Chem. Soc.* **1977**, *99*, 247. (c) Heathcock, C. H.; White, C. T. *J. Am. Chem. Soc.* **1979**, *101*, 7076. (d) Heatchock, C. H. *Science* **1981**, *214*, 395. (e) Danda, H.; Hansen, M. M.; Heathcock, C. H. *J. Org. Chem.* **1990**, *55*, 173.

(3) (a) Kim, B. M.; Williams, S. F.; Masamune, S. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 2 (Heathcock, C. H., Ed.), Chapter 1.7, p 239. (b) Masamune, S.; Ali, S.; Snitman, D. L.; Garvey, D. S. *Angew. Chem.* **1980**, *92*, 573. (c) Masamune, S.; Choy, W.; Kerdesky, F. A. J.; Imperiali, B. *J. Am. Chem. Soc.* **1981**, *103*, 1566. (d) Masamune, S.; Sato, T.; Kim, B.; Wollmann, T. A. *J. Am. Chem. Soc.* **1986**, *108*, 8279.

(4) (a) Mukaiyama, T. The Directed Aldol Reaction. In *Organic Reactions*; John Wiley & Sons: New York, 1982; Vol. 28, p 203. (b) Mukaiyama, T.; Narasaka, K.; Banno, K. *Chem. Lett.*, **1973**, 9, 1011. (c) Mukaiyama, T.; Banno, K.; Narasaka, K. *J. Am. Chem. Soc.* **1974**, *96*, 7503. (d) Kobayashi, S.; Uchiro, H.; Shiina, I.; Mukaiyama, T. *Tetrahedron* **1993**, *49*, 1761.

(5) (a) Kandasamy, S.; Notz, W.; Bui, T.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2001**, *123*, 5260. (b) Cordova, A.; Notz, W.; Barbas, C. F., III. *J. Org. Chem.* **2002**, *67*, 301.

(6) (a) Notz, W.; List, B. *J. Am. Chem. Soc.* **2000**, *122*, 7386. (b) List, B.; Pojarliev, P.; Castello, C. *Org. Lett.* **2001**, *3*, 573. (c) List, B.; Lerner, R. A.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2000**, *122*, 2395.

(7) (a) Yamada, Y. M. A.; Yoshikawa, N.; Sasai, H.; Shibasaki, M. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1871. (b) Yoshikawa, N.; Yamada, Y. M. A.; Das, J.; Sasai, H.; Shibasaki, M. *J. Am. Chem. Soc.* **1999**, *121*, 4168. (c) Yoshikawa, N.; Kumagai, N.; Matsunaga, S.; Moll, G.; Oshima, T.; Suzuki, T.; Shibasaki, M. *J. Am. Chem. Soc.* **2001**, *123*, 2466. (d) Yoshikawa, N.; Shibasaki, M. *Tetrahedron* **2001**, *57*, 2569.

(8) (a) Trost, B. M.; Silcoff, E. R.; Ito, H. *Org. Lett.* **2001**, *3*, 2497 (b) Trost, B. M.; Ito, H. *J. Am. Chem. Soc.* **2000**, *122*, 12003.

(9) A nondirect enantioselective cross-aldol reaction between two discrete aldehyde components has been achieved: Denmark, S. E.; Ghosh, S. K. *Angew. Chem., Int. Ed.* **2001**, *40*, 4759.

(10) Gijsen, H. J. M.; Wong, C.-H. *J. Am. Chem. Soc.* **1994**, *116*, 8422.

(11) Exposure of acetaldehyde to proline leads to the corresponding trimer dehydration adduct 5-hydroxy-(2*E*)-hexenal in 10% yield and 90% ee: see ref 5b.

(12) (a) Hajos, Z. G.; Parrish, D. R. *J. Org. Chem.* **1974**, *39*, 1615. (b) Eder, U.; Sauer, G.; Wiechert, R. *Angew. Chem.* **1971**, *10*, 496. (c) Agami, C.; Platzer, N.; Sevestre, H. *Bull. Chim. Soc. Fr.* **1987**, *2*, 358.

(13) We have discovered that a highly enantioselective aldehyde−aldehyde coupling sequence can be accomplished using simple imidazolidinone catalysts. Full details of this work will be communicated shortly.

(14) During the preparation of this manuscript, Barbas and co-workers reported the proline-catalyzed addition of aldehydes to imines with catalyst loadings and reaction efficiencies in accord with those outlined in this study: Córdova, A.; Watanabe, S.-I.; Tanaka, F.; Notz, W.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2002**, *124*, 1866.

(15) Syringe pump addition times were optimized for each aldehyde−aldehyde combination (see Supporting Information).

JA0262378