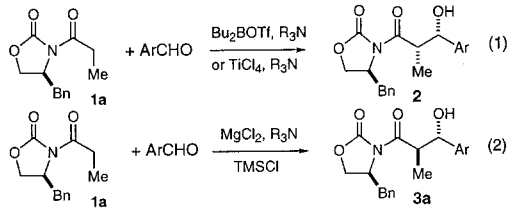
J|A|C|S
COMMUNICATIONS

Published on Web 12/27/2001

Diastereoselective Magnesium Halide-Catalyzed *anti*-Aldol Reactions of Chiral *N*-Acyloxazolidinones

David A. Evans,* Jason S. Tedrow, Jared T. Shaw, and C. Wade Downey
Department of Chemistry and Chemical Biology, Harvard University, Cambridge, Massachusetts 02138
Received August 13, 2001; Revised Manuscript Received September 25, 2001

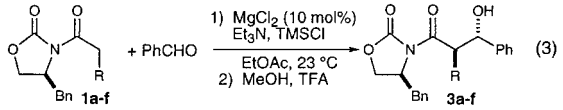
Chiral auxiliary-based aldol bond constructions remain the strategy of choice for accessing single isomers of β-hydroxy acid derivatives as chiral building blocks for bioactive compounds. Chiral *N*-acyloxazolidinones, derived from enantiopure amino alcohols, serve as ester surrogates with excellent control of enolate geometry and versatility in auxiliary cleavage.[1] Previous reports have illustrated the use of these substrates for syn-diastereoselective aldol reactions with chlorotitanium and dialkylboron enolates with high yields and selectivities (eq 1).[2] The corresponding *anti*-aldol process has not been fully realized with these chiral auxiliaries;[3] however, independent strategies for anti-selective enolate-based aldol reactions have been reported for (*Z*)-boryl enolates by Yan and Heathcock[4] and for (*E*)-boryl enolates by Masamune.[5] We now wish to report a highly diastereoselective direct *anti*-aldol reaction[6] with chiral acyloxazolidinones promoted by catalytic amounts of $MgCl_2$ in the presence of triethylamine and chlorotrimethylsilane (eq 2). This procedure has important implications in the eventual design of catalytic enantioselective aldol reactions using chiral metal complexes.



Our initial design of an aldol reaction, *catalytic in metal salt,* with imide enolates rested on finding a suitable metal salt capable of facilitating enolization of *N*-propionyl imide **1a** with an amine base, yet able to form a reversible complex with the amine base. Magnesium salts were chosen as candidate Lewis acids for this process due to their precedented use in carbonyl-based enolization with tertiary amines.[7] It was envisioned that the turnover step in the catalytic process would involve ammonium ion protonation of the metal aldolate, thus returning both the metal halide and the amine base to the reaction pool. However, protonation of the metal aldolate proved not to be a practical solution for metal halide turnover. We then focused on metal aldolate silylation[8−10] as a strategy for turning over the metal center while improving the prospects for kinetic aldol diastereoselection.

Choice of a silylation agent was contingent upon finding the proper level of reagent reactivity such that reaction with the metal aldolate product, but not with other reaction constituents (e.g. the metal enolate), might be achieved. Chlorotrimethylsilane (TMSCl) was fortuitously found to meet these criteria affording silylated anti-aldol products with high diastereoselectivity and yield.[11,12] Initial experiments demonstrated that 0.1−0.2 equiv of $MgCl_2$, $MgBr_2$, or $MgBr_2{\cdot}OEt_2$ are preferred over magnesium salts with more dissociating counterions such as $Mg(OTf)_2$ and $Mg(NTf_2)_2$. Tetrahydrofuran and ethyl acetate are the most effective solvents in promoting the reaction of **1a** with benzaldehyde to >90% conversion with >20:1 diastereoselectivity after 20 h at room temperature. Ethyl acetate proved to be optimal for a range of substrates due to faster reaction rates and was selected as the solvent of choice.

Table 1. Mg-Catalyzed *anti*-Aldol Reactions of Reactions of **1a**−**f** with Benzaldehye (Eq 3)[a]



entry	product	R	dr[b]	yield (%)[c]
1	**3a**	CH_3	32:1	91
2	**3b**	CH_2CH_3	32:1	88
3	**3c**	CH_2Ph	26:1	94
4	**3d**	CH_2CHMe_2	32:1	91
5	**3e**	$CH_2CH{=}CH_2$	28:1	91
6	**3f**	$CHMe_2$[d]	3.5:1	36% conv

[a] Reactions were conducted with 1.0 equiv 1, 0.1 equiv $MgCl_2$, 2.0 equiv of triethylamine, 1.5 equiv of TMSCl, 1.2 equiv of PhCHO at 0.5 M in EtOAc for 24 h. [b] dr = diastereomeric ratio reported as major isomer:Σ other diastereomers. Determined by GLC (Supporting Information). [c] Isolated yield of a single diastereomer. [d] Absolute configuration assigned by analogy.

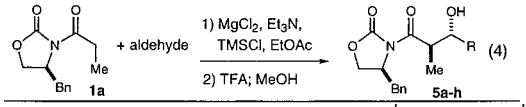
Table 1 documents the scope and limitations of representative *N*-acyloxazolidinones in reactions with benzaldehyde. A current limitation to this aldol procedure includes β-branching on the acyl substituent (entry 6). In addition, α-heteroatom-substituted acyloxazolidinones provide low diastereoselectivity with these conditions. Reactions of **1a** with benzaldehyde are effected using 10 mol % of $MgCl_2$ with 2.0 equiv of triethylamine and 1.5 equiv of TMSCl. Less reactive aldehydes require increasing the magnesium loading to 20 mol % to achieve full conversion (Procedure A). Alternatively, the use of the additive $NaSbF_6$ to precipitate the chloride ion byproduct increases the level of conversion. We have found that the addition of 30 mol % of $NaSbF_6$ is adequate to achieve full turnover for the substrates examined (Procedure B). These two procedures were screened with each aldehyde to maximize yield and diastereoselectivity.

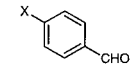
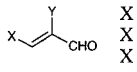
Variation of the aldehyde reaction component resulted in larger changes in diastereoselectivity in the reactions with *N*-propionyloxazolidinone **1a**. As summarized in Table 2, the $MgCl_2$-catalyzed aldol reaction performs well with a number of aromatic and unsaturated aldehydes, providing moderate-to-high selectivities of *anti*-aldol products.[13] Even sensitive aldehydes such as methacrolein provide a 16:1 diastereoselectivity and a 77% yield of the isolated *anti*-aldol adduct.

The following control experiments have provided some insight into the overall mechanism of this transformation. *This process does not proceed through a Mukaiyama aldol pathway, as the enolsilane of **1a** is not formed under these reaction conditions.* Furthermore, the independently prepared enolsilane of **1a** does not react with benzaldehyde under $MgCl_2$ catalysis in ethyl acetate.[14] Metal

10.1021/ja0119548 CCC: $22.00

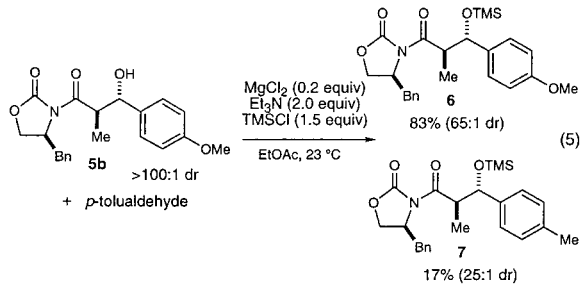
Table 2. Mg-Catalyzed *anti*-Aldol Reactions of **1a** with Representative Aldehydes (Eq 4)[a]

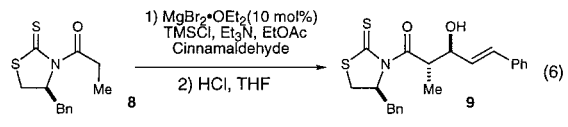


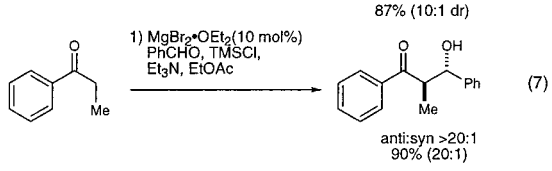
aldehyde		product	procedure[a,b]	dr[c]	yield (%)[d]
	X = Me	**5a**	A	24:1	-
	X = OMe	**5b**	A	32:1	91
	X = NO_2	**5c**	B	7:1	71
	X = Ph, Y = H	**5d**	B	21:1	92
	X = Ph, Y = Me	**5e**	A	28:1	92
	X = H, Y = Me[i]	**5f**	B	16:1	77
α-naphthaldehyde		**5g**	A	14:1	91
furfural		**5h**	B	6:1	80

[a] Procedure A: reactions were conducted with 1.0 equiv **1**, 0.2 equiv $MgCl_2$, 2.0 equiv of triethylamine, 1.5 equiv of TMSCl, 1.2 equiv of RCHO at 0.5 M in EtOAc for 24 h. [b] Procedure B: reaction conducted as in Procedure A but with 0.1 equiv $MgCl_2$ and the addition of 0.3 equiv of $NaSbF_6$ at 0.2 M in ethyl acetate. [c] Table 1 footnote b. [b] Isolated yield of a single diastereomer.

aldolate silylation is therefore essential for achieving a catalytic process. We have also carried out experiments that bear on the issue of product silylation and retro-aldolization (eq 5). In conjunction with this trapping experiment it was determined that *p*-tolualdehyde reacts under the indicated conditions twice as fast as *p*-methoxybenzaldehyde in a direct competition experiment. In the illustrated reaction, the diastereomerically pure aldol adduct **5b** (Table 2) is combined with an equivalent amount of *p*-tolualdehyde and subjected to the standard reaction conditions (Procedure A). The silylated aldol adduct **6** was isolated as the principal product (83%) while the crossover silylated aldol adduct **7** was isolated in 17% yield. The diastereomer ratios within each family of aldol adducts are noted. It is evident from these results that there exists a delicate balance between metal aldolate silylation and fragmentation (retro-aldolization). Analogous experiments with the silylated aldol adduct **6** show that, once silylated, the aldol products do not interconvert through product epimerization.







Chiral acylthiazolidinethiones have also been reported as useful ester surrogates in diastereoselective reactions, often providing a major diastereomer different from the corresponding oxazolidinone case.[15] Magnesium-catalyzed aldol reaction of chiral acylthiazolidinethione **8** with cinnamaldehyde and subsequent desilylative workup afforded **9** in 87% isolated yield of the major diastereomer (eq 6). Optimized conditions for this family of substrates include the use of $MgBr_2 \cdot OEt_2$. Chemical correlation with known material showed that **9** is the opposite *anti*-aldol diastereomer to that seen in the oxazolidinone series (eq 4).[16] Propiophenone readily undergoes the magnesium-catalyzed aldol reaction with benzaldehyde, affording 90% yield and 95:5 anti:syn diastereomeric ratio (eq 7). Further investigations into the mechanism and catalytic enantioselective variants of this process are currently underway and results will be reported in due course.

Acknowledgment. Support has been provided by the NSF and the NIH (GM 33328-18). We acknowledge Dr. Paul Reider (Merck) for the suggestion of ethyl acetate as a reaction solvent on the basis of practical considerations. J.T.S. gratefully acknowledges an NIH Postdoctoral Fellowship.

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

References

(1) (a) Evans, D. A.; Taber, T. R. *Tetrahedron Lett.* **1980**, *21*, 4675−4678. (b) Evans, D. A.; Bartroli, J.; Shih, T. L. *J. Am. Chem. Soc.* **1981**, *103*, 2127−2109.
(2) (a) Evans, D. A.; Rieger, D. L.; Bilodeau, M. T.; Urpi, F. *J. Am. Chem. Soc.* **1991**, *113*, 1047−1049. (b) Evans, D. A.; Nelson, J. V.; Taber, T. *Top. Stereochem.* **1982**, *13*, 111−115. (c) Gage, J. R.; Evans, D. A. *Org. Synth.* **1990**, *68*, 83−91.
(3) For an exception with halogenated enolates, see: Pridgen, L. N.; Abdel-Magid, A. F.; Lantos, I.; Shilcrat, S.; Eggleston, D. S. *J. Org. Chem.* **1993**, *58*, 5107−5117.
(4) (a) Walker, M. A.; Heathcock, C. H. *J. Org. Chem.* **1991**, *56*, 5747−5750. (b) Raimundo, B. C.; Heathcock, C. H. *Synlett* **1995**, 1213−1214. (c) Wang, Y.-C.; Hung, A.-W.; Chang, C.-S.; Yan, T.-H. *J. Org. Chem.* **1996**, *61*, 2038−2043.
(5) Abiko, A.; Liu, J.-F.; Masamune, S. *J. Am. Chem. Soc.* **1997**, *119*, 2586−2587.
(6) For other catalytic direct aldol reactions see: (a) Watanabe, K.; Yamada, Y.; Goto, K. *Bull. Chem. Soc. Jpn.* **1985**, *58*, 1401−1406. (b) Yamada, Y. M. A.; Yoshikawa, N.; Sasai, H.; Shibasaki, M. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1871−1873. (c) Yoshikawa, N.; Yamada, Y. M. A.; Das, J.; Sasai, H.; Shibasaki, M. *J. Am. Chem. Soc.* **1999**, *121*, 4168−4178. (d) Kumagai, N.; Matsunaga, S.; Yoshikawa, N.; Ohshima, T.; Shibasaki, M. *Org. Lett.* **2001**, *3*, 1539−1542. (e) Trost, B. M.; Ito, H. *J. Am. Chem. Soc.* **2000**, *122*, 12003−12004. (f) Trost, B. M.; Silcoff, E. R.; Ito, H. *Org. Lett.* **2001**, *3*, 2497−2500. (g) List, B.; Lerner, R. A.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2000**, *122*, 2395−2396. (h) Ito, Y.; Sawamura, M.; Hayashi, T. *J. Am. Chem. Soc.* **1986**, *108*, 6405−6406.
(7) (a) Evans, D. A.; Nelson, S. G. *J. Am. Chem. Soc.* **1997**, *119*, 6452−6453. (b) Swiss, K. A.; Choi, W. B.; Liotta, D. C.; Abdel-Magid, A. F.; Maryanoff, C. A. *J. Org. Chem.* **1991**, *56*, 5978−5980. (c) Hayashi, K.; Kogiso, H.; Sano, S.; Nagao, Y. *Synlett* **1996**, 1203−1205. (d) Olsen, R. S.; Fataftah, Z. A.; Rathke, M. W. *Synth. Commun.* **1986**, *16*, 1133−1139. (e) Tirpak, R. E.; Olsen, R. S.; Rathke, M. W. *J. Org. Chem.* **1985**, *50*, 4877−4879.
(8) Other aldol processes which utilize silylation as the turnover event: (a) Chini, M.; Crotti, P.; Gardelli, C.; Minutolo, F.; Pineschi, M. *Gazz. Chim. Ital.* **1993**, *123*, 673−676. (b) Kiyooka, S.-I.; Tsutsui, T.; Maeda, H.; Kaneko, Y.; Isobe, K. *Tetrahedron Lett.* **1995**, *36*, 6531−6534.
(9) Kelleher, R. G.; McKervey, M. A.; Vibuljan, P. *J. Chem. Soc., Chem. Commun.* **1980**, 486-488.
(10) (a) Furstner, A. *Pure Appl. Chem.* **1998**, *70*, 1071−1076. (b) Furstner, A. *Chem. Eur. J.* **1998**, *4*, 567−570.
(11) Other siylating agents (TMS-Br, TMS-OTf, TMS-NMe2) were found to be inferior in either diastereoselectivity or yield.
(12) Magnesium halides were found to be superior to other metal halides examined ($TiCl_4$, $AlCl_3$, $ScCl_3$, $ZnCl_2$, MnI_2).
(13) Aliphatic aldehydes (*i*-PrCHO, *t*-BuCHO, $PhCH_2CH_2CHO$) suffer from low conversion.
(14) For silylenol ether preparation see: Fuentes, L. M.; Shinkai, I.; Salzmann, T. N. *J. Am. Chem. Soc.* **1986**, *108*, 4675−6.
(15) (a) Hsiao, C. N.; Ashburn, S. P.; Miller, M. J. *Tetrahedron Lett.* **1985**, *26*, 4855−4858. (b) Crimmins, M. T.; Chaudhary, K. *Org. Lett.* **2000**, *2*, 775−777. (c) Crimmins, M. T.; King, B. W.; Tabet, E. A.; Chaudhary, K. *J. Org. Chem.* **2001**, *66*, 894−902. (d) Nagao, Y.; Yamada, S.; Kumagai, T.; Ochiai, M.; Fujita, E. *J. Chem. Soc., Chem. Commun.* **1985**, 1418−19. (e) Fujita, E.; Nagao, Y. *Adv. Heterocycl. Chem.* **1989**, *45*, 1−36. (f) Delaunay, D.; Toupet, L.; Corre, M. L. *J. Org. Chem.* **1995**, *60*, 6604−7.
(16) Meyer, H. H. *Liebigs Ann. Chem.* **1984**, 791−801.

JA0119548