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Diastereo- and Enantioselective Hydrogenative Aldol Coupling of Vinyl Ketones: Design of Effective Monodentate TADDOL-Like Phosphonite Ligands

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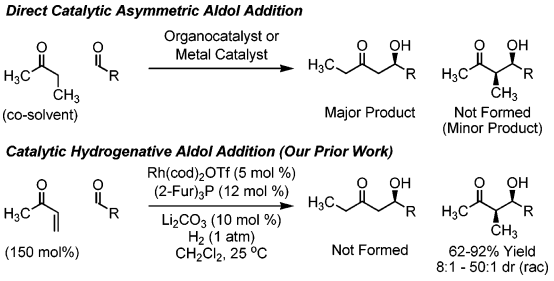
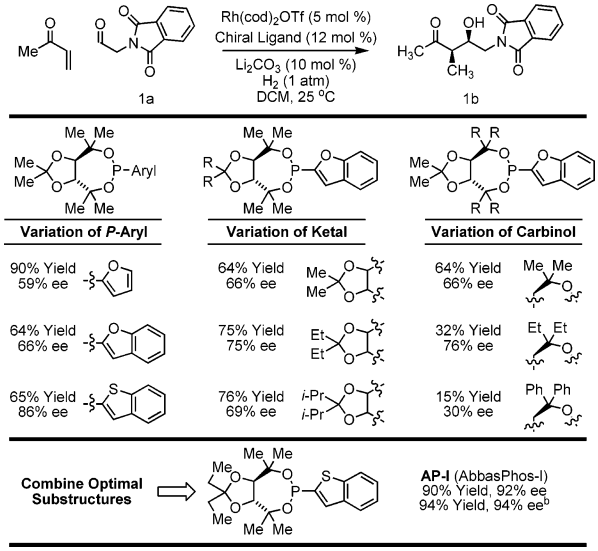
The reductive coupling of α,β-unsaturated carbonyl compounds to aldehydes and ketones, termed the "reductive aldol reaction", has become the topic of intensive investigation.[1] Following seminal studies by Revis (1987),[2a] catalysts for reductive aldol coupling based on rhodium,[2,3] cobalt,[4a−e] iridium,[4f] ruthenium,[4g] palladium,[4h] copper,[4i−p] nickel,[4q] and indium[4r,s] have been developed. Enantioselective variants of the reductive aldol coupling only have been achieved in connection with the use of α,β-unsaturated esters.[2d,h,j−m,4f,j,l,m−o] Enantioselective reductive aldol couplings of vinyl ketones, such as methyl vinyl ketone (MVK), would enable access to branched aldol adducts, providing a regiochemical complement to direct organocatalytic and metal catalyzed aldol couplings of nonsymmetric ketones, such as 2-butanone, which furnish linear aldol adducts.[5] *However, to date, enantioselective reductive aldol couplings of vinyl ketones have not been devised.*



In 2002, we reported that catalytic hydrogenation of vinyl ketones in the presence of aldehydes results in reductive aldol coupling to furnish branched aldol adducts as diastereomeric mixtures.[3a] Later (2006), it was found that high levels of *syn*-diastereoselectivity in hydrogen-mediated reductive aldol couplings of vinyl ketones are obtained through the use of tri-2-furylphosphine (Fur_3P) ligated rhodium catalysts.[3e−g,6] Efforts toward enantioselective variants of such hydrogenative aldol couplings were especially challenging due to the fact that (a) only trace quantities of product are obtained using chelating phosphine ligands, (b) π-acidic ligands such as Fur_3P are required to enforce high levels of diastereoselection,[6] yet (c) commercially available π-acidic chiral monodentate ligands, for example, BINOL-derived phosphites and phosphoramidites, are presumably too π-acidic and provide only trace quantities of product. Hence, the design, preparation and assay of novel chiral monodentate *P*-based ligands was undertaken.

Over a period of years numerous ligands were assayed, yet those displaying promising levels of asymmetric induction were not amenable to facile and systematic structural variation. Hence, a versatile template enabling well-defined structure-selectivity trends was sought. TADDOL-like phosphonites[7] present three structural elements that may be independently optimized: (a) the *P*-aryl moiety, (b) the ketal substructure, and (c) the groups appended to the tertiary carbinol center. In terms of enantioselectivity, the 2-benzothienyl moiety was best. The role of the ketal moiety was examined next. Here, improved selectivity is observed using the diethyl ketal. Finally, for substituents at the carbinol center, groups larger than the dimethyl carbinol moiety confer a substantial decrease in reactivity. Gratifyingly, using ligand **AP-I** ("AbbasPhos-I"), which combines the optimal 2- benzothienyl, diethyl ketal, and dimethyl carbinol substructures, aldehyde **1a** is transformed to the *syn*-aldol **1b** with exceptional levels of relative and absolute stereocontrol (Table 1).

Table 1. Key Results in the Optimization of Ligand Substructures in an Enantioselective Aldol Coupling of MVK to Aldehyde **1a**[a]



[a] Cited yields are of isolated material. Enantioselectivities were determined by chiral stationary phase HPLC analyses made in comparison to racemic diastereomeric mixtures, and ≥30:1 *syn*-diastereoselectivity was observed in each case. See Supporting Information for detailed experimental procedures. [b]Reaction was conducted at 0 °C.

The scope of ligand **AP-I** was examined in reductive aldol couplings of MVK and EVK to diverse aldehydes.[8] Optimal efficiencies and selectivities were observed using the preformed complex [Rh(cod)(**AP-I**)$_2$]OTf as a precatalyst. Beyond aldehydes **1a** and **2a**, β-heteroatom substituted aldehydes **3a**, **4a** and α-(hetero)aryl aldehydes **5a**, **6a**, and **7a** were found to engage in highly diastereo- and enantioselective hydrogenative aldol additions (Table 2).[9] Interestingly, using the first generation ligand **AP-I**, only moderate enantioselectivities were observed for aldehyde **4a**. Single-crystal X-ray diffraction analysis of [Rh(cod)(L)$_2$]OTf (L = the acetonide of **AP-I**) reveals a C_2-symmetric arrangement (Figure 1). Based upon the hypothesis that a similar metal−ligand arrangement is evident in the stereo-determining event, ligands **AP-II** and **AP-IV** were designed. For ligands **AP-II** and **AP-IV** the (benzo)-thiophene moiety is substituted such that the purported chiral pocket is deepened, potentially conferring heightened levels of enantioselection. The veracity of this analysis is supported by the fact that **AP-II** and **AP-IV** are both found to induce higher levels of optical enrichment, whereas **AP-III**, which projects the methyl residue into

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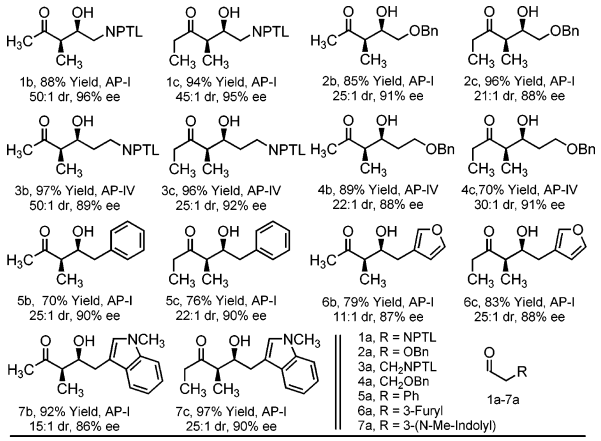
Table 2. Diastereo- and Enantioselective Aldol Coupling of MVK and EVK to Aldehydes **1a**−**7a**[a]



[a] Cited yields are of isolated material. Diastereo- and enantioselectivities were determined by chiral stationary phase HPLC analyses made in comparison to racemic diastereomeric mixtures.[8,9] All reactions were performed at 0 °C using the preformed complex [Rh(cod)(Ligand)$_2$]OTf and were reproduced a minimum of two times. See Supporting Information for detailed experimental procedures.

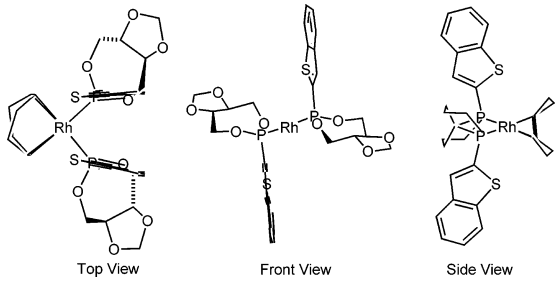
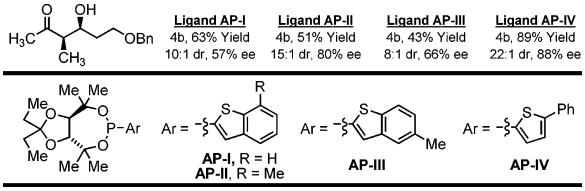


Figure 1. Structure of [Rh(cod)(L)$_2$]OTf (L = the acetonide of **AP-I**) determined by X-ray diffraction reveals C_2-symmetric arrangement. The figure graphics are depictions of crystallographic data imported into ChemDraw Ultra 9.0. For clarity, the following substructures were omitted. Top: The methyl groups and triflate ion. Front: The methyl groups, triflate ion, and COD. Side: The methyl groups, triflate ion, dioxolane rings, and phosphonite oxygen atoms.

Table 3. Effect of Ligands **AP-I**, **AP-II**, **AP-III**, and **AP-IV** in the Enantioselective Aldol Coupling of MVK to Aldehyde **4a**[a]



[a] As described in Table 2 footnotes.

an inactive volume of space, displays selectivities comparable to those of **AP-I** (Table 3).

In summary, we report the first enantioselective reductive aldol coupling of vinyl ketones, which were achieved through the design of an effective new class of TADDOL-like phosphonite ligands. This study further demonstrates that organometallics arising transiently in the course of catalytic hydrogenation offer a byproduct-free alternative to preformed organometallic reagents, for example enol(ate) derivatives, employed routinely in classical C=X (X = O, NR) addition processes.

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Supporting Information Available: Experimental procedures, spectral and HPLC data for new compounds, X-ray diffraction data for 5-bromophthalimido **1b**, the 2-bromo-5-nitrobenzoate of **3b**, and [Rh(cod)(L)$_2$]OTf. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) For an excellent review of the reductive aldol reaction, see: Nishiyama, H.; Shiomi, T. *Top. Curr. Chem.* **2007**, *279*, 105.

(2) For rhodium catalyzed reductive aldol reaction mediated by silane, see: (a) Revis, A.; Hilty, T. K. *Tetrahedron Lett.* **1987**, *28*, 4809. (b) Matsuda, I.; Takahashi, K.; Sato, S. *Tetrahedron Lett.* **1990**, *31*, 5331. (c) Taylor, S. J.; Morken, J. P. *J. Am. Chem. Soc.* **1999**, *121*, 12202. (d) Taylor, S. J.; Duffey, M. O.; Morken, J. P. *J. Am. Chem. Soc.* **2000**, *122*, 4528. (e) Zhao, C.-X.; Bass, J.; Morken, J. P. *Org. Lett.* **2001**, *3*, 2839. (f) Emiabata-Smith, D.; McKillop, A.; Mills, C.; Motherwell, W. B.; Whitehead, A. J. *Synlett*. **2001**, 1302. (g) Freiría, M.; Whitehead, A. J.; Tocher, D. A.; Motherwell, W. B. *Tetrahedron*. **2004**, *60*, 2673. (h) Nishiyama, H.; Shiomi, T.; Tsuchiya, Y.; Matsuda, I. *J. Am. Chem. Soc*. **2005**, *127*, 6972. (i) Willis, M. C.; Woodward, R. L. *J. Am. Chem. Soc*. **2005**, *127*, 18012. (j) Fuller, N. O.; Morken, J.P. *Synlett* **2005**, 1459. (k) Ito, J. I.; Shiomi, T.; Nishiyama, H. *Adv. Synth. Catal*. **2006**, *348*, 1235. (l) Shiomi, T.; Ito, J.-I.; Yamamoto, Y.; Nishiyama, H. *Eur. J. Org. Chem.* **2006**, 5594. (m) Shiomi, T.; Nishiyama, H. *Org. Lett.* **2007**, *9*, 1651.

(3) For rhodium catalyzed reductive aldol reaction mediated by hydrogen, see: (a) Jang, H. Y.; Huddleston, R. R.; Krische, M. J. *J. Am. Chem. Soc*. **2002**, *124*, 15156. (b) Huddleston, R. R.; Krische, M. J.; *Org. Lett*. **2003**, *5*, 1143. (c) Koech, P. K.; Krische, M. J. *Org. Lett*. **2004**, *6*, 691. (d) Marriner, G. A.; Garner, S. A.; Jang, H. Y.; Krische, M. J. *J. Org. Chem*. **2004**, *69*, 1380. (e) Jung, C. K.; Garner, S. A.; Krische, M. J. *Org. Lett*. **2006**, *8*, 519. (f) Han, S. B.; Krische, M. J. *Org. Lett*. **2006**, *8*, 5657. (g) Jung, C. K.; Krische, M, J. *J. Am. Chem. Soc.* **2006**, *128*, 17051.

(4) For catalytic reductive aldol couplings using other metals, see: (a) (Cobalt) Isayama, S.; Mukaiyama, T. *Chem. Lett.* **1989**, 2005. (b) Baik, T. G.; Luis, A. L.; Wang, L. C.; Krische, M. J. *J. Am. Chem. Soc.* **2001**, *123*, 5112. (c) Wang, L. C.; Jang, H.-Y.; Roh, Y.; Lynch, V.; Schultz, A. J.; Wang, X.; Krische, M. J. *J. Am. Chem. Soc.* **2002**, *124*, 9448. (d) Lam, H. W.; Joensuu, P. M.; Murray, G. J.; Fordyce, E. A. F.; Prieto, O.; Luebbers, T. *Org. Lett.* **2006**, *8*, 3729. (e) Lumby, R. J. R.; Joensuu, P. M.; Lam, H. W. *Org. Lett.* **2007**, *9*, 4367. (f) (Iridium) Zhao. C. X.; Duffey, M. O.; Taylor, S. J.; Morken, J. P. *Org. Lett.* **2001**, *3*, 1829. (g) (Ruthenium) Doi, T.; Fukuyama, T.; Minamino, S.; Ryu, I. *Synlett* **2006**, *18*, 3013. (Palladium) (h) Kiyooka, S. I.; Shimizu, A.; Torii, S. *Tetrahedron Lett.* **1998**, *39*, 5237. (Copper) (i) Ooi. T.; Doda, K.; Sakai, D.; Maruoka, K.; *Tetrahedron Lett.* **1999**, *40*, 2133. (j) Lam, H. W.; Joensuu, P. M. A. *Org. Lett*. **2005**, *7*, 4225. (k) Lam, H. W.; Murray, G. J.; Firth, J. D. *Org. Lett.* **2005**, *7*, 5743. (l) Deschamp, J.; Chuzel, O.; Hannedouche, J.; Riant, O. *Angew. Chem., Int. Ed*. **2006**, *45*, 1292. (m) Chuzel, O.; Deschamp, J.; Chauster, C.; Riant, O. *Org. Lett.* **2006**, *8*, 5943. (n) Zhao, D.; Oisaki, K.; Kanai, M.; Shibasaki, M. *Tetrahedron Lett.* **2006**, *47*, 1403. (o) Zhao, D.; Oisaki, K.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc*. **2006**, *128*, 14440. (p) Welle, A.; Diez-Gonzalez, S.; Tinant, B.; Nolan, S. P.; Riant, O. *Org. Lett.* **2006**, *8*, 6059. (q) Nickel: Chrovian, C. C.; Montgomery, J. *Org. Lett.* **2007**, *9*, 537. (Indium) (r) Shibata, I.; Kato, H.; Ishida, T.; Yasuda, M.; Baba, A. *Angew. Chem., Int. Ed*. **2004**, *43*, 711. (s) Miura, K.; Yamada, Y.; Tomita, M.; Hosomi, A. *Synlett* **2004**, 1985.

(5) (a) Yoshikawa, N.; Yamada, Y. M. A.; Das, J.; Sasai, H.; Shibasaki, M. *J. Am. Chem. Soc.* **1999**, *121*, 4168. (b) Sakthivel, K.; Notz, W.; Bui, T.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2001**, *123*, 5260. (c) Other organocatalysts for direct aldol coupling of 2-butanone generally provide mixtures of regioisomers: Tang, Z.; Yang, Z.-H.; Chen, X.-H.; Cun, L.-F.; Mi, A.-Q.; Jiang, Y.-Z.; Gong, L.-Z. *J. Am. Chem. Soc.* **2005**, *127*, 9285. (d) Luo, S.; Xu, H.; Li, J.; Zhang, L.; Cheng, J.-P. *J. Am. Chem. Soc.* **2007**, *129*, 3074.

(6) For Fur_3P effects in metal catalysis, see: (a) Farina, V.; Krishnan, B. *J. Am. Chem. Soc.* **1991**, *113*, 9585. (b) Farina, V. *Pure Appl. Chem.* **1996**, *68*, 73. (c) Anderson, N. G.; Keay, B. A. *Chem. Rev.* **2001**, *101*, 997.

(7) For TADDOL-derived phosphonites, see: (a) Seebach, D.; Hayakawa, M.; Sakaki, J.-I.; Schweizer, W. B. *Tetrahedron* **1993**, *49*, 1711. (b) Sakaki, J.-I.; Schweizer, W. B.; Seebach, D. *Helv. Chim. Acta* **1993**, *76*, 2654. (c) Haag, D.; Runsink, J.; Scharf, H.-D. *Organometallics* **1998**, *17*, 398.

(8) Aromatic aldehydes display good reactivity and diastereoselectivity, but poor enantioselectivities are observed. Additionally, unactivated aliphatic aldehydes exhibit poor reactivity, providing diminished yields of product. Studies aimed at addressing these deficiencies are in progress.

(9) The absolute stereochemical assignments of the aldol adducts are made in analogy to that determined for the 5-bromophthalimido derivative of aldol adduct **1b** and the 2-bromo-5-nitrobenzoate of **3b**, which were established by single crystal X-ray diffraction analysis using the anomalous dispersion method.

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