Efficient Lewis Acid Catalyzed Intramolecular Cannizzaro Reaction

Albert E. Russell, Steven P. Miller, and James P. Morken*

Department of Chemistry, Venable and Kenan Laboratories, The University of North Carolina at Chapel Hill, Chapel Hill, North Carolina 27599-3290

morken@unc.edu

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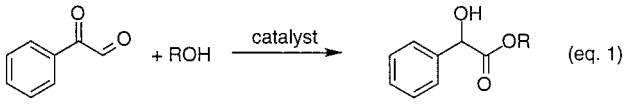
We have recently initiated a program directed toward the development of stereoselective metal-catalyzed intramolecular hydride transfer reactions. The catalytic aldol-Tishchenko reaction is one such process wherein an organized transition state results in diastereoselective product formation.[1] For similar reasons, we expected that an intramolecular Cannizzaro reaction (eq 1) might occur



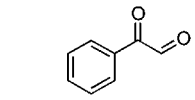
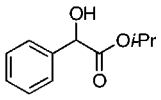
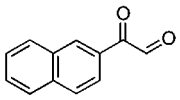
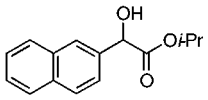
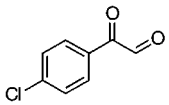
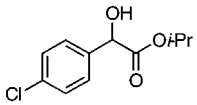
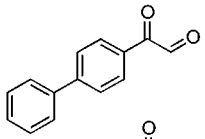
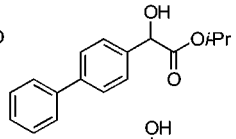
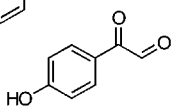
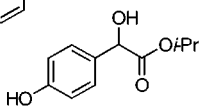
(eq. 1)

with stereocontrol in the presence of an appropriate Lewis acid catalyst. This transformation results in the production of synthetically useful α-hydroxy esters directly from readily available glyoxals[2] under neutral conditions. Current precedent for an intramolecular Lewis acid (as opposed to Bronsted base) catalyzed Cannizzaro reaction is limited to reaction conditions requiring high temperature (60 °C) and/or high catalyst loading (20 mol % catalyst) and, in some cases, involves competitive side reactions.[2,3] Herein, we report that the intramolecular Cannizzaro reaction may be brought about at room temperature with as little as 1 mol % of an appropriate Lewis acid catalyst. While initial studies indicate that the reaction may be subject to asymmetric catalysis, preliminary mechanistic experiments also indicate that common C_2-symmetric ligands are not appropriate for this reaction and that design of new ligand motifs may be required to realize high enantioselectivity in this metal-catalyzed process.

As a preliminary test reaction, catalytic conversion of phenyl glyoxal hydrate to isopropyl mandelate was examined in the presence of a number of metal salts. In these experiments, 2-propanol was used as a cosolvent thereby necessitating that catalysts are tolerant of protic reaction conditions.[4] The experimental protocol involves addition of 10% catalyst to an 2-propanol−dichloroethane solution of the glyoxal substrate (most often employed as the hydrate) followed by a 24 h reaction period. The reactions were carried out on the benchtop with no particular precautions to exclude moisture or oxygen from the reaction vessel. Of the 20 metal complexes examined, it was found that $Cu(ClO_4)_2 \cdot 6H_2O$, $Cu(OTf)_2$, and $Cr(ClO_4)_3 \cdot 6H_2O$ gave the highest levels of reactivity; reactions with $Fe(ClO_4)_3 \cdot 6H_2O$, $Mg(ClO_4)_2 \cdot 6H_2O$, $Al(ClO_4)_3 \cdot 9H_2O$, $Li(ClO_4) \cdot 3H_2O$, and $Y(ClO_4)_3$ provided no product. To explore substrate scope with $Cr(ClO_4)_3 \cdot 6H_2O$, the series of reactions presented in Table 1 was examined.[5] It was found that various aromatic glyoxals are converted to α-hydroxy esters with isolated yields ranging from 40 to 84%. Notably, under the influence of the chromium(III) catalyst, alcohol functionality is tolerated in the starting material (entry 5, Table 1).

To initiate studies in asymmetric catalysis, an arrayed catalyst evaluation approach was employed.[6] This catalyst discovery strategy revealed $Cu(OTf)_2$−PhBox[7] and $Ni(ClO_4)_2$−BINAP[8] as two metal−ligand combinations able to effect the Cannizzaro reaction in an enantiose-

Table 1. Chromium-Catalyzed Cannizzaro Reaction of Aryl Glyoxals[a]

entry	substrate	product	% yield[b]
1			55
2			84
3			64
4			64
5			40

[a] All reactions were carried out with 10 mol % $Cr(ClO_4)_3 \cdot 6H_2O$ at room temperature for 24 h in 2:1 2-propanol:dichloroethane solvent. [b]Percent yield is of isolated material after silica gel chromatography. All compounds were characterized by ^1H NMR, ^{13}C NMR, IR, and elemental analysis.

(1) (a) Mascarenhas, C. M.;, Duffey, M. O.; Liu, S.-Y.; Morken, J. P. *Org. Lett.* **1999**, *1*, 1427−1429. (b) Lu, L.; Chang, H. Y.; Fang, J. M. *J. Org. Chem.* **1999**, *64*, 843−853. (c) Mahrwald, R.; Costisella, B. *Synthesis* **1996**, 1087−1089.

(2) Fuson, R. C.; Emerson, W. S.; Gray, H. W. *J. Am. Chem. Soc.* **1939**, *61*, 480.

(3) (a) Maruyama, K.; Murakami, Y.; Yoda, K.; Mashino, T.; Nishinaga, A. *J. Chem. Soc., Chem. Commun.* **1992**, 1617−1618. (b) Jin, S.-J.; Arora, P. K.; Sayre, L. M. *J. Org. Chem.* **1990**, *55*, 3011−3018. (c) Okuyama, T.; Kimura, K.; Fueno, T. *Bull. Chem. Soc. Jpn.* **1982**, *55*, 2285−2286.

(4) There are few reports of chiral Lewis acid catalysts that are effective in protic solvents. For two recent reports, see: (a) Otto, S.; Boccaletti, G.; Engberts, B. F. N. *J. Am. Chem. Soc.* **1998**, *120*, 4238. (b) Kobayashi, S.; Nagayama, S.; Busujima, T.; *Chem. Lett.* **1999**, 71.

(5) Metal perchlorates pose an explosion hazard. See: *Prudent Practices for Handling Hazardous Chemicals in Laboratories*; National Academy Press: Washington, D.C., 1981; p 65.

(6) Taylor, S. J.; Morken, J. P. *J. Am. Chem. Soc.*, **1999**, *121*, 12202. For recent reviews of high-throughput screening see: (a) Bein, T. *Angew. Chem., Int. Ed.* **1999**, *38*, 323. (b) Shimizu, K. D.; Snapper, M. L.; Hoveyda, A. H. *Chem. Eur. J.* **1998**, *4*, 1885. (c) Francis, M. B.; Jamison, T. F.; Jacobsen, E. N. *Curr. Op. Chem. Biol.* **1998**, *2*, 422.

(7) 2,2′-Isopropylidenebis(4-phenyl-2-oxazoline). For reviews of Cu−bisoxazoline complexes in the asymmetric activation of carbonyls, see: Johnson, J. S.; Evans, D. A. *Acc. Chem. Res.* **2000**, *33*, 325. Jørgensen, K. A.; Johannsen, M.; Yao, S.; Audrain, H.; Thorhauge, J. *Acc. Chem. Res.* **1999**, *32*, 605.

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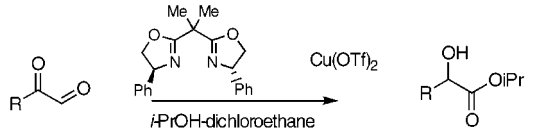
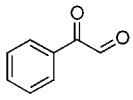
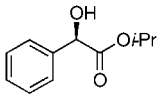
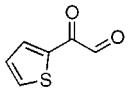
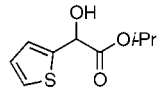
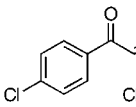
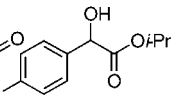
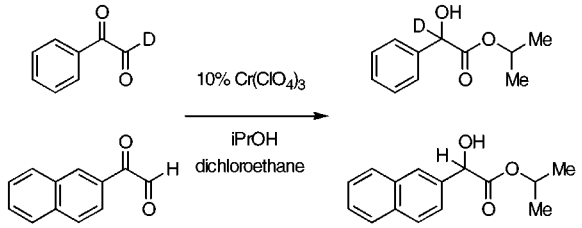
Table 2. Cu(II)-PhBox Catalyzed Asymmetric Cannizzaro Reaction[a]



substrate	product	% catalyst	% yield[b]	% ee[c]
		10	57	28 (R)
		5	53	28 (R)
		1	56	28 (R)
		10	68	17
		10	67	33

[a] All reactions were carried out at room temperature for 24 h in 2:1 2-propanol:dichloroethane solvent. [b]Percent yield is of isolated material after silica gel chromatography. All compounds were characterized by ^{1}H NMR, ^{13}C NMR, IR and elemental analysis. [c]Determined by chiral GLC analysis. Absolute configuration determined by comparison to authentic material.

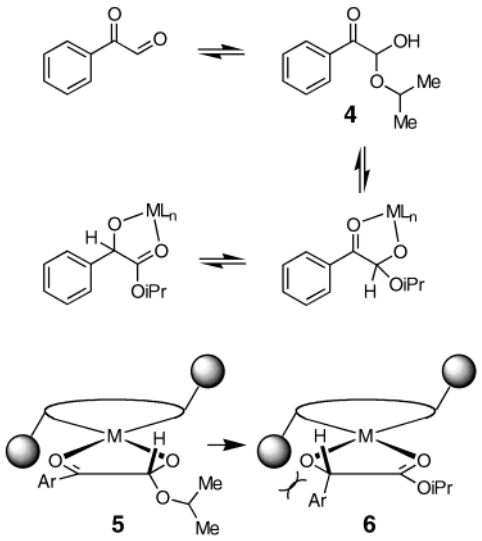
Scheme 1



lective fashion. In the presence of 10 mol % of a 1:1 complex of $Cu(OTf)_2$ and (*S*,*S*)-Ph-box (see Table 2), phenyl glyoxal hydrate is converted to *R*-isopropyl mandelate in 28% ee and 57% yield. Notably, similar levels of enantioselectivity and yield can be obtained with 5 mol % and 1 mol % catalyst loading. When nonaromatic substituted bis(oxazoline) ligands were employed in place of PhBox, significantly diminished yields were obtained. For instance, when 10 mol % *t*-Bu-box was used as the ligand the Cannizzaro adduct could not be detected by ^{1}H NMR analysis of the crude mixture. Such unusual reactivity discrepancies, upon substitution of aromatic oxazoline-derived ligands for their alkyl-substituted counterparts, have been noted in the recent literature by Evans[9] and Jørgensen.[10]

To provide a mechanistic foundation for rational catalyst modification, the crossover experiment in Scheme 1 was carried out. Subjection of a 1:1 mixture of deuterium-labeled phenyl glyoxal[11] and nonlabeled 2-naphthylglyoxal to the catalytic reaction conditions resulted in the corresponding Cannizzaro reaction products. Both ^{1}H and ^{2}H NMR spectroscopic analysis show that <5% deuterium is incorporated in the naphthyl-derived product and <5% hydrogen is incorporated at the carbinol position of the mandelate product. Since no crossover occurs in the hydride transfer step, it is reasonable to speculate that the Lewis acid-catalyzed Cannizzaro reaction proceeds by an intramolecular 1,2 hydride shift. This experiment also indicates that the current reaction does not proceed through an enediol intermediate similar to that invoked for the Lobry de Bruyn-Alberda van Ekenstein reaction,[12] as the enediol is known to participate in proton exchange with solvent and would therefore result in nonstoichiometric deuterium incorporation in the crossover experiment described above.[13]

Scheme 2



On the basis of our observations, we propose the reaction mechanism described in Scheme 2. Initial reaction of the arylglyoxal with 2-propanol provides hemiacetal **4.** Subsequent coordination of **4** to the catalyst followed by intramolecular hydride transfer, presumably by a three-center transition state, might then provide the observed reaction product. In support of this conjecture is that ^{1}H NMR ($CDCl_3$) analysis of the arylglyoxal hydrate in the presence of 5 equiv of 2-propanol shows only the presence of hemiacetal **4**; resonances for the aldehyde and hydrate could not be detected. Under this paradigm, enantioselective transformation would result from a dynamic resolution whereby the chiral transition-metal complex selectively binds and catalyzes the rearrangement of one enantiomer of an equilibrating mixture of the stereoisomers of **4**.[14] This mechanistic scheme highlights the challenge in design of an effective catalyst for enantioselective transformation. The enantiomer of **4** that is expected to bind a C_2 symmetric catalyst in a

(8) Miyashita, A.; Yasuda, A.; Takaya, H.; Toriumi, K.; Ito, T.; Souchi, T.; Noyori, R. *J. Am. Chem. Soc.* **1980**, *102*, 7932.

(9) Evans, D. A.; Burgey, C. S.; Paras, N. A.; Vojkovsky, T.; Tregay, S. W. *J. Am. Chem. Soc.* **1998**, *120*, 5824. For mechanistic investigations, see: Evans, D. A.; Johnson, J. S.; Burgey, C. S.; Campos, K. R. *Tetrahedron Lett.* **1999**, *40*, 2879.

(10) Johannsen, M.; Jørgensen, K. A. *J. Org. Chem.* **1995**, *60*, 5757.

(11) Hall, S. S.; Doweyko, A. M.; Jordan, F. *J. Am. Chem. Soc.* **1978**, *100*, 5934.

(12) For a review of this reaction, see: Speck, J. C. *Adv. Carbohydr. Chem.* **1958**, *13*, 63−103.

(13) In contrast, $Mg(NO_3)_2$-catalyzed rearrangement of analogous α-ketohemimercaptals in basic D_2O results in significant deuterium incoporation. See: Hall, S. S.; Poet, A. *Tetrahedron Lett.* **1970**, *33*, 2867−2868.

(14) At present, we cannot rule out enantioselective addition of 2-propanol to metal-coordinated arylglyoxal as a mechanism for enantioselective transformation. Steric interactions that would govern this addition process should be similar to those proposed for binding of the chiral metal complex to hemiacetal **4**.

"matched" fashion (^{i}PrO directed away from steric bulk, see **5**) will experience a more substantial steric penalty upon hydride transfer and pyramidalization of the newly forming stereocenter (aryl directed toward steric bulk of ligand, see **6**) than does the "mismatched" enantiomer of hemiacetal **4**. We suspect that these counteracting steric interactions, generated by the C_2 symmetric environment about the ligand, lead to low selectivity and that design of new ligand motifs may be required to realize a highly selective transformation.

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Supporting Information Available: Characterization data for all compounds and experimental details are available This material is available free of charge via the Internet at http://pubs.acs.org.

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