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Pd(II)/Brønsted Acid Catalyzed Enantioselective Allylic C−H Activation for the Synthesis of Spirocyclic Rings

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Supporting Information

ABSTRACT: A Pd(II)/Brønsted acid catalyzed migratory ring expansion for the synthesis of indene derivatives possessing a stereogenic spirocyclic carbon center was developed. This transformation is believed to mechanistically proceed via enantioselective allylic C−H activation with concomitant semipinacol ring expansion to the nascent π-allylpalladium species. Enantioselectivities as high as 98% ee were attainable.

The Pd(II)-catalyzed allylic C−H activation of alkenes with subsequent nucleophilic attack on the resulting π-allyl Pd complex constitutes an efficient and atom-economical method for the construction of C−C, C−N, and C−O bonds.[1] While previous work in this has focused predominantly on internal alkenes,[1c] significant progress has recently been made by White's group[2] and others[3] on the allylic oxidation, amination, and alkylation of terminal alkenes. Despite these advances, the development of *enantioselective* reactions has met with limited success. Although chiral Pd(II) catalysts have been used for the asymmetric allylic acetoxylation of cyclohexene,[4] and more recently a chiral Lewis acid strategy was employed by White et al. to induce the same reaction of terminal alkenes,[2e] enantioselectivity in both cases remained modest (≤65% ee). Moreover, there is no report of asymmetric Pd(II)-catalyzed direct allylic amination or alkylation of alkenes.

Chiral spirocyclic indenes and indanes represent a structural motif present in biologically active natural products such as fredericamycin A, an antitumor compound with antibiotic properties,[5] and acutumine, an alkaloid possessing antiamnesic and selective T-cell cytotoxicity.[6] Additionally, their rigid structures make them an ideal platform for the development of chiral ligands such as the Spinol-based ligands, which have been applied successfully for various reactions[7] (Figure 1). At present

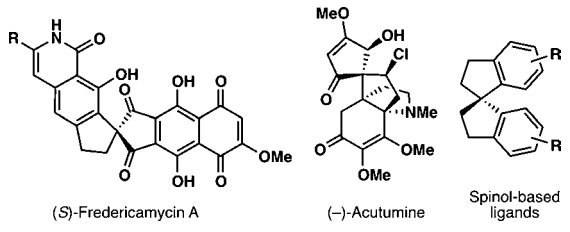
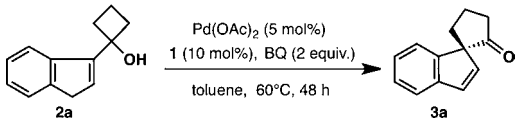


Figure 1. Representative spirocyclic compounds.

the catalytic-enantioselective construction of such quaternary spirocyclic carbon centers remains challenging.[8] Herein we report a procedure for their construction based on a novel asymmetric Pd(II)/Brønsted acid cocatalyzed semipinacol rearrangement via direct allylic C−H activation.

In our initial efforts to transform substrate **2a** to the desired product **3a** (Table 1), several neutral and cationic Pd(II)

Table 1. Screen of Reaction Conditions[a]



entry	ligand	oxidant	conv. (%)	yield (%)	% ee[b]
1	**1a**	BQ	<10	n.d.	n.d.
2	**1b**	BQ	<10	n.d.	n.d.
3	**1c**	BQ	>90	62	0
4[c]	**1d**	BQ	>95	73	0
5	**1e**	BQ	<10	n.d.	n.d.
6	**1f**	BQ	58	42	70
7	**1g**	BQ	88	45	34
8	**1h**	BQ	70	46	77
9	**1i**	BQ	0	0	_
10[d]	**1j**	BQ	43	22	0
11[e]	**1h**	BQ	66	43	76
12[f]	**1h**	BQ	77	49	75
13[g]	**1h**	BQ	83	60	63
14	**1h**	NQ	<5	0	-
15[h]	**1h**	O_2	36	20	75
16[i]	**1h**	MnO_2	30	14	28
17[j]	**1h**	BQ	84	52	77
18[j,k]	**1h**	BQ	74	49	77
19[j,l]	**1h**	BQ	89	67	75

[a]Reactions were run on a 0.1 mmol scale in 1.0 mL of toluene. Conversions were based on recovered starting material, and isolated yields were reported. [b]Determined by chiral HPLC. [c]At 45 °C. [d]At 21 °C. [e]At 50 °C. [f]$PhCF_3$ as solvent. [g]PhCl as solvent. [h]10 mol % of BQ with an oxygen balloon. [i]20 mol % of BQ with 1 equiv of MnO_2. [j]10 mol % of $Pd(OAc)_2$ and 20 mol % of **1h** in 2.0 mL of solvent. [k]1.0 equiv of BQ was used. [l]In $PhCF_3$ at 55 °C.

complexes along with various chiral oxazoline ligands were screened (see Supporting Information). Given the disappointing results obtained in this preliminary study, we sought out potentially more reactive complexes and specifically were intrigued with the possibility of using chiral Brønsted acids in combination with a Pd(II) precatalyst.[9] Early in 1990, a report

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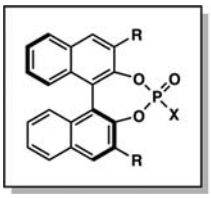
described the use of BINOL-derived phosphoric acid **1a** as a ligand in $PdCl_2$ catalyzed asymmetric hydrocarboxylation of two vinyl arenes.[10] Surprisingly, no further work has been reported in exploiting the potential of these additives in other Pd(II)-catalyzed oxidative reactions. With their attenuation of reactivity, inertness to oxidative conditions, and recent successful combined uses with metal salts in various reactions,[11] the use of chiral phosphoric acids in the realm of Pd(II) chemistry has unrealized potential (Figure 2).



1a: R = H, X = OH
1b: R = Ph, X = OH
1c: R = biphenyl, X = OH
1d: R = 3,5-bis-$CF_3C_6H_3$, X = OH
1e: R = 9-anthracenyl, X = OH
1f: R = triphenylsilyl, X = OH
1g: R = 2,4,6-trimethyl-C_6H_2, X = OH
1h: R = 2,4,6-triisopropyl-C_6H_2, X = OH
1i: R = 2,4,6-triisopropyl-C_6H_2, X = SH
1j: R = 2,4,6-triisopropyl-C_6H_2, X = NHTf

Figure 2. Chiral Brønsted acids evaluated in this study.

Consistent with our above expectation, the addition of phosphoric acids had a dramatic effect on the reactivity of Pd(II) complexes and, furthermore, gave the desired product in good yields. After some experimentation, $Pd(OAc)_2$ was identified as the metal catalyst of choice. Screening of a series of BINOL-derived Brønsted acids then furnished optimal results (Table 1, entries 1−10).[12] *In the absence of either $Pd(OAc)_2$ or the Brønsted acid, essentially no conversion of the starting material was observed under the otherwise same reaction conditions.*[13] It was found that phosphoric acid **1d** with the electron-withdrawing CF_3 substituents, which is supposed to be relatively more acidic, displayed the best catalytic efficiency even at a lower temperature (entry 4) while the sterically hindered **1h** gave the highest enantioselectivity (entry 8). In view of this result, we prepared Brønsted acids **1i** and **1j** with the same skeleton as that of **1i** but with increased acidity[14] with the expectation of obtaining both good enantioselectivity and conversion. With **1i**, however, no reaction took place, probably due to the strong coordination capacity of the thiol group (entry 9). Catalyst **1j** displayed exceptionally high reactivity albeit with no enantioselectivity: racemic product **3a** was obtained even when the reaction was run at room temperature (entry 10). Lowering of the reaction temperature to minimize the formation of Pd black resulted in only a slight influence on yield and enantioselectivity (entry 11). The use of noncoordinating aromatic solvents and 1,4-benzoquinone (BQ) as the oxidant was crucial for this reaction. Rate acceleration was observed as the polarity of the solvent increased, but with diminished enantioselectivity (entries 12−13). It should be noted that when toluene was used as the solvent, a sharp dependence of the conversion and yield on the water content of the commercial solvent was also observed while the enantioselectivity essentially remained unchanged.[15] While the use of 1,4-naphthoquinone (NQ) or MnO_2 as the oxidant were not effective, the use of O_2 in the presence of 10 mol % of BQ led to a sluggish reaction but gave comparable enantioselectivity (entries 14−16). Doubling the amount of both catalysts could further improve the conversion and yield, while decreasing the amount of BQ slightly slowed down the reaction with little influence on the enantioselectivity (entries 17−19).

We next examined the scope of this reaction (Table 2).[16] For substrates **2b**−**2h** with a substituent at the 4-position of the cyclobutane ring, in general, excellent enantioselectivity was

Table 2. Scope of the Semipinacol Rearrangement Reaction[a]

entry	substrate	product	yield (%)[b]	d.r.[c]	% ee
1	**2a**	**3a**	67(89)[d]	N/A	75
2	**2b**	**3b**	59(70)[d]	8:1	97
3	**2c**	**3c**	64(82)	5:1	97
4	**2d**	**3d**	58(90)	10:1	98
5	**2e**	**3e**	52(85) 22(32)[e]	6:1 6:1	80 96
6	**2f**	**3f**	69(94) 71(95)[f]	N/A N/A	77 86
7	**2g**	**3g**	43(74)	6:1	96
8	**2h**	**3h**	78(91) 74(86)[f]	4:1 4:1	96 96
9	**2i**	**3i**	40(100)[f]	N/A	48
10	**2j**	**3j**	50(70)[f]	N/A	84
11	**2k**	**3a**	<3(25)[g]	N/A	n.d.

[a]0.1 mmol scale, $Pd(OAc)_2$ (10 mol %), **1h** (20 mol %), BQ (2.0 equiv), in $PhCF_3$ (2.0 mL) at 55 °C for 72 h. [b]Isolated yields. Numbers in parentheses are conversions based on recovered starting material. [c]Determined by ^1H NMR analysis. [d]Reaction time: 48 h. [e]In $PhCH_3$ at 60 °C for 48 h. [f]In $PhCH_3$ at 50 °C for 72 h. [g]Yield estimated by ^1H NMR analysis.

obtained with moderate to good diastereoselectivity (entries 2−8). Functionality such as aryl chloride and benzyl ether was well tolerated. Moreover, substrates with alkyl substituents at this position gave somewhat better yields than those with aromatic ones, except for **3g** with an additional coordinative oxygen atom (entry 7). In the case of acid sensitive substrate **2i**, which has two possibilities of bond migration (methylene vs phenyl) in the semipinacol rearrangement process, only the methylene migration product **3i** was obtained in moderate yield and enantioselectivity (entry 9). This result deserves attention because of the failure of previous work to induce this type of ring expansion of related allylic alcohols derived from benzocyclobutanones.[17] Substrate **2j** with a substituted indene ring also worked well in this reaction (entry 10). The use of related substrates without the indene structure failed to undergo the desired reaction.[18] We consequently proposed that the reaction proceeded via allylic C−H activation, with the greater reactivity (acidity) of indenyl methylene protons accountable for the substrate specificity. Thus, substrate **2k** was expected to give similar results to that of **2a**, so that a common allylic Pd intermediate might be shared by both substrates. However, the

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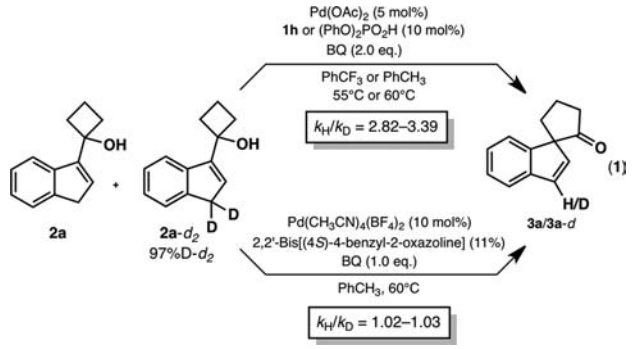
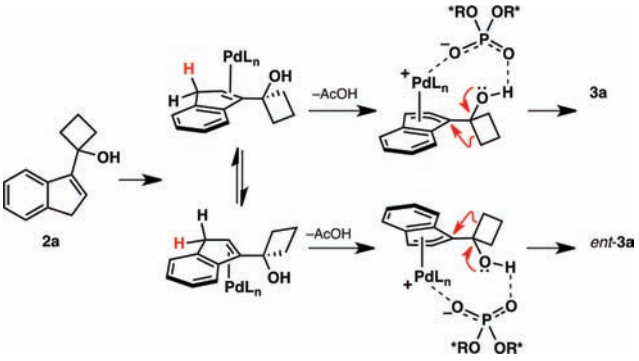
desired reaction hardly took place, probably due to the steric hindrance of the tertiary C−H bond in **2k** (entry 11).

An intermolecular kinetic isotopic effect experiment (KIE) study with substrate **2a**-d_2 disclosed a primary kinetic isotopic effect for this reaction (see Supporting Information for more details), which is clearly in support of our above hypothesis that an allylic C−H bond is broken prior to or during the rate-limiting step (eq 1). In contrast, use of the more reactive catalyst $Pd(CH_3CN)_4(BF_4)_2$ did not result in an observable kinetic isotope effect (k_H/k_D = 1.02−1.03). The data in this case are consistent with a mechanism in which alkene coordination to the metal center depletes electron density in the alkene through ligand to metal electron donation; rearrangement followed by fast β-hydride elimination then furnishes the observed product.



Based on the above experimental results, a tentative mechanism was proposed (Scheme 1). First, mixing of $Pd(OAc)_2$

Scheme 1. Proposed Reaction Mechanism



and the phosphoric acid additive produces an active Pd(II) species via acid-catalyzed ligand exchange. Coordination of the substrate then forms a diastereomeric mixture of equilibrating alkene complexes. These complexes subsequently undergo rate-limiting C−H insertion, possibly through proton abstraction by a ligated acetate ligand[19] to produce diastereomeric π-allylpalladium intermediates.[20] Here, the chiral phosphoric acid may possibly serve as a counteranion/anionic ligand as proposed by List et al. in a Pd(0)-catalyzed α-allylation of aldehydes.[21] The transient π-allylpalladium intermediate subsequently undergoes semipinacol ring expansion in accordance with literature precedent[22] to generate the observed product and a Pd(0) species, which is reoxidized to Pd(II) by BQ. Unfortunately, our efforts to observe the postulated π-allylpalladium intermediate were unsuccessful, and we cannot conclusively rule out the possibility of an alternative reaction mechanism at this time.[23,24]

In summary, we have developed an enantioselective semipinacol rearrangement initiated by Pd(II)-catalyzed direct allylic C−H activation to give chiral spirocyclic indenes. Our results indicate that a chiral Brønsted acid strategy could be a valuable method for the development of asymmetric Pd(II)-catalyzed oxidative reactions of alkenes through direct allylic C−H activation. Efforts toward this direction as well as a detailed understanding of the mechanism are currently underway in our laboratories.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, details on condition screening, and spectral data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

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■ REFERENCES

(1) For recent reviews: (a) Beccalli, E. M.; Broggini, G.; Martinelli, M.; Sottocornola, S. *Chem. Rev.* **2007**, *107*, 5318. (b) Popp, B. V.; Stahl, S. S. *Top. Organomet. Chem.* **2006**, *22*, 149. (c) Jensen, T.; Fristrup, P. *Chem.—Eur. J.* **2009**, *15*, 9632 and references therein.

(2) (a) Chen, M. S.; White, C. W. *J. Am. Chem. Soc.* **2004**, *126*, 1346. (b) Chen, M. S.; Prabagaran, N.; Labenz, N. A.; White, C. W. *J. Am. Chem. Soc.* **2005**, *127*, 6970. (c) Fraunhoffer, K. J.; Prabagaran, N.; Sirois, L. E.; White, C. W. *J. Am. Chem. Soc.* **2006**, *128*, 9032. (d) Delcamp, J. H.; White, C. W. *J. Am. Chem. Soc.* **2006**, *128*, 15076. (e) Covell, D. J.; White, C. W. *Angew. Chem., Int. Ed.* **2008**, *47*, 6448. (f) Vermeulen, N.; Delcamp, J. H.; White, C. W. *J. Am. Chem. Soc.* **2010**, *132*, 11323. Amination: (g) Reed, S. A.; White, C. W. *J. Am. Chem. Soc.* **2008**, *130*, 3316. (h) Fraunhoffer, K. J.; White, C. W. *J. Am. Chem. Soc.* **2007**, *129*, 7274. (i) Rice, G. T.; White, C. W. *J. Am. Chem. Soc.* **2009**, *130*, 11707. (j) Reed, S. A.; Mazzotti, A. R.; White, C. W. *J. Am. Chem. Soc.* **2009**, *130*, 11701. (k) Young, A. J.; White, C. W. *J. Am. Chem. Soc.* **2008**, *130*, 14090.

(3) (a) Mitsudome, T.; Umetani, T.; Nosaka, N.; Mori, K.; Mizugaki, T.; Ebitani, K.; Kaneda, K. *Angew. Chem., Int. Ed.* **2006**, *45*, 481. (b) Pilarski, L. T.; Selander, N.; Böse, D.; Szabó, K. J. *Org. Lett.* **2009**, *11*, 5518. (c) Lin, B.-L.; Labinger, J. A.; Bercaw, J. E. *Can. J. Chem.* **2009**, *87*, 264. (d) Thiery, E.; Aouf, C.; Belloy, J.; Harakat, D.; Le Bras, J.; Muzart, J. *J. Org. Chem.* **2010**, *75*, 1771. (e) Henderson, W. H.; Check, C. T.; Proust, N.; Stambuli, J. P. *Org. Lett.* **2010**, *12*, 824. (f) Campbell, A. N.; White, P. B.; Guzei, I. A.; Stahl, S. S. *J. Am. Chem. Soc.* **2010**, *132*, 15116. Amination: (g) Larock, R. C.; Hightower, T. R.; Hasvold, L. A.; Peterson, K. P. *J. Org. Chem.* **1996**, *61*, 3584. (h) Liu, G.; Yin, G.; Wu, L. *Angew. Chem., Int. Ed.* **2008**, *47*, 4733. (i) Nahra, F.; Liron, F.; Prestat, G.; Mealli, C.; Messaoudi, A.; Poli, G. *Chem.—Eur. J.* **2009**, *15*, 11078. (j) Shimizu, Y.; Obora, Y.; Ishii, Y. *Org. Lett.* **2010**, *12*, 1372. (k) Yin, G.; Wu, Y.; Liu, G. *J. Am. Chem. Soc.* **2010**, *132*, 11978. Alkylation: (l) Lin, S.; Song, C.-X.; Cai, G.-X.; Wang, W.-H.; Shi, Z.-J. *J. Am. Chem. Soc.* **2008**, *130*, 12901.

(4) (a) El-Qisiari, A. K.; Qaseer, H. A.; Henry, P. M. *Tetrahedron Lett.* **2002**, *43*, 4229. (b) Yang, H.; Khan, A. K.; Nicholas, K. M. *J. Mol. Catal.* **1994**, *91*, 319. (c) Kozitsyna, N. Yu.; Vargaftik, M. N.; Moiseev, I. I. *J. Organomet. Chem.* **2000**, *593*−*594*, 274.

(5) (a) Albel, U.; Simon, W.; Eckard, P.; Hansske, F. G. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 3292. For two enantioselective total syntheses:

(b) Kita, Y.; Higuchi, K.; Yoshida, Y.; Iio, K.; Kitagaki, S.; Akai, S.; Fujioka, H. *Angew. Chem., Int. Ed.* **1999**, *38*, 683. (c) Kita, Y.; Higuchi, K.; Yoshida, Y.; Iio, K.; Kitagaki, S.; Ueda, K.; Akai, S.; Fujioka, H. *J. Am. Chem. Soc.* **2001**, *123*, 3214.

(6) For a recent enantioselective total synthesis of (−)-acutumine: Li, F.; Tartakoff, S. S.; Castle, S. L. *J. Am. Chem. Soc.* **2009**, *130*, 6674.

(7) For a review: (a) Xie, J.-H.; Zhou, Q.-L. *Acc. Chem. Res.* **2008**, *41*, 581. For very recent examples: (b) Zhu, S.-F.; Cai, Y.; Mao, H.-X.; Xie, J.-H.; Zhou, Q.-L. *Nat. Chem.* **2010**, *2*, 546. (c) Zhu, S.-F.; Song, X.-G.; Li, Y.; Cai, Y.; Zhou, Q.-L. *J. Am. Chem. Soc.* **2010**, *132*, 16374. (d) Coulter, M. M.; Kou, K. G. M.; Galligan, B.; Dong, V. M. *J. Am. Chem. Soc.* **2010**, *132*, 16330. (e) Čorić, I.; Müller, S.; List, B. *J. Am. Chem. Soc.* **2010**, *132*, 17370.

(8) For recent reviews on quaternary carbon centers: (a) Douglas, C. J.; Overman, L. E. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 3363. (b) Christoffers, J.; Baro, A. *Adv. Synth. Catal.* **2005**, *347*, 1473. (c) Trost, B. M.; Jiang, C. *Synthesis* **2006**, 369.

(9) (a) Boele, M. D. K.; van Strijdonck, G. D. F.; de Vries, A. H. M.; Kamer, P. C. J.; de Vries, J. G.; van Leeuwen, P. W. N. M. *J. Am. Chem. Soc.* **2002**, *124*, 1586. (b) Fujiwara, Y.; Jia, C. *Pure Appl. Chem.* **2001**, *73*, 319. Brønsted acids have also been shown to promote the regeneration of Pd(II) from Pd(0)−BQ complexes: (c) Grennberg, H.; Gogoll, A.; Bäckvall, J.-E. *Organometallics* **1993**, *12*, 1790.

(10) Alper, H.; Hamel, N. *J. Am. Chem. Soc.* **1990**, *112*, 2803.

(11) For an excellent review: Rueping, M. R.; Koenigs, R. M.; Atodiresei, I. *Chem.—Eur. J.* **2010**, *16*, 9350.

(12) See Supporting Information for full details on screen of conditions such as different Pd salts, solvents, oxidants, and additives.

(13) Phosphoric acid **1h** and/or its silver salt have recently been shown to catalyze the semipinacol rearrangement of 2-oxo allylic alcohols to give chiral spirocyclic ethers: 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.

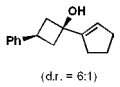
(14) (a) Nakashima, D.; Yamamoto, H. *J. Am. Chem. Soc.* **2006**, *128*, 9626. (b) Cheon, C. H.; Yamamoto, H. *J. Am. Chem. Soc.* **2008**, *130*, 9246. (c) Jiao, P.; Nakashima, D.; Yamamoto, H. *Angew. Chem., Int. Ed.* **2008**, *47*, 2411.

(15) Too little or much water content in toluene all led to very low conversions (see Table S4 in the Supporting Information for details). We presume that an appropriate amount of water may facilitate the regeneration of the Pd(II) species, because when dried toluene was used, the precipitation of Pd black soon became obvious within 3 h. However, too much water may be detrimental to the active Pd(II) complex.

(16) The absolute configuration of **3b** was assigned using Mosher ester analysis of the corresponding alcohol product after $NaBH_4$ reduction. The relative configurations of **3e** and **3h** were assigned by 1D NOESY. See Supporting Information for details.

(17) (a) Johnson, C. R.; Herr, R. W. *J. Org. Chem.* **1973**, *38*, 3153. (b) Frimer, A. A.; Weiss, J.; Gottlieb, H. E.; Wolk, J. L. *J. Org. Chem.* **1994**, *59*, 780.

(18) The following two substrates lacking an indene moiety failed to rearrange under the standard reaction conditions:



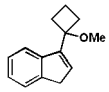
(19) An alternate mechanism involving the formation of a benzylic carbocation or metallocyclopropane/π-complex is not supported by the kinetic isotope data.

(20) For examples of π-allylpalladium intermediates in an indene framework, see: (a) Hansson, S.; Heumann, A.; Rein, T.; Åkermark, B. *J. Org. Chem.* **1990**, *55*, 975. (b) Nakasuji, K.; Yamaguchi, M.; Murata, I.; Tatsumi, K.; Nakamura, A. *Organometallics* **1984**, *3*, 1257. (c) Trost, B. M.; Organ, M. G. *J. Am. Chem. Soc.* **1994**, *116*, 10320. (d) Gais, H.-J.; Bondarev, O.; Hetzer, R. *Tetrahedron Lett.* **2005**, *46*, 6279.

(21) Mukherjee, S.; List, B. *J. Am. Chem. Soc.* **2007**, *129*, 11336.

(22) For examples of a π-allylpalladium intermediate that undergoes a Wagner−Meerwein shift, see: (a) Trost, B. M.; Xie, J. *J. Am. Chem. Soc.* **2006**, *128*, 6044. (b) Trost, B. M.; Yasukata, T. *J. Am. Chem. Soc.* **2001**, *123*, 7162 and references therein.

(23) Compound **4** failed to exhibit any reaction whereas **5** rapidly decomposed when subjected to stoichiometric amounts of Pd(II)/diphenylphosphate. It is possible that the free hydroxyl group facilitates coordination of Pd.



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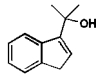

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(24) The phosphoric acid may promote the reaction through coordination to BQ via H-bonding. Such a model has been proposed in the chiral Lewis acid strategy for asymmetric allylic C−H oxidation of terminal alkenes developed by White and co-workers; see ref 2e.