J|A|C|S COMMUNICATIONS

Published on Web 06/07/2010

Catalytic Asymmetric Transacetalization

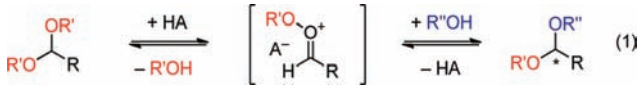
Ilija Čorić, Sreekumar Vellalath, and Benjamin List*

Max-Planck-Institut für Kohlenforschung, Kaiser-Wilhelm-Platz 1, D-45470, Mülheim an der Ruhr, Germany

Received April 9, 2010; E-mail: list@mpi-muelheim.mpg.de

Stereogenic acetals are ubiquitous in natural products, ranging from simple carbohydrates to complex spiroketal polyketides.[1] Controlling their relative and absolute configuration can be extremely important. For example, starch and cellulose only vary in the configuration at their anomeric acetal stereocenter.[2] The importance of chiral acetals is further illustrated by their occurrence in a variety of chiral pharmaceuticals and their potential as diastereocontrolling elements in organic synthesis.[3,4] Nevertheless, methods for the *enantioselective* synthesis of stereogenic acetals are very limited and usually based on chiral starting materials or reagents.[5] Catalytic enantioselective approaches employ enzymatic resolutions or metal-catalyzed desymmetrizations, in which the acetal carbon is not a reaction center.[6] Only a single catalytic asymmetric formation of acetals was previously achieved via a metal-catalyzed hydroetherification of enol ethers.[7] Here we report a Brønsted acid catalyzed asymmetric transacetalization reaction that furnishes chiral acetals with excellent enantioselectivity.

Recent advances in enantioselective Brønsted acid catalysis have enabled the generation of chiral *N*,*N*- and *N*,*O*-acetals.[8] The enantiodifferentiation in these reactions is based on the ability of chiral phosphoric acids to asymmetrically control the addition of nucleophiles to imines.[9] While related enantioselective additions to oxocarbenium ion intermediates could potentially lead to chiral *O*,*O*-acetals, this reactivity is much less explored.[10] We have a long-standing interest in catalytic asymmetric acetalizations and are now focusing on the transacetalization reaction in which one alkoxy group of an acetal is exchanged with another one (eq 1).

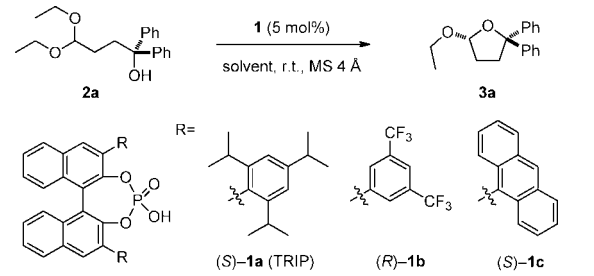


(1)

Although transacetalization reactions usually require relatively strong Brønsted acid catalysts, we reasoned that an intramolecular variant might be amenable to mild asymmetric Brønsted acid catalysis. We envisioned that this design could potentially address problems resulting from the reversibility of the reaction and product racemization. As Brønsted acids generally activate acetals by catalyzing the formation of an oxocarbenium ion intermediate, we expected that a chiral counteranion would provide an asymmetric environment for the subsequent alcohol attack.[10,11]

We began our investigation by studying the reaction of alcohol **2a** to acetal **3a** using Brønsted acid catalyst **1a** (TRIP), with bulky 2,4,6-(*i*Pr)$_3$C$_6$H$_2$ substituents in 3,3′-positions.[12] Several reports have established TRIP as one of the more useful and general phosphoric acid catalysts.[13] With 5 mol % of (*S*)-TRIP in $CHCl_3$, the intramolecular transacetalization of substrate **2a** proceeded with a promising er of 76:24 (Table 1, entry 1). Gratifyingly, a prolonged reaction time did not lead to any observable decrease in optical purity, suggesting that, under the reaction conditions, the rates of the reverse reaction and product racemization via an oxocarbenium ion were not competitive. Adding molecular sieves to the reaction

Table 1. Optimization of Reaction Conditions[a]



entry	catalyst	solvent	time	er
1[b]	**1a**	$CHCl_3$	6 h	76.0:24.0
2	**1a**	$CHCl_3$	4 h	91.0:9.0
3	**1a**	toluene	2 h	87.0:13.0
4	**1a**	hexane	1 h	71.0:29.0
5	**1a**	benzene	2 h	90.0:10.0
6	**1a**	$CHCl_3$/benzene 1:1	3 h	91.5:8.5
7	**1b**	$CHCl_3$/benzene 1:1	<1 h	22.0:78.0
8	**1c**	$CHCl_3$/benzene 1:1	<1 h	82.0:18.0
9[c]	**1a (1 mol %)**	**benzene**	**48 h**	**94.5:5.5**

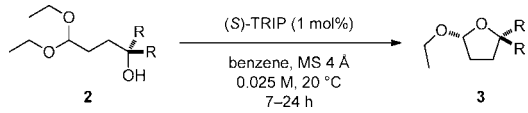
[a] Unless otherwise specified, reactions were performed on 0.025 mmol scale (0.1 M solution), 4 Å MS (10 mg) at room temperature. [b] Without MS. [c] 0.025 M solution, 20 °C.

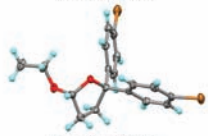
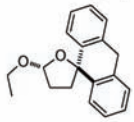
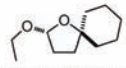
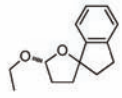
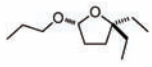
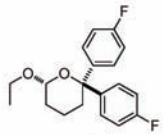
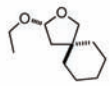
mixture gave a significant increase in enantioselectivity (entry 2). This suggested that ethanol, which is formed during the reaction, has a detrimental effect on the enantioselectivity. Additional solvent and catalyst screenings (including acids **1b** and **1c**) left TRIP remaining as the optimal catalyst. Remarkably, reducing both catalyst loading and concentration improved the enantioselectivity and an er of 94.5:5.5 was achieved with only 1 mol % of TRIP (entry 9).

Having established these optimized conditions, we set out to explore the substrate scope. Substrates **2** were easily available in one or two steps from commercial materials. In some cases neat substrates **2** undergo a slow intramolecular transacetalization spontaneously. However this can be avoided by storing the substrates as solutions in diethyl ether or ethyl acetate and evaporating the solvent shortly before the enantioselective transacetalization. Exploration of the substrate scope revealed that various tertiary alcohols form five-membered cyclic acetals **3** in excellent yields and with high enantiomeric ratios (Table 2). Interestingly, aliphatic and aromatic substituents on the alcohol are tolerated equally well. Both electron-rich and -poor aromatic substituents are suitable. In the case of aliphatic substituents, increased bulkiness led to higher enantioselectivity, with isopropyl substituted alcohol **3h** giving the highest enantiomeric ratio of 98:2 (entry 8). Intramolecular transacetalization can also be applied to the parallel kinetic resolution of chiral tertiary alcohols. Acetal **3l**, which contains a quaternary carbon stereogenic center, was obtained from the corresponding racemic alcohol precursor in excellent yield and high enantioselectivity for both diastereomers (er 91:9 and er 96:4,

10.1021/ja102753d

Table 2. Substrate Scope of the Enantioselective Intramolecular Transacetalization Reaction[a]



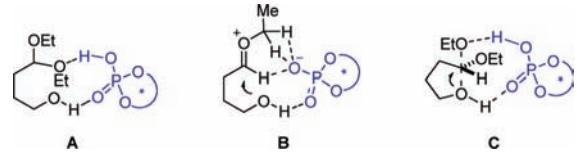
entry	product		yield/%	er
1	R = C_6H_5	**3a**	95	94.5:5.5
2	R = 4-(MeO)C_6H_4	**3b**	96	95.5:4.5
3	R = 4-FC_6H_4	**3c**	98	97.0:3.0
4[b]	 R = 4-BrC_6H_4	**3d**	99	97.0:3.0
5[c]		**3e**	86	95.5:4.5
6	R = Me	**3f**	84	94.5:5.5
7	R = Et	**3g**	92	97.0:3.0
8	R = *i*-Pr	**3h**	93	98.0:2.0
9	R = *t*-Bu	**3i**	90	98.0:2.0
10	R = CH_2Ph	**3j**	98	97.0:3.0
11		**3k**	94	97.0:3.0
12	 dr (*cis*/*trans*) = 1.1:1	**3l**	96	91.0:9.0 (*cis*) 96.0:4.0 (*trans*)
13		**3m**	95	95.0:5.0
14[c]		**3n**	96	82.0:18.0
15[c]		**3o**	94	82.5:17.5
16[d]		**3p**	76	79.0:21.0

[a] Unless otherwise specified, reactions were performed on 0.3 mmol scale with molecular sieves (50 mg/0.1 mmol). All yields refer to isolated yields. Enantiomeric ratios were determined by HPLC or GC analysis on a chiral stationary phase. [b] Reaction performed on 0.9 mmol scale. [c] Reaction time: **3e**, 7 days; **3n**, 4 days; **3o**, 30 min. [d] For yield determination see Supporting Information.

entry 12). The effect of the pre-existing stereogenic center on the stereoselectivity appears to be small. Longer *O*-alkyl substituents (ethyl vs *n*-propyl, entry 13) are well tolerated. Our reaction could also be extended to a six-membered acetal (entry 14) and ones that are derived from primary alcohols (entries 15 and 16). Products **3n**, **3o**, and **3p** were formed in high yield but lower enantioselectivity.

The absolute configuration of acetal **3d** was determined to be (*R*) by single-crystal X-ray analysis. Configurations of other products were assigned by analogy. Product **3d** was obtained on a 0.9 mmol scale in 99% isolated yield and with an er of 97:3.

Regarding the mechanism of the reaction, we speculate that the bifunctional character of the phosphoric acid is crucial for the observed reactivity and enantioselectivity. A hydrogen bonded assembly such as **A** might account for the selective activation of the hydroxyl acetal. The hydroxyl moiety in the substrate serves as a directing group and also increases the acidity of the phosphoric acid through hydrogen bonding. Subsequent cyclization might proceed through an oxocarbenium intermediate, in which the phosphate anion provides a chiral environment through hydrogen bonding interactions with the oxocarbenium ion moiety and the hydroxyl group (**B**) or by a more S_N2-like pathway (**C**).



In summary, we report the first catalytic enantioselective intramolecular transacetalization reaction, furnishing chiral acetals with the acetal carbon as the only stereogenic center. We are unaware of previous reports on phosphoric acid catalyzed enantioselective addition of nucleophiles to simple *O*,*O*-acetals. Further studies of this novel transformation and similar processes are currently underway in our laboratories.

Acknowledgment. We thank the Alexander von Humboldt Foundation (fellowship for S.V.), the Max-Planck-Society, the DFG (Priority Program Organocatalysis SPP1179), and the Fonds der Chemischen Industrie (Award to B.L.).

Supporting Information Available: Experimental procedures, compound characterization, and X-ray data for compound **3d**. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) Aho, J. E.; Pihko, P. M.; Rissa, T. K. *Chem. Rev.* **2005**, *105*, 4406.
(2) Carey, F. A. *Organic Chemistry*, 6th ed.; McGraw-Hill: 2006.
(3) (a) Felix, W.; Rimbach, G.; Wengenroth, H. *Arzneim.-Forsch.* **1969**, *19*, 1860. (b) Mavragani, C. P.; Moutsopoulos, H. M. *Clinic Rev. Allerg. Immunol.* **2007**, *32*, 287.
(4) (a) Seebach, D.; Sting, A. R.; Hoffmann, M. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2708. (b) Schmalz, H.-G.; Heβler, E.; Bats, J. W.; Dürner, G. *Tetrahedron Lett.* **1994**, *35*, 4543. (c) Rehnberg, N.; Sundin, A.; Magnusson, G. *J. Org. Chem.* **1990**, *55*, 5477. (d) Carreira, E. M.; Kvaerno, L. *Classics in Stereoselective Synthesis*; Wiley-VCH: 2009.
(5) (a) Matsutani, H.; Ichikawa, S.; Yaruva, J.; Kasumoto, T.; Hiyama, T. *J. Am. Chem. Soc.* **1997**, *119*, 4541. (b) Davies, S. G.; Correia, L. M. A. R. B. *Chem. Commun.* **1996**, 1803. (c) Spantulescu, M. D.; Boudreau, M. A.; Vederas, J. C. *Org. Lett.* **2009**, *11*, 645. (d) Uchiyama, M.; Oka, M.; Harai, S.; Ohta, A. *Tetrahedron Lett.* **2001**, *42*, 1931. (e) Rychnovsky, S. D.; Bax, B. M. *Tetrahedron Lett.* **2000**, *41*, 3593.
(6) (a) Fletcher, S. J.; Rayner, C. M. *Tetrahedron Lett.* **1999**, *40*, 7139. (b) Weatherhead, G. S.; Houser, J. H.; Ford, J. G.; Jamieson, J. Y.; Schrock, R. R.; Hoveyda, A. H. *Tetrahedron Lett.* **2000**, *41*, 9553. (c) Hoveyda, A. H.; Schrock, R. R. *Chem.—Eur. J.* **2001**, *7*, 945. (d) Burke, S. D.; Müller, N.; Beaudry, C. M. *Org. Lett.* **1999**, *1*, 1827. (e) Frauenrath, H.; Philipps, T. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 274. (f) Frauenrath, H.; Reim, S.; Wiesner, A. *Tetrahedron: Asymmetry* **1998**, *9*, 1103.
(7) (a) Nagano, H.; Katsuki, T. *Chem. Lett.* **2002**, *31*, 782. For an attempt at direct carbonyl acetalization, see: (b) Barbaro, P.; Bianchini, C.; Oberhauser, W.; Togni, A. *J. Mol. Catal. A* **1999**, *145*, 139.
(8) (a) Rowland, G. B.; Zhang, H.; Rowland, E. B.; Chennamadhavuni, S.; Wang, Y.; Antilla, J. C. *J. Am. Chem. Soc.* **2005**, *127*, 15696. (b) Liang, Y.; Rowland, E. B.; Rowland, G. B.; Perman, J. A.; Antilla, J. C. *Chem. Commun.* **2007**, 4477. (c) Li, G.; Fronczek, F. R.; Antilla, J. C. *J. Am. Chem. Soc.* **2008**, *130*, 12216. (d) Cheng, X.; Vellalath, S.; Goddard, R.; List, B. *J. Am. Chem. Soc.* **2008**, *130*, 15786. (e) Rueping, M.; Antonchick, A. P.; Sugiono, E.; Grenader, K. *Angew. Chem., Int. Ed.* **2009**, *48*, 908.
(9) (a) Terada, M. *Chem. Commun.* **2008**, 4097. (b) Akiyama, T. *Chem. Rev.* **2007**, *107*, 5744.
(10) (a) Reisman, S. E.; Doyle, A. G.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2008**, *130*, 7198. (b) Terada, M.; Tanaka, H.; Sorimachi, K. *J. Am. Chem. Soc.* **2009**, *131*, 3430. (c) Zhang, Q.-W.; Fan, C.-A.; Zhang, H.-J.; Tu, Y.-Q.; Zhao, Y.-M.; Gu, P.; Chen, Z.-M. *Angew. Chem., Int. Ed.* **2009**, *48*, 8572.
(11) Mayer, S.; List, B. *Angew. Chem., Int. Ed.* **2006**, *45*, 4193.
(12) Hoffmann, S.; Seayad, A. M.; List, B. *Angew. Chem., Int. Ed.* **2005**, *44*, 7424.
(13) Adair, G.; Mukherjee, S.; List, B. *Aldrichimica Acta* **2008**, *41*, 31.

JA102753D