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Catalytic Asymmetric Prins Cyclizations: Cation Generation and Trapping with (BINAP)Pt Dications

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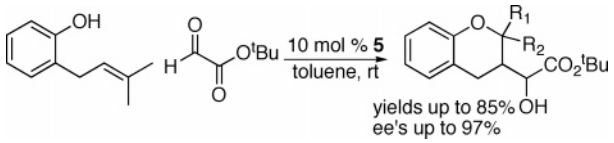
ABSTRACT

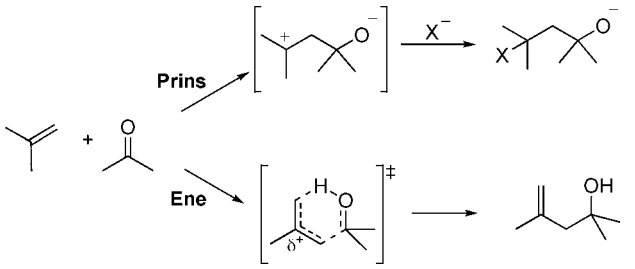


(*R*)-[(tolBINAP)Pt(NC$_6$F$_5$)$_2$][SbF$_6$]$_2$ (5) catalyzes the highly enantioselective Prins reaction between 2-allylphenols and glyoxylate esters. Other Lewis acid catalysts favor glyoxylate-ene products.

The nucleophilic addition of an alkene to an aldehyde to generate a cation, which subsequently rearranges or is trapped, is referred to as a Prins reaction.[1] When used in an intramolecular mode, Prins cyclizations are capable of generating a wide variety of heterocycles, usually with net addition of an external nucleophile to the resulting carbocation.[2,3] Other types of Prins reactions include pinacol-terminated[1c] and direct trapping by a pendant nucleophile;[4] our contribution is of this latter variety.

Mechanistically related to the Prins reaction is the carbonyl-ene reaction,[5] wherein a proton from the nucleophilic alkene is transferred to the developing charge on the carbonyl oxygen, thus generating a homoallylic alcohol (Scheme 1).

Scheme 1. Prins vs Carbonyl-Ene Reactions



Both experimental[6] and computational[7] studies have suggested that under the influence of Lewis acid induced

(1) For reviews, see: (a) Adams, D. R.; Bhatnagar, S. P. *Synthesis* **1977**, 661−672. (b) Sinder, B. In *The Prins Reaction and Carbonyl Ene Reactions*; Trost, B. M., Fleming, I., Heathcock, C. H., Ed.; Pergamon Press: New York, 1991; Vol. 2, pp 527−561. (c) Overman, L. E.; Pennington, L. D. *J. Org. Chem.* **2003**, *68*, 7143−7157.

(2) For some recent examples, see: (a) Delgard, J. E.; Rychnovsky, S. D. *J. Am. Chem. Soc.* **2004**, *126*, 15662−15663. (b) Jasti, R.; Vitale, J.; Rychnovsky, S. D. *J. Am. Chem. Soc.* **2004**, *126*, 9904−9905. (c) Miranda, P. O.; Díaz, D. D.; Padrón, J. I.; Ramíez, M. A.; Martín, V. S. *J. Org. Chem.* **2005**, *70*, 57−62. (d) Miranda, P. O.; Díaz, D. D.; Padrón, J. I.; Bermejo, J.; Martin, V. S. *Org. Lett.* **2003**, *5*, 1979−1982. (e) Yang, X.; Mague, J. T.; Li, C. *J. Org. Chem.* **2001**, *66*, 739−747. (f) Yadav, J. S.; Reddy, M. S.; Prasad, A. R. *Tetrahedron Lett.* **2005**, *46*, 2133-2136. (g) Yu, C.; Yoon, S.; Hong, Y.; Kim, J. *Chem. Commun.* **2004**, 1840−1841. (h) Chan, K. P.; Loh, T. P. *Tetrahedron Lett.* **2004**, *45*, 8387−8390. (i) Hart, D. J.; Bennett, C. E. *Org. Lett.* **2003**, *5*, 1499−1502.

(3) For a recent mechanistic study that includes numerous citations, see: Barry, C. S.; Bushby, N.; Harding, J. R.; Hughes, R. A.; Parker, G. D.; Roe, R.; Willis, C. L. *Chem. Commun.* **2005**, 3727−3729.

(4) Mikami, K.; Shimizu, M. *Tetrahedron* **1996**, *52*, 7287−7296.

(5) For reviews on the ene reaction, see: (a) Mikami, K.; Nakai, T.; In *Catalytic Asymmetric Synthesis*, 2nd ed.; Ojima, I., Ed.; Wiley-VCH: New York, 2000; pp 543−568. (b) Dias, L. C. *Curr. Org. Chem.* **2000**, *4*, 305−342. (c) Santelli, M.; Pons, M. *Lewis Acids and Selectivity in Organic Synthesis*; CRC Press: Boca Raton, FL, 1995.

(6) Mikami, K.; Wakabayashi, H.; Nakai, T. *J. Org. Chem.* **1991**, *56*, 4337−4339. (b) Song, Z.; Beak, P. *J. Am. Chem. Soc.* **1990**, *112*, 8126−8134. (c) Snider, B. B.; Ron, E. *J. Am. Chem. Soc.* **1985**, *107*, 8160−8164. (d) Stephenson, L. M.; Orfanopoulos, M. *J. Org. Chem.* **1981**, *46*, 2200−2201.

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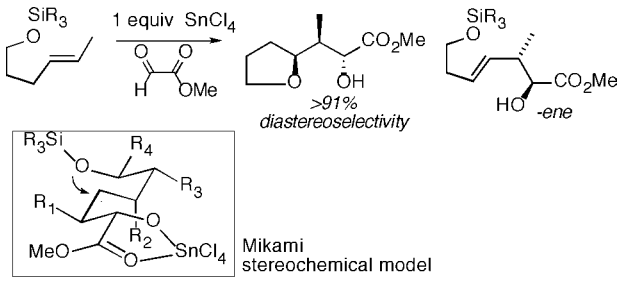
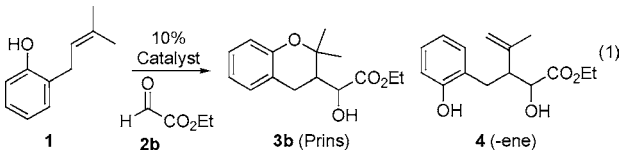
polarization the hetero-ene reaction proceeds through a discrete cationic intermediate prior to proton transfer. Several reports have shown that with especially strong Lewis acids an intramolecular trapping is possible (a Prins reaction;[4,6a,8] e.g., Scheme 2). While many excellent catalysts have been

Scheme 2. Mikami's Glyoxylate-Initiated Prins Cyclization



developed for enantioselective ene-reactions (and especially for glyoxylate-ene reactions),[5] a chiral variant of the Prins cyclization is unknown. We report herein results from our search for such a catalyst.

We began our investigation with the Lewis acid-catalyzed reaction of 2-prenylphenol (**1**) and ethyl glyoxylate (**2b**) (eq 1), reasoning that cation generation at the tertiary center would lead to subsequent trapping by phenol and chroman ring formation.



A variety of Lewis acids known to be excellent catalysts for the glyoxylate-ene reaction were screened (Table 1). In most cases, the major compound was the glyoxylate-ene product **4**, indicating that with these catalysts, proton transfer is either too fast for efficient trapping by the phenol or that the overall process occurs without the intermediacy of a putative electrophilic alkenyl carbon. Interestingly, the Cu(II)^{t}BuBOX-catalyzed glyoxylate-ene reaction, which computationaly proceeds via a cationic intermediate,[7c] provides the ene product almost exclusively. The highly enantioselective (BINOL)TiX_2 catalysts were completely unreactive with these substrates. In contrast to each of these established catalysts, P_2Pt^{2+} catalysts were uniquely able to generate the chroman (**3b**) as the sole product (Table 1).[9]

An extensive examination of readily available chiral diphosphines showed that tolBINAP was best at providing **3b** with good enantioselectivities.[10] During the course of optimizing it was noted that the enantioselectivity was solvent dependent, and increased with decreasing polarity (Table 2), perhaps suggesting a tighter transition state structure in the less polar solvents; donor solvents completely inhibit catalysis. Counter-intuitive, however, was the shift from the Prins to the ene product when the very polar nitromethane was used. Since P_2PtCl_2's are insoluble in toluene, the Pt dication was preferably isolated as its bis(pentafluorobenzonitrile)[11] adduct (**5**), rather than generated in situ with $AgSbF_6$. When **5** was used in the reaction of **1** with **2b**, **3b** was generated in 85% yield as a 1:1.2 mixture of diastereomers (78 and 48% ee, respectively).[12] Stereochemical analysis indicated that the carbinol stereocenter was under

Table 1. Ratio of Prins/Ene Products as a Function of Catalyst[a]

catalyst	**3b/4**[b]
(BINOL)$TiCl_2$	
$Cu(OTf)_2$	62:38
$Sc(OTf)_3$	15:85
(tBuBox)$Cu(SbF_6)_2$	2:98[c]
(BIPHEP)$Pt(SbF_6)_2$	83:17
(BINAP)$Pt(SbF_6)_2$	100:0

[a] Reaction conditions: 0.4 mmol of **1**, 1.2 mmol of **2b**, 10 mol % of catalyst, 3 mL of CH_2Cl_2, 25 °C. [b] Determined by GC. [c] 81% ee.

Table 2. Solvent Effects on Reaction Selectivities[a]

solvent	ϵ[b]	**3/4**[c]	dr	% ee of $\mathbf{3_1b}$[c,d]
CH_3NO_2	38.6	33:67	2:1	0
CH_2ClCH_2Cl	10.4	100:0	1.9:1	22
CH_2Cl_2	8.9	100:0	1.9:1	30
PhCl	5.62	100:0	1.2:1	58
PhF	5.42	100:0	1:1	54
1:1 CH_2Cl_2/$PhCH_3$	5.64	100:0	1.2:1	56
1:2 CH_2Cl_2/$PhCH_3$	4.55	100:0	1.1:1	57
1:3 CH_2Cl_2/$PhCH_3$	4.01	100:0	1:1	66
1:7.5 CH_2Cl_2/$PhCH_3$	3.88	100:0	1:1	70

[a] Reaction conditions: 0.4 mmol of **1**, 1.2 mmol of **2b**, 10 mol % of (*R*)-(BINAP)$PtCl_2$, 20% $AgSbF_6$, 3 mL of solvent, 25 °C. [b] The dielectric constant for mixed solvent systems represents weighted averages of the individual components. [c] Determined by GC. [d] One (major) of two observed diastereomers (vida infra).

(7) Yamanaka, M.; Mikami, K. *Helv. Chim. Acta* **2002**, *85*, 4262−4271. (b) Mikami, K.; Ohmura, H.; Yamanaka, M. *J. Org. Chem.* **2003**, *68*, 1081−1085. (c) Morao, I.; McNamara, J. P.; Hillier, I. H. *J. Am. Chem. Soc.* **2003**, *125*, 628−629.

(8) The reactivity described in the following reference was described as an ene reaction, but it could alternatively be interpreted to result from the interception of a cationic intermediate: Ziegler, F. E.; Wang, T. F. *J. Am. Chem. Soc.* **1984**, *106*, 718−721.

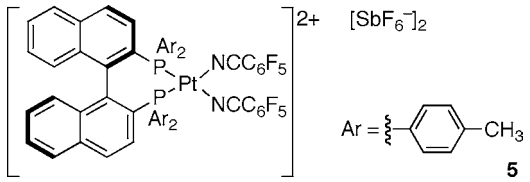
(9) Another mechanistic possibilty, the generation of **4** and subsequent conversion to **3,** was ruled out because isolated **4** does not convert to **3** under the reaction conditions; instead, a second molecule of glyoxylate adds in an ene fashion.

(10) Chiral diphosphines that were screened include: CHIRAPHOS, OMe-BIPHEPs, xyly-BINAP, DUPHOS, SEGPHOS, in addition to JOSIPHOS, WALLYPHOS, and MANYPHOS derivatives and others.

(11) Becker, J. J.; Van Orden, L. J.; White, P. S.; Gagné, M. R. *Org. Lett.* **2002**, *4*, 727−730.

(12) Relative stereochemistry was determined by comparing predicted NOEs from calculated lowest energy rotamers and experimental data (see the Supporting Information). Absolute stereochemistry at the hydroxyl carbon was determined by ^{1}H NMR analysis of the Mosher esters; see: Seco, J. M.; Quiñoá, E.; Riguera, R. *Chem. Rev.* **2004**, *104*, 17−117.

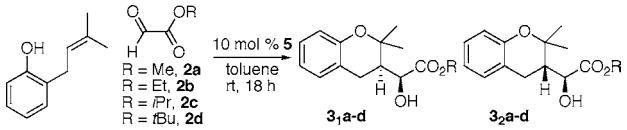
catalyst control; however, the facial bias of the nucleophilic alkene was not. Good facial control in additions to glyoxylate esters is well established for chiral P_2Pt^{2+} catalysts.[13]



5

To further improve the selectivity, we shifted our attention to the effect of the glyoxylate ester's size on enantioselectivity. Results (Table 3) showed that one product's ee was much more sensitive to the size of the glyoxylate ester (24 → 94%) than the other (74 → 96%), with **2d** giving the best selectivites for both diastereomers (96 and 94% ee, respectively). Despite the sensitivity of the aldehyde's facial bias, however, the diastereofacial selectivity of the nucleophilic alkene was largely unaffected by the glyoxylate ester substitutent; efforts to improve the reaction dr's have thus far been unsuccessful.

Table 3. Effect of Glyoxylate Ester Size on Enantioselectivity[a]



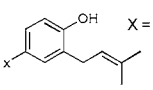
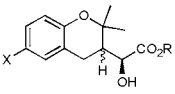
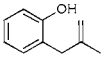
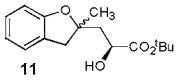
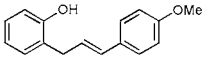
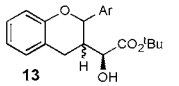
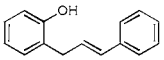
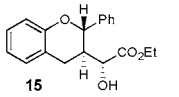
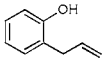
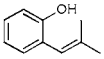
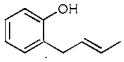
glyoxylate	**3/4**[b]	dr (**3₁/3₂**)	% ee of **3**
2a	100:0	1:1.5[c]	74:24[b]
2b	100:0	1:1.2[b]	78:48[d]
2c	100:0	1:1[b]	82:86[d]
2d	100:0	1:1[b]	96:94[d]

[a] Reaction conditions: 0.4 mmol of **1**, 1.2 mmol of **2b**, 10 mol % of **5**, 3 mL of toluene, 25 °C. [b] Determined by GC. [c] Determined by ^{1}H NMR. [d] Determined by SFC.

The optimum catalytic system was then applied to several classes of substrates (Table 4). Results showed that several phenols were capable reactants and provided the Prins product cleanly and with good to excellent ee's. The exception to this was the **2d**/**6** combination, which gave numerous unidentified products; **2b**/**6**, however, was well behaved and gave products in the expected ee range.

A 1,1-disubstituted olefin was also tested (entry 5), and although the expected benzofuran Prins product was obtained, the yields were diminished because of competing ene chemistry. Additionally, *p*-OMe styryl groups are competent nucleophiles providing the aryl substituted chroman in good yield and ee (entry 6).

Table 4. Prins Cyclizations of 2-Allylphenols with Glyoxylate Esters

entry	alkene	glyoxylate	product	yield[a]	%*ee*[b]
1		X = H (**1**) **2d**	 **3d**	76% (*1:1*)	96:94
2		X = OMe (**6**) **2d**	**7d**	–[c]	92:90
3		**2b**	**7b**	60% (*1:1*)	76:48
4		X = Cl (**8**) **2d**	**9d**	72% (*1.9:1*)	92:88
5	 **10**	**2d**	 **11**	42% (*1.2:1*)	53:88
6	 **12**	**2d**	 **13**	81% (*1:1*)	92:97
7[d]	 **14**	**2b**	 **15**	84% (*7.5:1*)	68:nd
8		**2b**	---	0%	---
9		**2b**	---	0%	---
10		**2b**	---	0%	---

[a] Isolated. [b] Enantioselectivities for the two diastereomers (see the Supporting Information). [c] This substrate yielded only traces of product with **2d** but reacted cleanly with **2b**. [d] With 0.05% added HOTf.

The unsubstituted 2-cinnamyl phenol (**14**) (entry 7), however, was unreactive under the standard conditions, thus bracketing the nucleophilicity necessary for addition.[14] The insufficient nucleophilicity of the cinnamyl case could be compensated for by the addition of small amounts of Brønsted acid co-catalyst (0.05% HOTf). Although the acid sensitivity of the *tert*-butyl ester precluded the use of **2d**, a successful and moderately diastereoselective (7.5:1) Prins reaction was achieved with **14** and **2b**.[15] We hypothesize that double activation[16] of the glyoxylate ester (H^+ and Pt^{2+}) lowers the threshold nucleophilicity required for addition.[17] Allyl, crotyl, and styrene nucelophiles were not competent (entries 8−10), even with added Brønsted acid, confirming the notion of a minimum alkene nucleophilicity for accessing cationic intermediates.[14]

(13) (a) Ghosh, A. K.; Matsuda, M. *Org. Lett.* **1999**, *1*, 2157−2159. (b) Becker, J. J.; White, P. S.; Gagné, M. R. *J. Am. Chem. Soc.* **2001**, *123*, 9478−9479. (c) Koh, J. H.; Larsen, A. O.; Gagné, M. R. *Org. Lett.* **2001**, *3*, 1233−1236. (d) Pignat, K.; Vallotto, J.; Pinna, F.; Strukul, G. *Organometallics* **2000**, *19*, 5160−5167. (e) Hao, J.; Hatano, M.; Mikami, K. *Org. Lett.* **2000**, *2*, 4059−4062. (f) Oi, S.; Tereda, E.; Ohuchi, K.; Kato, T.; Tachibana, Y.; Inoue, T. *J. Org. Chem.* **1999**, *64*, 8660−8662. (g) Oi, S.; Kashiwaga, K.; Inoue, Y. *Tetrahedron Lett.* **1998**, *39*, 6253−6256. (h) Doherty, S.; Goodrich, P.; Hardacre, C.; Luo, H.; Nieuwenhuyzen, M.; Rath, R. K. *Organometallics* **2005**, *24*, 5945−5955.

(14) Mayr, H.; Kempf, B.; Ofial, A. R. *Acc. Chem. Res.* **2003**, *36*, 66−77.

(15) The facial selectivity at the aldehyde is somehow reversed in this case, which provides **15** with the opposite absolute configuration at the carbinol center (see ref 12).

(16) For examples of double activation in carbonyl addition reactions, see: (a) Aspinall, H. C.; Bissett, J. S.; Greeves, N.; Levin, D. *Tetrahedron Lett.* **2002**, *43*, 319−321. (b) Vaugeois, J.; Simard, M.; Wuest, J. D. *Coord. Chem. Rev.* **1995**, *145*, 55−73. (c) Wuest, J. D. *Acc. Chem. Res.* **1999**, *32*, 81−89. (d) Gravel, M.; Lachance, H.; Lu, X.; Hall, D. G. *Synthesis* **2004**, 1290−1302.

The observation of good enantioselectivity yet poor diastereoselectvity in these reactions is difficult to rationalize. From the data, it appears that a bulky glyoxylate −OR group works with the chiral diphosphine to create an environment with a good carbonyl facial bias, however, this arrangement communicates little diastereofacial selectivity onto the prochiral alkene nucleophiles. Efforts to obtain a better understanding of the competing transition states and thus improve the diastereoselectivities are in progress.

Acknowledgment. We gratefully thank the NIGMS (GM-60578) for financial support.

Supporting Information Available: Experimental procedures, characterization data, and relative stereochemistry determinations. This material is available free of charge via the Internet at http://pubs.acs.org.

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(17) The observation of moderate enantioselectivity precludes the possibility of pure Brønsted catalysis. We envision a doubly activated glyoxylate similar to