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Chiral Phosphaalkene−Oxazoline Ligands for the Palladium-Catalyzed Asymmetric Allylic Alkylation

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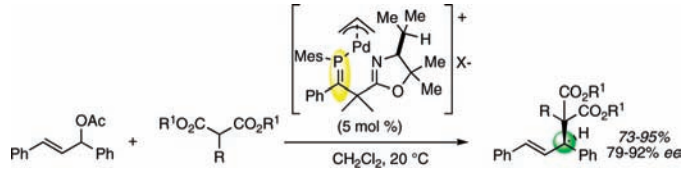
ABSTRACT



Enantioselective catalysis in moderate to excellent yields and ee's has been accomplished using a phosphaalkene-based ligand system. Specifically, the palladium-catalyzed allylic alkylation of 1,3-diphenyl-2-propenyl acetate using a chiral P(sp^2),N(sp^2) ligand proceeds with a variety of malonate nucleophiles in 73−95% yield (79−92% ee).

Innovations in the design of nonconventional ligand frameworks can serve as a foundation for the discovery of new reactivities in synthetic organic chemistry. To these ends, there has been considerable interest in the development of nonconventional phosphaalkene (PhAk) ligands that contain P(sp^2) moieties for catalytic applications.[1,2] Such ligands offer novel σ-donating and π-accepting properties and consequently have been employed successfully in numerous achiral transformations.[3] The application of enantiomerically pure versions of PhAk ligands in asymmetric catalysis remains at a primitive stage. Although chiral aromatic phosphaferrocene and phosphinine ligands have successfully been used in asymmetric catalysis,[4] the current state-of-the-art catalysis with acyclic PhAk ligands involves a singular example of Pd-catalyzed asymmetric hydroamination (21% ee).[5]

Herein, we report a breakthrough in the evolution of low-coordinate phosphorus ligands for catalysis, namely, the application of an enantiomerically pure PhAk−oxazoline in the Pd-catalyzed asymmetric allylic alkylation. Our results demonstrate that this novel ligand gives synthetically useful yields and high ee's using a range of functionalized β-dicarbonyl nucleophiles.

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(2) Bates, J. I.; Dugal-Tessier, J.; Gates, D. P. *Dalton Trans.* **2010**, *39*, 3151–3159.

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(4) For reviews, see: (a) Müller, C.; Vogt, D. *Dalton Trans.* **2007**, 5505–5523. (b) Fu, G. C. *Acc. Chem. Res.* **2006**, *39*, 853–860. For recent examples, see: (c) Willms, H.; Frank, W.; Ganter, C. *Organometallics* **2009**, *28*, 3049–3058. (d) Willms, H.; Frank, W.; Ganter, C. *Chem.—Eur. J.* **2008**, *14*, 2719–2729. (e) Suárez, A.; Downey, C. W.; Fu, G. C. *J. Am. Chem. Soc.* **2005**, *127*, 11244–11245. (f) Shintani, R.; Fu, G. C. *Angew. Chem., Int. Ed.* **2003**, *42*, 4082–4085. (g) Shintani, R.; Fu, G. C. *J. Am. Chem. Soc.* **2003**, *125*, 10778–10779. (h) Breit, B.; Winde, R.; Mackewitz, T.; Paciello, R.; Harms, K. *Chem.—Eur. J.* **2001**, *7*, 3106–3121.

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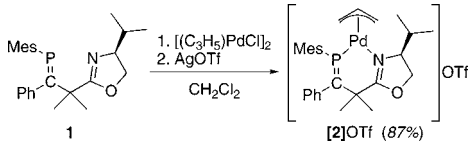
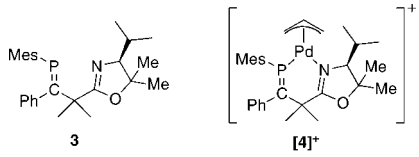
We have recently embarked on a program to develop chiral P(sp^2),N(sp^2) ligands and have developed a modular route to the air-stable and enantiomerically pure PhAk−oxazoline ligand (PhAk−Ox, **1**).[6] The Pd-catalyzed alkylation of allylic substrates using **1** was selected to assess the potential of these ligands which bear resemblance to the highly successful Pfaltz−Helmchen P(sp^3),N(sp^2) phosphinooxazoline (PHOX) ligands.[7,8] The successful implementation of PhAk−Ox in catalytic asymmetric allylic alkylation provides an entry point to broader application in asymmetric catalysis. Moreover, these experiments also provide a benchmark for the development of later-generation versions of the PhAk−Ox ligand system.

The Pd-catalyzed allylic alkylation necessitated the synthesis of the PhAk−Ox−palladium allyl complex **[2]**OTf from the reaction of $[(C_3H_5)PdCl]_2$, AgOTf, and **1** in CH_2Cl_2. Complex **[2]**OTf was isolated in high yield and was fully characterized by ^{31}P, ^{1}H, and ^{13}C NMR spectroscopy, and satisfactory elemental microanalysis was obtained.

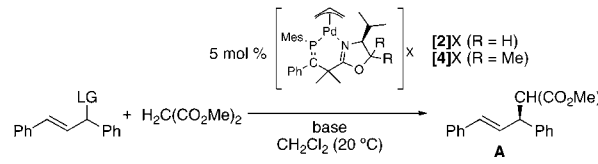


The Pd complex **[2]**OTf showed considerable potential. For example, the reaction between racemic 1,3-diphenyl-2-propenyl ethyl carbonate and dimethyl malonate in the presence of **[2]**OTf (5 mol %) afforded the substituted malonate (**A**) with a very promising 83% ee, albeit in modest isolated yield (35%) (Table 1, entry 1). Efforts to optimize the performance of **[2]**OTf by employing different base systems resulted in a major breakthrough with bis(trimethylsilyl)acetamide (BSA) and potassium acetate which improved the yield of **A** to 70% while maintaining enantioselectivity (85% ee).[9]



In an effort to improve the enantioselectivity of this process further, modifications to the ligand skeleton were undertaken. In the PHOX ligand series, the addition of a *gem*-dialkyl moiety at C5 of the 4-^{i}Pr−Ox results in higher enantioselectivities.[10] The presence of *gem*-dialkyl groups influences the positioning of the ^{i}Pr methyl moieties with respect to the metal center, thus increasing the enantioselectivity. Therefore, ligand **3** and the palladium−allyl **[4]**OTf were prepared following procedures analogous to those outlined above. Attempts to ascertain the orientation of the ^{i}Pr methyl moieties in **[4]**OTf through X-ray diffraction were unsuccessful since suitable crystals could not be obtained. Thus, **3**·$PdCl_2$ was prepared and analyzed crystallographically to reveal three conformational forms in the asymmetric unit (Figure 1). In the solid state, two of the three isomers (b and c, 60%) have the methyl groups on the isopropyl moiety projecting toward the Pd atom in **3**·$PdCl_2$. This contrasts with **1**·$PdCl_2$ in which the methyl groups on the isopropyl unit are oriented away from the Pd atom in the solid state (see Supporting Information).

Table 1. Initial Results Using PhAk−Ox Pd Complexes **[2]**X and **[4]**X in Asymmetric Allylic Alkylation



entry	LG	catalyst	base[a]	% yield[b]	% ee[c]
1	OCO_2Et	**[2]**OTf	NaH	35	83
2	OCO_2Et	**[2]**OTf	Cs_2CO_3	36	50
3	OCO_2Et	**[2]**OTf	BSA/KOAc	70	85
4	OCO_2Et	**[4]**OTf	BSA/KOAc	74	91
5	OCO_2Et	**[4]**BF_4	BSA/KOAc	52	70
6	OAc	**[4]**OTf	BSA/KOAc	83	92

[a] NaH (1 equiv); Cs_2CO_3 (1 equiv); BSA (1 equiv)/KOAc (0.01 equiv). [b] Isolated yields. [c] ee was determined using chiral SFC-HPLC.

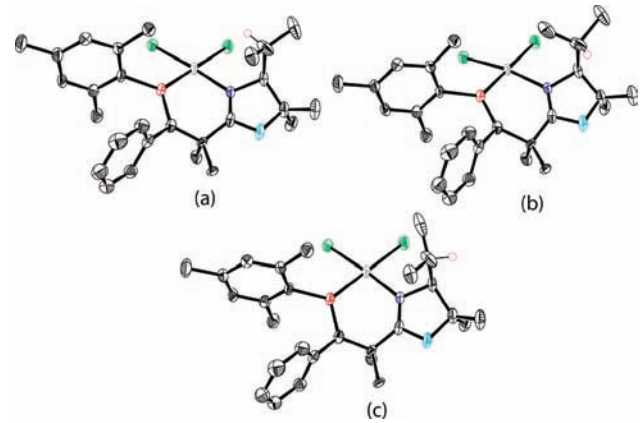


Figure 1. Molecular structures showing the three conformations of **3**·$PdCl_2$ in the solid state: (a) 40%, (b) 37%, and (c) 23% (50% probability ellipsoids). All hydrogen atoms are omitted for clarity.

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(6) Dugal-Tessier, J.; Dake, G. R.; Gates, D. P. *Angew. Chem., Int. Ed.* **2008**, *47*, 8064–8067.

(7) (a) Helmchen, G.; Pfaltz, A. *Acc. Chem. Res.* **2000**, *33*, 336–345. For initial publication, see: (b) von Matt, P.; Pfaltz, A. *Angew. Chem., Int. Ed.* **1993**, *32*, 566–568. (c) Sprinz, J.; Helmchen, G. *Tetrahedron Lett.* **1993**, *34*, 1769–1772. (d) Dawson, G. J.; Frost, C. G.; Williams, M. J.; Coote, S. J. *Tetrahedron Lett.* **1993**, *34*, 3149–3150.

(8) For reviews of Pd-catalyzed allylic alkylation, see: (a) Trost, B. M. *J. Org. Chem.* **2004**, *69*, 5813–5837. (b) Trost, B. M.; Crawley, M. L. *Chem. Rev.* **2003**, *103*, 2921–2943. (c) Lu, Z.; Ma, S. M. *Angew. Chem., Int. Ed.* **2008**, *47*, 258–297. (d) Braun, M.; Meier, T. *Synlett* **2006**, 661–676.

Importantly, the use of the modified catalyst **[4]**OTf led to improved performance in allylic alkylation. Malonate **A** was obtained in high enantioselectivity (91%; cf. 85% for **[2]**OTf) and good yield (74%; cf. 70% with **[2]**OTf) (Table 1, entry 4). Changing the catalyst counterion to $[BF_4]^-$ gave poorer results (entry 5). In the midst of these optimization experiments, it was observed that product mixtures were often contaminated with 1,3-diphenyl-2-propenyl ethyl ether. This undesired side product results from the addition of ethoxide (formed from $EtOCO_2^-$) to the putative π-allyl intermediate. This has been observed previously[11] and is avoided by employing acetate as the leaving group. To our delight, racemic 1,3-diphenyl-2-propenyl acetate reacted readily with dimethyl malonate using catalyst **[4]**OTf to afford **A** in 83% yield and 92% ee (entry 6), an improvement over the analogous carbonate (74%, 91% ee).

The scope of nucleophiles in allylic alkylations with 1,3-diphenyl-2-propenyl acetate catalyzed by **[4]**OTf was explored further. Standard experimental conditions for these studies were [**4**]OTf (5 mol %), BSA (1 equiv), and KOAc (0.01 equiv) in CH_2Cl_2 at 20 °C. The results are summarized in Figure 2 and generally show **[4]**OTf to be an effective

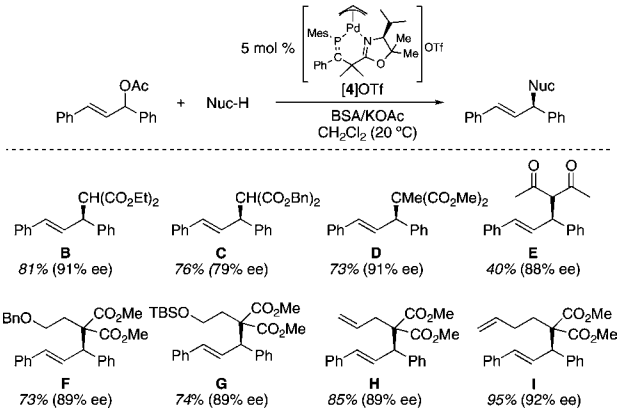
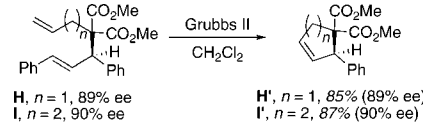


Figure 2. Preliminary investigation of the scope of enantioselective allylic alkylation using PhAk−Ox catalyst [**4**]OTf showing functional group tolerance (isolated yields, ee's determined by chiral SFC-HPLC).

catalyst. A few points merit comment. The dibenzyl malonate **C** was formed in lower yield and enantioselectivity relative to its dimethyl (**A**) or diethyl (**B**) congeners. Diketone **E**, formed by the addition of acetylacetone to 1,3-diphenyl-2-propenyl acetate, was produced in 88% ee but only in 40% yield. Importantly, β-dicarbonyl compounds that contain ether or alkene functions are also well tolerated in reactions catalyzed by [**4**]OTf, giving alkylated malonates **F**−**I** in good yields with excellent enantioselectivities.

Acyclic dialkenes **H** and **I** can be further synthetically manipulated using catalytic amounts (5 mol %) of the Grubbs II catalyst [(IMes)$(PCy_3)RuCl_2$(=CHPh)]. The ring-closing metathesis of **H** and **I** proceeded smoothly to produce cyclopentene **H′** and cyclohexene **I′** in good yields. Importantly, HPLC analysis of the starting materials and products in this sequence demonstrated that no erosion of the stereochemical configuration took place.



This work demonstrates the first application of a chiral phosphaalkene (PhAk) derived ligand that supports metal-catalyzed processes for organic chemistry in high yields and enantioselectivities. The modular nature within the ligand design bodes well for utility and optimization in other applications involving metal catalysis. Importantly, it is expected that the future reactivity studies will exploit the unique capabilities of the PhAk fragment. Further studies examining these possibilities are ongoing in our laboratories.

Acknowledgment. We gratefully acknowledge NSERC of Canada (Discovery, Strategic and Research Tool grants to G.R.D. and D.P.G. and a PGS D scholarship to J.D.-T.), Merck & Co. Inc., and Merck-Frosst Canada Inc. for support of this work. We acknowledge Doris Tang (UBC), Megan Boyd (UBC), and Hyukin Kwon (UBC) for assistance in molecule construction. We are grateful to Prof. Glenn Sammis (UBC) and his research group for access to SFC-HPLC equipment.

Supporting Information Available: Experimental procedures, characterization data for all previously unreported compounds, and CIF files. This material is available free of charge via the Internet at http://pubs.acs.org.

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(9) The absolute configuration of **A**−**E** was determined by comparison of optical rotation values to literature data. The absolute configuration of **H** and **I** was determined by comparison of the optical rotation data of the RCM products **H′** and **I′** to literature data. Compounds **F** and **G** were assigned by analogy. See Supporting Information for details.

(10) (a) Bélanger, E.; Pouliot, M. F.; Paquin, J. F. *Org. Lett.* **2009**, *11*, 2201–2204. (b) Bull, S. D.; Davies, S. G.; Key, M.-S.; Nicholson, R. L.; Savory, E. D. *Chem. Commun.* **2000**, 1721–1722. (c) Bull, S. D.; Davies, S. G.; Garner, A. C.; Kruchinin, D.; Key, M.-S.; Roberts, P. M.; Savory, E. D.; Smith, A. D.; Thomson, J. E. *Org. Biomol. Chem.* **2006**, *4*, 2945–2964.

(11) For recent examples, see: (a) Austeri, M.; Linder, D.; Lacour, J. *Chem.—Eur. J.* **2008**, *14*, 5737–5741. (b) Kuwano, R.; Kusano, H. *Org. Lett.* **2008**, *10*, 1979–1982.