Organocatalysis

DOI: 10.1002/anie.201004778

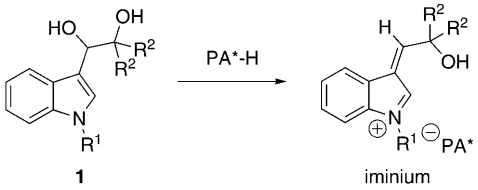
Chiral Brønsted Acid Catalyzed Pinacol Rearrangement**

*Tao Liang, Zhenjie Zhang, and Jon C. Antilla**

The Brønsted acid catalyzed conversion of cyclic or acyclic vicinal diols to aldehydes or ketones through dehydration and subsequent [1,2]-alkyl, [1,2]-aryl, or hydride shift is a truly venerable reaction known as the pinacol rearrangement.[1] Because of the likelihood of multiple carbocation formation during the reaction, the regioselectivity can vary, and widespread usage has suffered.[2] While strategies exist where a stable carbocation or predictable carbocation can mitigate regioselectivity issues, most applications have relied upon a more general variant termed the semipinacol rearrangement.[3] The semipinacol rearrangement, more than often, relies upon the presence of a more predictable carbocation position, and synthetic utility has thus been found.[4] For these reasons, predictable and stereoselective variants of the pinacol rearrangement are highly desired and interesting.

In light of recent and relatively wide spread use of chiral phosphoric acids as catalysts for asymmetric transformations,[5] it occurred to us that the pinacol rearrangement, widely known to be catalyzed by phosphoric acids,[6] could be controlled through a catalytic enantioselective process. During the course of our investigation into this reaction a report by Tu and co-workers detailed the catalytic enantioselective semipinacol rearrangement of 2-oxo allylic alcohols utilizing chiral phosphoric acids.[7] However, despite the elegance of this initial report, it was evident that strained cyclobutanes along with a relatively high catalyst loading (10 mol%) were required for this transformation. Therefore, we felt additional important challenges still remained in this area. We were further interested because, to the best of our knowledge, no example of a catalytic enantioselective pinacol rearrangement has been reported to date.[8]

We believed that the ability to control the regioselectivity of the rearrangement would be imperative and that a transformation of this type would be largely substrate dependent. We hypothesized that access to a desirable iminium intermediate could be realized through phosphoric acid mediated dehydration of an indolyl diol (**1**) (Scheme 1). This type of indolyl iminium was first reported by Rueping et al.[9a] for the Friedel–Crafts addition of indoles to β,γ-unsaturated α-keto esters. This intermediate has also been invoked by You et al.[9b] for a tandem double Friedel–Crafts reaction and by Gong et al.[9c] for the asymmetric alkylation of enamides. We believed that an indolyl diol like **1** would prove successful, especially when one considers the success of iminium chemistry utilizing chiral phosphoric acid catalysis.[5e–g,i–k]

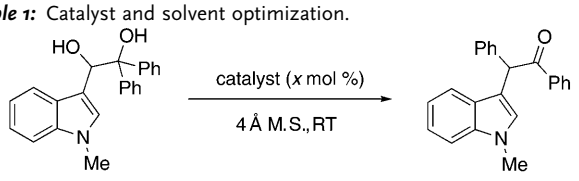


1 iminium

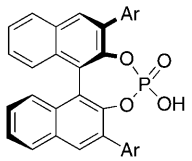
Scheme 1. Dehydration strategy for the chiral phosphoric acid catalyzed pinacol rearrangement.

In view of our previous success[10] in developing catalytic asymmetric reactions using chiral phosphoric acids, we began to investigate the pinacol rearrangement of indolyl diol **1a** in the presence of chiral phosphoric acid **3a** and 4 Å molecular sieves. To our delight, the reaction proceeded smoothly to afford α-indolyl ketone **2a** in 93% yield and 38% *ee* (Table 1,

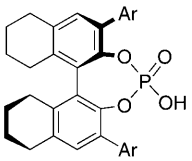
Table 1: Catalyst and solvent optimization.



1a **2a**



(*R*)-**3a**: Ar = 1-naphthyl
(*R*)-**3b**: Ar = 9-anthryl
(*R*)-**3c**: Ar = 2,4,6-(*i*Pr)$_3$C$_6$H$_2$



(*R*)-**4**: Ar = 1-naphthyl

Entry[a]	Catalyst (*x* mol%)	Solvent	*t* [h]	Yield [%][b]	*ee* [%][c]
1	(*R*)-**3a** (10)	1,2-DCE	48	93	38
2	(*R*)-**3b** (10)	1,2-DCE	48	63	33
3	(*R*)-**3c** (10)	toluene	4	93	70
4	(*R*)-**4** (10)	toluene	4	93	93
5	(*R*)-**4** (10)	benzene	4	93	94
6[d]	(*R*)-**4** (10)	benzene	4	91	91
7	(*R*)-**4** (5)	benzene	4	94	95
8	(*R*)-**4** (2.5)	benzene	4	94	96
9	(*R*)-**4** (1)	benzene	18	60	95

[a] Unless otherwise specified, reactions were conducted using 0.1 mmol **1a** (0.05 M solution). [b] Yield of isolated product. [c] Determined by HPLC analysis using a chiral column. [d] Reaction conducted at 0°C.

[*] T. Liang, Prof. Dr. J. C. Antilla
Department of Chemistry, University of South Florida
4202 E. Fowler Ave, Tampa FL 33620 (USA)
Fax: (+1) 813-974-1733
E-mail: jantilla@cas.usf.edu
Z. Zhang
Department of Chemistry X-Ray Facility, University of South Florida
Tampa, FL 33620 (USA)

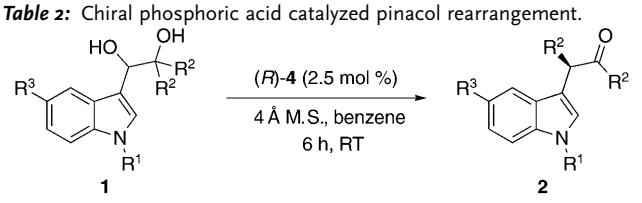
[**] We thank the National Institutes of Health (NIH GM-082935) and the National Science Foundation CAREER program (NSF-0847108) for financial support.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201004778.

entry 1). This preliminary result encouraged us to evaluate additional binol-based and H_8-binol-based chiral phosphoric acids as catalysts. The enantioselectivity increased to 70% with the use of catalyst **3c** in toluene (Table 1, entry 3). Improvement to 94% *ee* was achieved with catalyst **4**,[11] an H_8-binol phosphoric acid variant, in aromatic solvents (Table 1, entries 4 and 5). It should be noted that decreasing the temperature of the reaction caused the enantioselectivity to decrease (Table 1, entry 6). Interestingly, lowering the catalyst loading provided a positive effect, with respect to both yield and enantioselectivity (Table 1, entries 5 and 7–9); albeit with reduced rate when 1 mol% of catalyst was used.

With the optimal reaction conditions in hand, the substrate scope of the newly developed pinacol rearrangement was assessed (Table 2). To ensure reaction completion, 2.5 mol% of catalyst **4** was used. A lower catalyst loading would presumably be tolerated in individual cases. The reaction is tolerant towards the indole-protecting group, with regard to enantioselectivity as well as reaction efficiency. Methyl, benzyl, or allylic substitution of the 1-position of the indole resulted in high enantioselectivity (94–96% *ee*) for each rearrangement (Table 2, entries 1–3). The electronics of the aryl migrating group were next evaluated. Electron-withdrawing (Table 2, entries 4 and 5) and electron-donating substituents (Table 2, entries 6 and 7) at the *para* position of the phenyl ring provided a substrate that migrated efficiently to furnish a product with high enantioselectivity. Notably, the more sterically hindered 2-naphthyl-substituted diol (**2i**) provided the desired rearrangement product with high yield and enantioselectivity, although a longer reaction time was required (Table 2, entry 9). Investigation into the effect of substitution on the indole ring revealed the reaction to be highly versatile to both electron-withdrawing and electron-donating groups at the 5-position, providing products with high enantioselectivities (Table 2, entries 10–14).

Table 2: Chiral phosphoric acid catalyzed pinacol rearrangement.

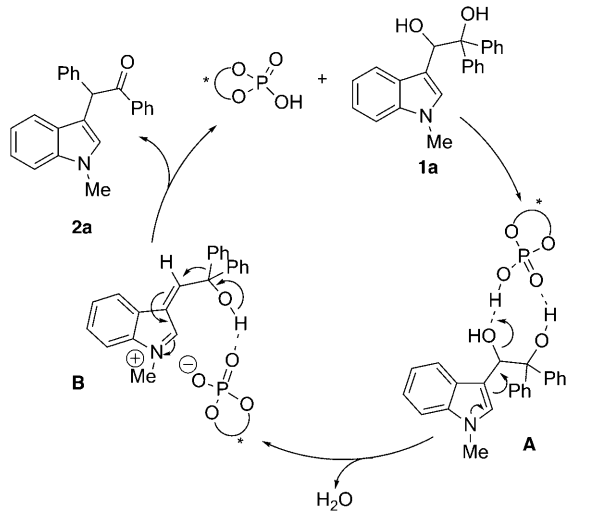


1 **2**

Entry[a]	**2**	Yield [%][b]	*ee* [%][c]
1	**2a**: R^1 = Me, R^2 = Ph, R^3 = H	94	96
2	**2b**: R^1 = Bn, R^2 = Ph, R^3 = H	84	95
3	**2c**: R^1 = Allyl, R^2 = Ph, R^3 = H	88	94
4	**2d**: R^1 = Me, R^2 = 4-FC_6H_4, R^3 = H	90	94
5	**2e**: R^1 = Me, R^2 = 4-ClC_6H_4, R^3 = H	99	93
6	**2f**: R^1 = Me, R^2 = 4-MeC_6H_4, R^3 = H	99	96
7	**2g**: R^1 = Me, R^2 = 4-$MeOC_6H_4$, R^3 = H	97	91
8	**2h**: R^1 = Me, R^2 = 3,5-$Me_2C_6H_3$, R^3 = H	94	93
9[d]	**2i**: R^1 = Me, R^2 = 2-naphthyl, R^3 = H	93	93
10	**2j**: R^1 = Me, R^2 = Ph, R^3 = F	95	96
11	**2k**: R^1 = Me, R^2 = Ph, R^3 = Cl	86	94
12	**2l**: R^1 = Me, R^2 = Ph, R^3 = Br	86	96[e]
13	**2m**: R^1 = Me, R^2 = Ph, R^3 = Me	95	94
14	**2n**: R^1 = Me, R^2 = Ph, R^3 = MeO	83	96

[a] Reaction Conditions: 0.1 mmol **1**, 0.0025 mmol (*R*)-**4**, and 2.0 mL benzene. [b] Isolated Yield. [c] Determined by chiral HPLC analysis. [d] The reaction was complete in 14 h. [e] The absolute configuration was determined to be (*R*)-**2l** by single-crystal X-ray diffraction analysis;[12] see the Supporting Information.

Scheme 2 illustrates a plausible mechanistic pathway detailing the chiral phosphoric acid induced dehydration of indolyl alcohol **1a** followed by subsequent pinacol rearrangement. Intermediate **A** results from hydrogen-bonding interactions of the bifunctional chiral phosphoric acid catalyst with diol **1a.** Dehydration of intermediate **A** would presumably give rise to the iminium intermediate **B**, which possesses potential two-point binding with the chiral phosphate through hydrogen-bonding and electrostatic interactions. Subsequent rearrangement via a [1,2]-aryl shift would furnish product **2a**, with regeneration of the chiral phosphoric acid catalyst.



Scheme 2. Proposed mechanism for the chiral phosphoric acid catalyzed asymmetric pinacol rearrangement.

In summary, we report the first catalytic enantioselective pinacol rearrangement. Chiral phosphoric acids are utilized as highly efficient Brønsted acids in transforming indolyl diols to chiral α-indolyl ketones with high yield and enantioselectivity. Further studies to expand the substrate scope,[13] with the aim of developing further efficient enantioselective transformations, are currently under investigation in our laboratory and will be reported in due course.

Experimental Section

General procedure for chiral phosphoric acid catalyzed pinacol rearrangement: 2-(1-methyl-1*H*-indol-3-yl)-1,1-diphenylethane-1,2-diol (**1a**) (0.10 mmol, 34.3 mg), catalyst **4** (0.0025 mmol, 1.5 mg), and benzene (2.0 mL) were added to a flame-dried reaction tube charged with 30 mg 4 Å M.S. (powder). The resulting solution was stirred at room temperature for 6 h. The crude product was purified

directly by flash column chromatography on silica gel (hexanes/EtOAc = 10:1 to 5:1) to afford product **2a** (30.6 mg, 94% yield, 96% *ee*). Enantiomeric excess was determined by HPLC analysis using a chiral column.

Received: August 1, 2010
Revised: September 10, 2010
Published online: November 12, 2010

Keywords: asymmetric catalysis · indolyl diols · organocatalysis · phosphoric acids · pinacol rearrangement

[1] R. Fittig, *Justus Liebigs Ann. Chem.* **1860**, *114*, 54 – 63.
[2] L. Kurti, B Czakó in *Strategic Applications of Named Reactions in Organic Synthesis*, Academic Press/Elsevier, San Diego, **2005**, pp. 350 – 351.
[3] a) M. Tiffeneau, J. Levey, *C. R. Hebd. Seances Acad. Sci.* **1923**, *176*, 312 – 314. For a review, see b) D. J. Coveney in *Comprehensive Organic Synthesis*, *Vol. 3* (Eds.: B. M. Trost, I. Fleming), Pergamon, Oxford, **1991**, pp. 777 – 801. For selected publications, see c) T. Shionhara, K. Suzuki, *Synthesis* **2003**, 141 – 146; d) C.-A. Fan, B.-M. Wang, Y.-Q. Tu, Z.-L. Song, *Angew. Chem.* **2001**, *113*, 3995 – 3998; *Angew. Chem. Int. Ed.* **2001**, *40*, 3877 – 3880; e) Y. Sugihara, S. Iimura, J. Nakayama, *Chem. Commun.* **2002**, 134 – 135. For examples of selected stereocontrolled semipinacol rearrangements, see f) C. M. Marson, A. J. Walker, J. Pickering, A. D. Hobson, *J. Org. Chem.* **1993**, *58*, 5944 – 5951; g) X.-D. Hu, C.-A. Fan, F.-M. Zhang, Y.-Q. Tu, *Angew. Chem.* **2004**, *116*, 1734 – 1737; *Angew. Chem. Int. Ed.* **2004**, *43*, 1702 – 1705; h) T. Shinohara, K. Suzuki, *Tetrahedron Lett.* **2002**, *43*, 6937 – 6940; i) S. Matsubara, H. Yamamoto, K. Oshima, *Angew. Chem.* **2002**, *114*, 2961 – 2964; *Angew. Chem. Int. Ed.* **2002**, *41*, 2837 – 2840; j) M. D. B. Fenster, B. O. Patrick, G. R. Dake, *Org. Lett.* **2001**, *3*, 2109 – 2112.
[4] a) M. Seki, T. Sakamoto, H. Suemune, K. Kanematsu, *J. Chem. Soc. Perkin Trans. 1* **1997**, 1707 – 1714; b) G. R. Pettit, J. W. Lippert III, D. L. Herald, *J. Org. Chem.* **2000**, *65*, 7438 – 7444; c) J. A. Wendt, P. J. Gauvreau, R. D. Bach, *J. Am. Chem. Soc.* **1994**, *116*, 9921 – 9926; d) K. Suzuki, K. Tomooka, E. Katayama, T. Matsumoto, G. Tsuchihashi, *J. Am. Chem. Soc.* **1986**, *108*, 5221 – 5229.
[5] For reviews on chiral phosphoric acids, see: a) T. Akiyama, *Chem. Rev.* **2007**, *107*, 5744 – 5758; b) M. Terada, *Chem. Commun.* **2008**, 4097 – 4112. For recent publications, see: c) J. Itoh, K. Fuchibe, T. Akiyama, *Angew. Chem.* **2008**, *120*, 4080 – 4082; *Angew. Chem. Int. Ed.* **2008**, *47*, 4016 – 4018; d) M. Terada, K. Soga, N. Momiyama, *Angew. Chem.* **2008**, *120*, 4190 – 4193; *Angew. Chem. Int. Ed.* **2008**, *47*, 4122 – 4125; e) X. Cheng, R. Goddard, G. Buth, B. List, *Angew. Chem.* **2008**, *120*, 5157 – 5159; *Angew. Chem. Int. Ed.* **2008**, *47*, 5079 – 5081; f) W.-H. Hu, X.-F. Xu, J. Zhou, W.- J. Liu, H.-X. Huang, J. Hu, L.-P. Yang, L.-Z. Gong, *J. Am. Chem. Soc.* **2008**, *130*, 7782 – 7783; g) G. Li, F. R. Fronczek, J. C. Antilla, *J. Am. Chem. Soc.* **2008**, *130*, 12216 – 12217; h) K. Sorimachi, M. Terada, *J. Am. Chem. Soc.* **2008**, *130*, 14452 – 14453; i) M. Rueping, A. P. Antonchick, *Angew. Chem.* **2008**, *120*, 10244 – 10247; *Angew. Chem. Int. Ed.* **2008**, *47*, 10090 – 10093; j) M. Rueping, A. P. Antonchick, E. Sugiono, K. Grenader, *Angew. Chem.* **2009**, *121*, 925 – 927; *Angew. Chem. Int. Ed.* **2009**, *48*, 908 – 910; k) H. Liu, G. Dagousset, G. Masson, P. Retailleau, J.-P. Zhu, *J. Am. Chem. Soc.* **2009**, *131*, 4598 – 4599; l) M. Terada, H. Tanaka, K. Sorimachi, *J. Am. Chem. Soc.* **2009**, *131*, 3430 – 3431; m) M. Terada, Y. Toda, *J. Am. Chem. Soc.* **2009**, *131*, 6354 – 6355; n) N. Momiyama, H. Tabuse, M. Terada, *J. Am. Chem. Soc.* **2009**, *131*, 12882 – 12883; o) Q. Cai, Z.-A. Zhao, S.-L. You, *Angew. Chem.* **2009**, *121*, 7564 – 7567; *Angew. Chem. Int. Ed.* **2009**, *48*, 7428 – 7431; p) S. Müller, B. List, *Angew. Chem.* **2009**, *121*, 10160 – 10163; *Angew. Chem. Int. Ed.* **2009**, *48*, 9975 – 9978; q) Z.-X. Han, H. Xiao, X.-H. Chen, L.-Z. Gong, *J. Am. Chem. Soc.* **2009**, *131*, 9182 – 9183; r) N. Li, X.-H. Chen, J. Song, S.-W. Luo, W. Fan, L.-Z. Gong, *J. Am. Chem. Soc.* **2009**, *131*, 15301 – 15310; s) X.-H. Chen, Q. Wei, S.-W. Luo, H. Xiao, L.-Z. Gong, *J. Am. Chem. Soc.* **2009**, *131*, 13819 – 13825; t) Q. Gu, Z.-Q. Rong, C. Zheng, S.- L. You, *J. Am. Chem. Soc.* **2010**, *132*, 4056 – 4057; u) V. N. Wakchaure, B. List, *Angew. Chem.* **2010**, *122*, 4230 – 4233; *Angew. Chem. Int. Ed.* **2010**, *49*, 4136 – 4139.
[6] B. Rickborn in *Comprehensive Organic Synthesis Vol. 3* (Eds.: B. M. Trost, I. Fleming), Pergamon, Oxford, **1991**, pp. 731 – 732.
[7] Q.-W. Zhang, C.-A. Fan, H.-J. Zhang, Y.-Q. Tu, Y.-M. Zhao, P. Gu, Z.-M. Chen, *Angew. Chem.* **2009**, *121*, 8724 – 8726; *Angew. Chem. Int. Ed.* **2009**, *48*, 8572 – 8574.
[8] For another account of a Brønsted base-catalyzed asymmetric semipinacol rearrangement, see E. Zhang, C.-A. Fan, Y.-Q. Tu, F.-M. Zhang, L.-Y. Song, *J. Am. Chem. Soc.* **2009**, *131*, 14626.
[9] a) M. Rueping, B. J. Nachtsheim, S. A. Moreth, M. Bolte, *Angew. Chem.* **2008**, *120*, 603 – 606; *Angew. Chem. Int. Ed.* **2008**, *47*, 593 – 596; b) F.-L. Sun, M. Zeng, Q. Gu, S.-L. You, *Chem. Eur. J.* **2009**, *15*, 8709 – 8712; c) Q.-X. Guo, Y.-G. Peng, J.-W. Zhang, L. Song, Z. Feng, L.-Z. Gong, *Org. Lett.* **2009**, *11*, 4620 – 4623.
[10] a) G. B. Rowland, H. Zhang, E. B. Rowland, S. Chennamadhavuni, Y. Wang, J. C. Antilla, *J. Am. Chem. Soc.* **2005**, *127*, 15696 – 15697; b) G. B. Rowland, E. B. Rowland, Y. Liang, J. A. Perman, J. C. Antilla, *Org. Lett.* **2007**, *9*, 2609 – 2611; c) G. Li, G. B. Rowland, E. B. Rowland, J. C. Antilla, *Org. Lett.* **2007**, *9*, 4065 – 4068; d) G. Li, Y. Liang, J. C. Antilla, *J. Am. Chem. Soc.* **2007**, *129*, 5830 – 5831.
[11] The catalyts used in this study were washed with HCl before usage to ensure pure acid, with no phosphate salt contamination (see the Supporting Information). For reports describing recent observations on chiral phosphate salt catalysis, see a) M. Hatano, K. Moriyama, T. Maki, K. Ishihara, *Angew. Chem.* **2010**, *122*, 3911 – 3914; *Angew. Chem. Int. Ed.* **2010**, *49*, 3823 – 3826; b) M. Klussmann, L. Ratjen, S. Hoffmann, V. Wakchaure, R. Goddard, B. List, *Synlett* **2010**, 2189 – 2192.
[12] CCDC 792000 ((*R*)-**21**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
[13] In preliminary study using non-aryl substrates, lower selectivities were observed. For example, benzyl- and allyl-substituted precursors provided good reactivity but only a 10% *ee* and 27% *ee* for each respective rearrangement product.

