ORGANIC LETTERS

2001
Vol. 3, No. 8
1233−1236

Asymmetric Pt(II)-Catalyzed Ene Reactions: Counterion-Dependent Additive and Diphosphine Electronic Effects[1]

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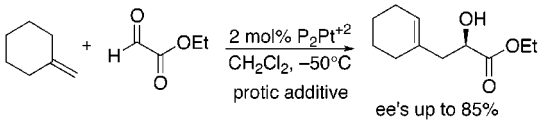
Received February 12, 2001

ABSTRACT



Catalysis of the glyoxylate–ene reaction by dicationic P_2Pt(II) complexes is subject to anion-dependent additive effects. For [((*S*)-MeOBiphep)-Pt](OTf)$_2$ catalysts, acidic phenols such as 3-CF_3-C_6H_3OH or C_6F_5OH provide substantial rate increases but do not affect the more active SbF_6-based catalysts. Enantioselectivity and reactivity also increased with diphosphine basicity, with 4-*t*-Bu-substituted MeOBiphep ligands yielding the highest enantioselectivities.

In comparison to Cu(II)-based Lewis acid catalysts,[2] much less is known about the utility of other late transition metal Lewis acid catalysts for asymmetric synthesis. The glyoxylate−ene reaction is one example in which Cu(II)-based Lewis acids define the state of the art.[3] When compared to these and BINOL-Ti-type catalysts,[4] late metal analogues are significantly less developed, though several enantioselective Pd/Pt[5] catalysts have emerged for other Lewis acid-catalyzed reactions (e.g., Diels−Alder).

Recently, Mikami demonstrated that dicationic (BINAP)-Pd(CH_3CN)$_2$−(SbF_6)$_2$ catalysts were capable of catalyzing (10 mol %) the glyoxylate−ene reaction at elevated temperatures (60 °C) with good enantioselectivities (up to 88%).[6,7] This paper prompted us to report our own work with chiral dicationic Pt(II) Lewis acid catalysts for the glyoxylate−ene reaction. This transformation provides a convenient and well-behaved platform for addressing fundamental issues related to ion-pairing and stereoelectronic effects in the reactivity of chiral P_2Pt^{2+} fragments.

For the studies discussed herein, we examined catalysts derived from the modular MeOBiphep ligands developed by Schmid and co-workers,[8] which in contrast to BINAP-based diphosphines can be readily modified at the P-aryl position

(1) We dedicate this paper to Prof. David A. Evans of Harvard University, on the occasion of his 60th birthday.

(2) For general Cu(II) Lewis acid references, see: (a) Johnson, J. S.; Evans, D. A. *Acc. Chem. Res.* **2000**, *33*, 325−335. (b) Jørgensen, K. A.; Johannsen, M.; Yao, S.; Audrain, H.; Thorhauge, J. *Acc. Chem. Res.* **1999**, *32*, 605−613. (c) Gothelf, K. V.; Jørgensen, K. A. *Chem. Commun.* **2000**, 1449−1458. (d) Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3558−3588.

(3) Evans, D. A.; Trigay, S. W.; Burgey, C. S.; Paras, N. A.; Vojkovsky, T. *J. Am. Chem. Soc.* **2000**, *122*, 7936−7943.

(4) (a) Dias, L. C. *Curr. Org. Chem.* **2000**, *4*, 305−342. (b) Mikami, K.; Shimizu, M. *Chem. Rev.* **1992**, *92*, 1021−1050.

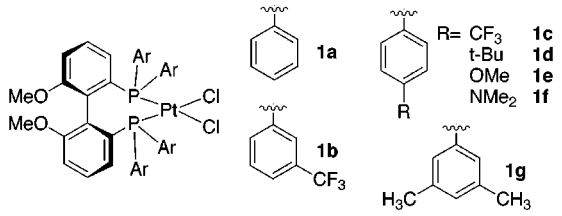
(5) See, for example: (a) Pignat, K.; Vallotto, J.; Pinna, F.; Strukul, G. *Organometallics* **2000**, *19*, 5160−5167. (b) Ghosh, A. K.; Matsuda, H. *Org. Lett.* **1999**, *1*, 2157−2159. (c) Oi, S.; Terada, E.; Ohuchi, K.; Kato, T.; Tachibana, Y.; Inoue, Y. *J. Org. Chem.* **1999**, *64*, 8660−8667. (d) Blacker, A. J.; Clarke, M. L.; Loft, M. S.; Mahon, M. F.; Williams, J. M. J. *Organometallics* **1999**, *18*, 2867−2873. (e) Hori, K.; Kodama, H.; Ohta, T.; Furukawa, I. *J. Org. Chem.* **1999**, *64*, 5017−5023. (f) Fujimura, O. *J. Am. Chem. Soc.* **1998**, *120*, 10032−10039. (g) Sodeoka, M.; Shibasaki, M. *Pure Appl. Chem.* **1998**, *70*, 411−414. (h) Kanemasa, S.; Kanai, T. *J. Am. Chem. Soc.* **2000**, *122*, 10710−10711. (i) Hattori, T.; Suzuki, Y.; Uesugi, O.; Oi, S.; Miyano, S. *Chem. Commun.* **2000**, 73−74.

(6) Hao, J.; Hatano, M.; Mikami, K. *Org. Lett.* **2000**, *2*, 4059−4062.

(7) For a Pd catalyzed asymmetric α-imino ester−ene reaction, see: Drury, W. J., III; Ferraris, D.; Cox, C.; Young, B.; Lectka, T. *J. Am. Chem. Soc.* **1998**, *120*, 11006−11007.

10.1021/ol015702n CCC: $20.00 © 2001 American Chemical Society
Published on Web 03/22/2001

Scheme 1. Precatalysts Investigated



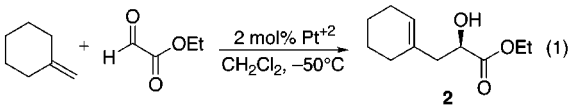
(**1a**−**g**, Scheme 1). The reaction of methylenecyclohexane and ethyl glyoxylate (eq 1, Table 1) was chosen for testing.

Table 1. Activity and Enantioselectivity for eq 1 as a Function of Counterion and Additive

entry[a]	additive	X⁻	convn (%)[b]	% ee[c]
1		OTf	36	74
2		BF_4	47	75
3		SbF_6	67	77
4	CF_3CH_2OH	OTf	24	74
5	NC_5F_5	OTf	36	74
6	3-CF_3-C_6H_4OH	OTf	74	77
7	3-CF_3-C_6H_4OH	SbF_6	68	78
8	C_6F_5OH	OTf	77	77

[a] 2 mol % of catalyst,[10] methylenecyclohexane (0.5 mmol), ethyl glyoxylate (1.5 mmol), and additive (1.0 mmol, if present) in 1.5 mL of CH_2Cl_2 at −50 °C (5 h). [b] Conversion for a 5 h run, measured by GC and corrected for response factors. [c] % ee measured by chiral phase GC (Cyclodex-β).

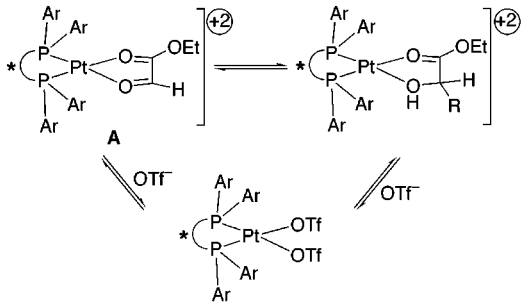
In situ activation of the parent MeOBiphep ligand complex (**1a**) with 2 equiv of AgOTf generated the desired [((*S*)-MeOBiphep)Pt](OTf)$_2$ complex, which catalyzed the formation of **2** with moderate enantioselectivity,[9] but at an



inconveniently slow rate (entry 1, Table 1).[10] Taking a cue from the work of others,[5b,11] we examined less coordinating counterions known to often enhance reactivity and selectivity (entries 1−3). Not unexpectedly, reactivity increased on going from OTf⁻ to BF_4^- to SbF_6^- (36 to 47 to 67% conversion), though the enantioselectivity changed only slightly, 74 to 75 and 77% ee, respectively.

In the interest of cost and molecular weight, we preferred to optimize this reaction using the triflate anion. Suspecting that the slower rate was a result of turnover-limiting triflate substitution rather than C−C bond formation, we thought that we might be able to improve this step. Scheme 2

Scheme 2. Ligand/Counterion Exchange Processes in the Glyoxylate−Ene Reaction



highlights some of the relevant equilibria that compete with the activated complex **A**. Since ligand and counterion substitution at square-planar Pt(II) complexes is usually associative,[12] we envisioned that weakly coordinating additives[13] could accelerate reaction turnover by facilitating ligand exchange without deactivating the Lewis acid.

The work of Tilset (with CF_3CH_2OH)[14] and Bercaw (NC_5F_5)[15] on electrophilic Pt(II) models for Shilov chemistry provided the intellectual lead for these experiments; however, as shown in entries 4−5 of Table 1, these additives either inhibited or had no effect on the rate of reaction. On the other hand, acidic phenols such as 3-CF_3-C_6H_3OH or C_6F_5-OH increased the rate and enantioselectivity of triflate-based catalysts to a level above that of SbF_6^- catalysts (no effect on SbF_6^- catalysts, entry 7). Moreover, when compared to no additive, reactions run with acidic phenols gave more reproducible conversion and selectivity data (vide infra).

A thorough examination of protic additives was carried out as described in Table 2 for [((*S*)-MeOBiphep)Pt](OTf)$_2$. Notable is the inhibitory effect of Lewis basic additives such as *tert*-butyl alcohol and water and the uniform acceleration of acidic alcohols and phenols. The structure of the alcohol or phenol does not affect the stereochemistry-determining step, as the % ee values are similar for the most acidic additives. Rate acceleration also increases with additive concentration (compare entries 1 and 7−9).

Relevant to these observations are reports by Evans documenting that protic additives such as $(CF_3)_2CHOH$

(8) (a) Schmid, R.; Broger, E. A.; Cereghetti, M.; Crameri, Y.; Foricher, J.; Lalonde, M.; Müller, R. K.; Scalone, M.; Schoettel, G.; Zutter, U. *Pure Appl. Chem.* **1996**, *68*, 131−138. (b) Schmid, R.; Foricher, J.; Cereghetti, M.; Schönholzer, P. *Helv. Chim. Acta* **1991**, *74*, 370−389.

(9) As in the Mikami case (footnote 6), the (*S*)-MeOBiphep ligand provides the (*R*)-enantiomer of product.

(10) The active catalyst was generated in situ by combining 4 mol % of AgOTf and 2 mol % of **1a** in CH_2Cl_2 at room temperature for 30 min and then cooling to −50 °C for the reaction. AgOTf and $AgSbF_6$ are not catalysts under these conditions.

(11) For example, see: (a) Evans, D. A.; Murray, J. A.; Matt, P. v.; Norcross, R. D.; Miller, S. J. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 798−800. (b) Kündig, E. P.; Saudan, C. M.; Bernardinelli, G. *Angew. Chem., Int. Ed.* **1999**, *38*, 1220−1223.

(12) (a) Cross, R. J. *Adv. Inorg. Chem.* **1989**, *34*, 219−292. (b) See also: Johansson, L.; Tilset, M. *J. Am. Chem. Soc.* **2001**, *123*, 739−740.

(13) For a recent review documenting additive effects in asymmetric catalysis, see: Vogl, E. M.; Gröger, H.; Shibasaki, M. *Angew. Chem., Int. Ed.* **1999**, *38*, 1571−1577.

(14) Heiberg, H.; Johansson, L.; Gropen, O.; Ryan, O. B.; Swang, O.; Tilset, M. *J. Am. Chem. Soc.* **2000**, *122*, 10831−10845.

(15) Holtcamp, M. W.; Labinger, J. A.; Bercaw, J. E. *J. Am. Chem. Soc.* **1997**, *119*, 848−849.

Table 2. Comparison of Activity and Enantioselectivity for eq 1 as a Function of Protic Additive

entry[a]	additive	convn (%)[b]	% ee[c]
1		36	74
2	*t*-BuOH	0	
3	H_2O	0	
4	$HOCMe(CF_3)_2$	80	76
5	$HOC(CF_3)_3$	77	80
6	$HOCH(CF_3)_2$	78	80
7	3-CF_3-C_6H_4OH[d]	45	75
8	3-CF_3-C_6H_4OH[e]	61	77
9	3-CF_3-C_6H_4OH	74	77
10	C_6F_5OH	77	77

[a] 2 mol % of catalyst,[10] methylenecyclohexane (0.5 mmol), ethyl glyoxylate (1.5 mmol), and additive (1.0 mmol, if present) in 1.5 mL of CH_2Cl_2. [b] Conversion for a 5 h run, measured by GC and corrected for response factors. [c] % ee measured by chiral phase GC (Cyclodex-β). [d] 0.05 mmol. [e] 0.5 mmol.

accelerate [Cu((*S*,*S*)-*t*-Bu-box)](X_2) (X = OTf^-, SbF_6^-) Lewis acid-catalyzed Mukaiyama Michael-type reactions by decomposing a turnover-inhibiting catalyst−product complex.[2a,16] The additive appears to selectively affect catalyst turnover and not the stereodefining step.

With a convenient reaction protocol in hand, we optimized enantioselectivity by varying the P-Ph portion of the [((*S*)-MeOBiphep)Pt]($OTf)_2$ catalyst. As shown in Table 3, the

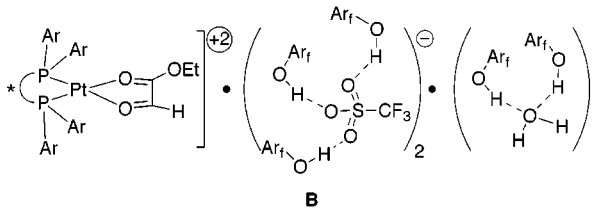
Table 3. Comparison of Activity and Enantioselectivity for eq 1 as a Function of Chiral Ligand

entry[a]	complex	convn (%)[b]	% ee[c]
1	**1a**	77	77
2	**1b**	52	69
3	**1c**	63	68
4	**1d**	79	85
5	**1e**	78	83
6	**1f**	0	
7	**1g**	48	56

[a] 2 mol % of catalyst,[10] methylenecyclohexane (0.5 mmol), ethyl glyoxylate (1.5 mmol), and C_6F_5OH (1.0 mmol) in 1.5 mL of CH_2Cl_2, −50 °C. [b] Conversion for a 5 h run, measured by GC and corrected for response factors. [c] % ee measured by chiral phase GC (Cyclodex-β).

diphosphine basicity does indeed influence the enantioselectivity[17] and activity. Interestingly, electron-withdrawing groups (**1b**,**c**) slowed the reaction and lowered the % ee, while electron-donating groups were beneficial to both, with a maximum at the 4-*tert*-butyl-substituted metal−ligand complex, **1d** (entry 4). The 4-NMe_2 substituent (**1f**) gave no product, possibly due to amine poisoning of the Lewis acid (entry 6), and for 3,5-dimethyl substituents (**1g**), steric encumbrance reduces reactivity and selectivity. In the best case (**1d**), the product was obtained in 97% yield after 8 h at −50 °C.

We tested the above additives because we thought they would catalyze the rate of product and/or counterion substitution at the metal. Since the effect is counterion dependent, these data point to the break-up of contact ion pairs between P_2Pt^{2+} and OTf^- or SbF_6^- as a turnover-defining event in catalysis. Although the additive plays a minor role with less coordinating, kinetically more labile anions such as SbF_6^-, associative exchange catalysis of the stronger binding triflate could substantially increase the rate of accessing **B**.



B

Another possible role for the acidic additives is reducing the coordinating power of the counterion though hydrogen bonding. This could stabilize the solvent-separated ion pair (**B**) and play a *thermodynamic* role in accelerating catalysis. The higher propensity of triflate to H-bond[18] would magnify the effect and lead to a larger activation compared to the already weakly bound SbF_6^- anion.

Regarding electronic variations on the MeOBiphep catalyst, one could use either the kinetic or thermodynamic argument to predict that the more electrophilic the metal, the stronger and hence more inhibiting, contact ion pair formation will be. The electronic effects on reaction rate are consistent with this notion (4-CF_3 < 4-H < 4-*t*-Bu, Table 3). In either case, these acidic phenol additives mechanistically differ from those reported by Evans in Cu(II)-catalyzed Mukaiyama Michael reactions.[2a,3,19]

Related to the above scenario is the increased reproducibility of reactions run with acidic phenol additives. Water is a competitive inhibitor of catalysis; however, the acidic phenols can reverse its effects. For example, adding 2 equiv of H_2O (relative to catalyst) to the reaction in eq 1 lowers the conversion from 36 to 27% (72% ee), but the reactivity and selectivity return to the expected levels (72% conversion, 76% ee, cf. entry 6, Table 1) with 3-CF_3-C_6H_3OH (1 mmol).

(16) (a) Evans, D. A.; Rovis, T.; Kozlowski, M. C.; Downey, C. W.; Tedrow, J. S. *J. Am. Chem. Soc.* **2000**, *122*, 9134−9142. (b) Evans, D. A.; Willis, M. C.; Johnson, J. N. *Org. Lett.* **1999**, *1*, 865−868. (c) Evans, D. A.; Rovis, T.; Kozlowski, M. C.; Tedrow, J. S. *J. Am. Chem. Soc.* **1999**, *121*, 1994−1995.

(17) For recent examples of electronic effects in asymmetric catalysis, see: (a) Murakami, M.; Minamida, R.; Itami, K.; Sawamura, M.; Ito, Y. *Chem. Commun.* **2000**, 2293−2294. (b) RajanBabu, T. V.; Redetich, B.; You, K. K.; Ayers, T. A.; Casalnuovo, A. L.; Calabrese, J. C. *J. Org. Chem.* **1999**, *64*, 3429−3447. (c) Schnyder, A.; Togni, A.; Wiesli, U. *Organometallics* **1997**, *16*, 255−260.

(18) For an example of catalyst immobilization to a silica support by H-bonding of the triflate counterion to acidic surface sites, see: de Rege, F. M.; Morita, D. K.; Ott, K. C.; Tumas, W.; Broene, R. D. *Chem. Commun.* **2000**, 1797−1798.

(19) For examples where C_6F_6OH additives either chemically modify the catalyst or the (complex) counterion, see: (a) Sun, Y.; Metz, M. V.; Stern, C. L.; Marks, T. J. *Organometallics* **2000**, *19*, 1625−1627. (b) Ishii, A.; Soloshonok, V. A.; Mikami, K. *J. Org. Chem.* **2000**, *65*, 1597−1599. (c) Sato, H.; Tojima, H.; Ikimi, K. *J. Mol. Catal. A: Chem.* **1999**, *144*, 285−293.

The mechanism is postulated to be similar to the OTf^- H-bonding scenario, where water now becomes sequestered into an H-bonded network that provides a uniformly "dry" reaction media.[20]

In summary, this study reports that [((*S*)-MeOBiphep)Pt]-$(X)_2$ (X = OTf^-, SbF_6^-) is an enantioselective catalyst for the glyoxylate−ene reaction (ee's up to 85%) and achiral acidic phenol additives accelerate the rate of the OTf^--based catalysts by disrupting contact ion pairs and sequestering traces of water. If general, acidic phenol additives may be a powerful tool for addressing the recurring problems of detrimental counterion coordination[21] and water poisoning in the chemistry of electrophilic cationic metal complexes. Experiments to further characterize the additive effect are ongoing, as are additional applications of the method.

Acknowledgment. This work was partially supported by the NSF (CHE-0075717), NIGMS (R01 GM60578-01), the Petroleum Research Fund, Union Carbide, and DuPont. M.R.G. is a Camille Dreyfus Teacher Scholar (2000). We particularly thank Dr. Rudolph Schmid (Hoffmann-La Roche, Basel) for helpful discussions on MeOBiphep synthesis.

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(20) Extensive H-bonding between triflate and coordinated water ligands is observed in the X-ray structures of (dppp)Pd$(OH_2)(OTf)_2$ and (dppp)-Pd$(OH_2)_2(OTf)_2$, see: Stang, P. J.; Cao, D. H.; Poulter, G. T.; Arif, A. M. *Organometallics* **1995**, *14*, 1110−1114.

(21) (a) Strauss, S. H. *Chem. Rev.* **1993**, *93*, 927−942.(b) Beck, W.; Sünkel, K. *Chem. Rev.* **1988**, *88*, 1405−1421.