Published in final edited form as:
J Am Chem Soc. 2008 March 5; 130(9): 2746–2747. doi:10.1021/ja710862u.

Diastereo- and Enantioselective Hydrogenative Aldol Coupling of Vinyl Ketones: Design of an Effective Monodentate TADDOL-Based Phosphonite Ligand

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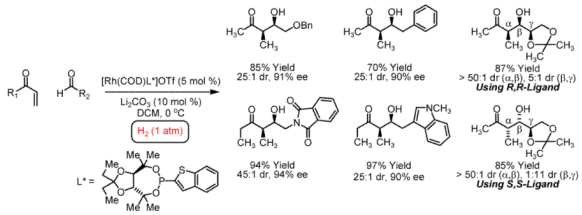
Abstract



We report the first enantioselective reductive aldol couplings of vinyl ketones, which required the design of a novel monodentate TADDOL-based phosphonite ligand. Specifically, hydrogenation of commercially available methyl vinyl ketone (MVK) or ethyl vinyl ketone (EVK) in the presence of aldehydes using chirally modified cationic rhodium catalysts produces aldol adducts **1b-7b** and **1c-7c** with excellent levels of diastereo- and enantiocontrol. Through the use of (*R*,*R*)-ligand or (*S*,*S*)-ligand good levels of catalyst-directed diastereofacial selectivity are achieved in hydrogenative aldol couplings of MVK and EVK to glyceraldehyde acetonide, as demonstrated by the formation of aldol adducts **6b**, **6c**, **7b**, and **7c**. The absolute stereochemical assignment of adducts **1b-5b** and **1c-5c** was made in analogy to that determined for the 5-bromophthalimido derivative of aldol adduct **2b**, which was established by single crystal x-ray diffraction analysis using the anomalous dispersion method. A structure of the catalyst ligand complex [Rh(COD)(Ligand-Q)$_2$]OTf has been established by single crystal x-ray crystal, as reported in the supporting information.

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,4 iridium,[5] ruthenium,[6] palladium,[7] copper,[8,9] nickel,[10] and indium[11,12] 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,5,9b,d,e,f,g 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 non-symmetric ketones, such as 2-butanone, which furnish linear aldol adducts.[13] However, to date, enantioselective reductive aldol couplings of vinyl ketones have not been devised.

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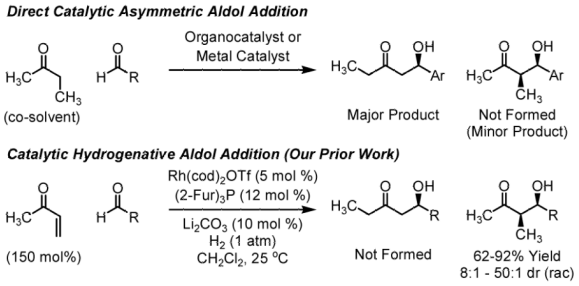
Supporting information available: Experimental procedures, spectral and HPLC data for new compounds, x-ray diffraction data for 5-bromophthalimido **2b** and [Rh(COD)(Ligand-Q)$_2$]OTf. This material is available free of charge *via* the internet at http://pubs.acs.org.



In 2002, we reported that rhodium catalyzed 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,f,g,[14] 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, 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.

Representative ligands are depicted in Table 1. BINOL-derived phosphonites **A-D**, menthone-based ligands **E-H**, the C_2-symmetric cyclopentanol ligand **I**, and ligands **J** and **K**, which incorporate chiral ketals, enforce poor levels of asymmetric induction. In order to establish well-defined structure- selectivity trends, a versatile template amenable to systematic structural variation was sought. Toward this end, TADDOL-based phosphonites were examined. Tetramethyl- TADDOL acetonide was transformed to *P*-aryl phosphonites **L-Q**. The 2-benzothienyl moiety, as found in ligand **Q**, was identified as the optimum *P*-aryl substituent. Attempts to further optimize ligand architecture using *P*-(2-benzofuryl) derivatives reveals a substantial decrease in reactivity for the tetraethyl and tetraphenyl ligands **R** and **S**. The role of the ketal moiety was examined next. For *P*-(2-benzofuryl) phosphonites ligand **T**, which incorporates a diethyl ketal, an improvement in selectivity is observed. Using ligand **W**, which combines the optimal 2-benzothienyl and diethyl ketal substructures, aldehydes **1a** and **2a** are transformed to aldols **1b** and **2b** with exceptional relative and absolute stereocontrol.

The scope of ligand **W** was examined in reductive aldol couplings of MVK and EVK to diverse aldehydes. Optimal efficiencies and selectivities were observed using the preformed complex [Rh(COD)(Ligand-W)$_2$]OTf as precatalyst. Beyond aldehydes **1a** and **2a**, which possess heteroatom substitution at the α-position, α-aryl aldehydes **3b**, **4b**, and **5b** were found to engage in highly diastereo- and enantioselective hydrogenative aldol additions. Using chiral ligand **W**, aromatic aldehydes display good reactivity and diastereoselectivity, but are not subject to high levels of asymmetric induction. Additionally, unactivated aliphatic aldehydes provide diminished yields of product. The absolute stereochemical assignment of aldol adducts **1b-5b** and **1c-5c** was made in analogy to that determined for the 5-bromophthalimido derivative of aldol adduct **2b**, which was established by single crystal x-ray diffraction analysis using the anomalous dispersion method. Finally, catalyst-directed diastereofacial selectivity was investigated in the reductive aldol coupling of MVK and EVK to *R*-glyceraldehyde acetonide. As demonstrated by the formation of adducts **6b**, **6c**, **7b** and **7c**, through the use of (*R*,*R*)-ligand **W** or (*S*,*S*)-ligand **W**, one may invert the

diastereofacial preference in the aldol addition while maintaining exceptional levels of *syn*-aldol selectivity (Table 2).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Acknowledgment is made to the Robert A. Welch Foundation, Johnson & Johnson, Merck, the NIH-NIGMS (RO1-GM069445) and the Higher Education Commission, Pakistan for partial support of this research. Adam Berro and Quan Truong are acknowledged for assisting ligand preparation.

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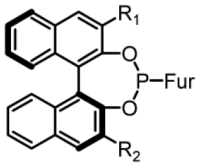
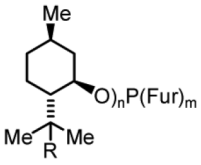
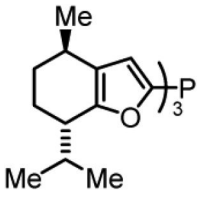
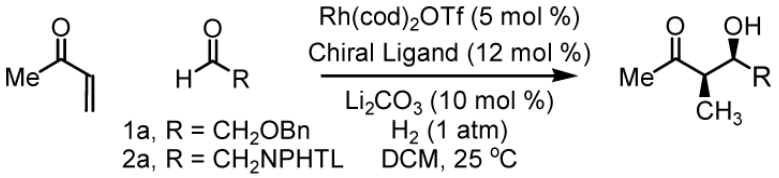
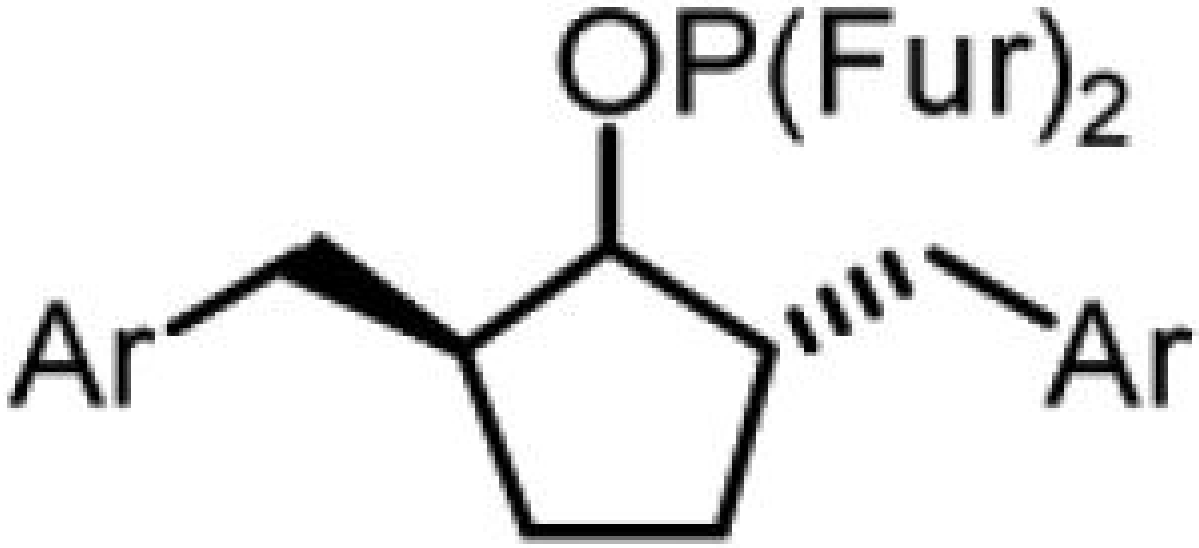
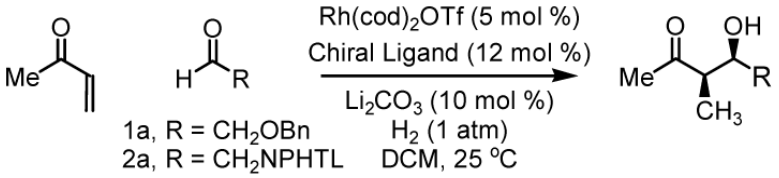
Table 1

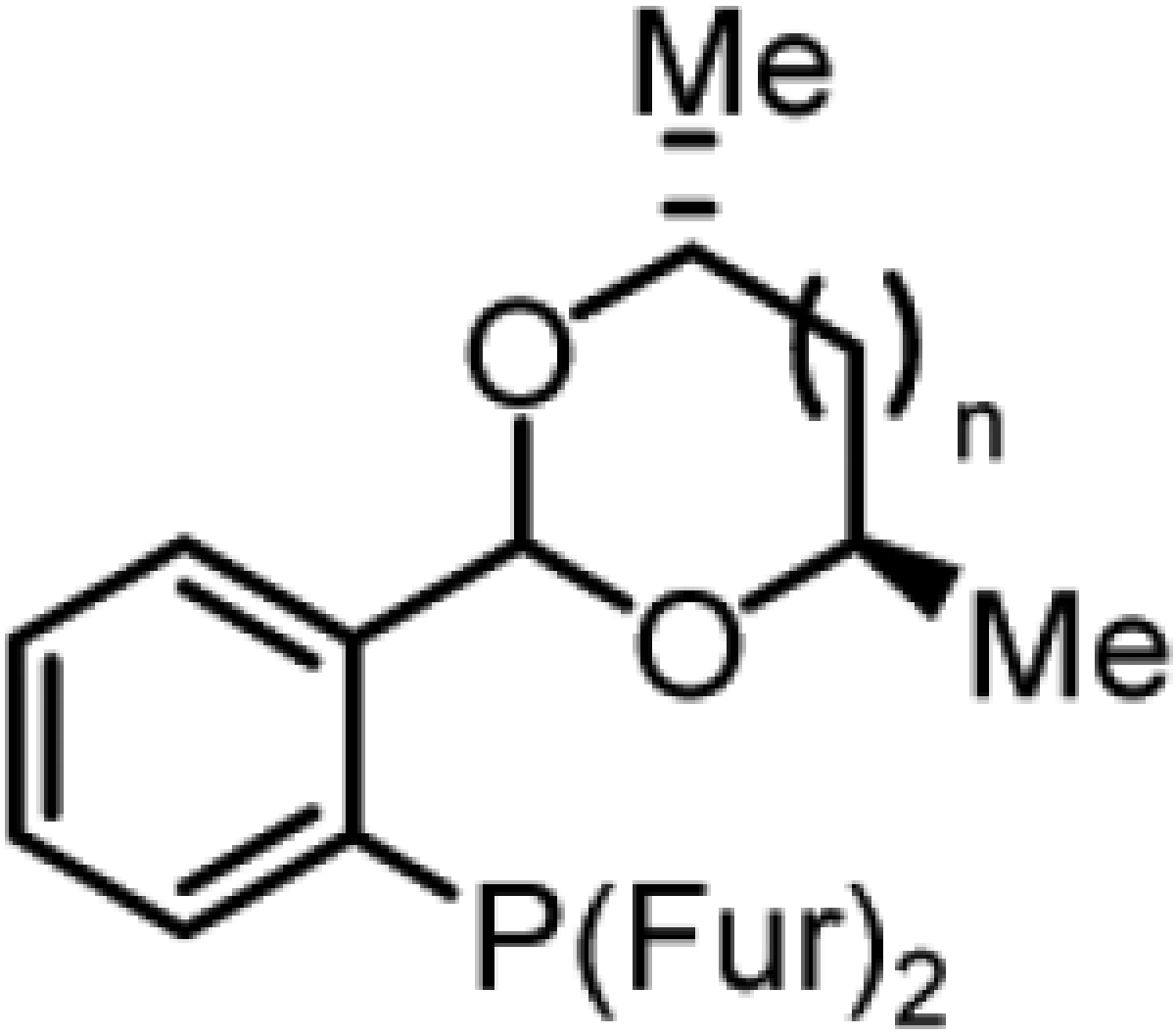
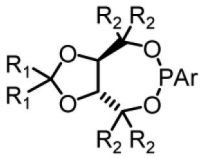
Optimization of chiral ligand in the enantioselective hydrogenative aldol coupling of MVK[a]

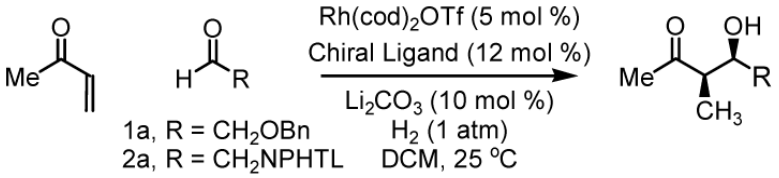
Ligand	RCHO	Yield (dr)
		
A, R_1 = R_2 = H	1a	83 (9:1)
B, R_1 = H, R_2 = Me	1a	79 (8:1)
C, R_1 = Me, R_2 = Me	1a	trace (---)
D, R_1 = H, R_2 = Ph	1a	50 (3:1)
		
E, R = H, n = 1, m = 2	1a	80 (8:1)
F, R = H, n = 2, m = 1	1a	60 (11:1)
G, R = Ph, n = 1, m = 2	1a	71 (17:1)
		
H	1a	42 (8:1)



Ligand	RCHO	Yield (dr)
	1a	48 (5:1)
I, Ar = mesityl		



Ligand	RCHO	Yield (dr)
		
J, n = 0	1a	52 (9:1)
K, n = 1	1a	40 (4:1)
		
L, R_1 = R_2 = Me, Ar = 2-Fur	1a	76 (12:1)



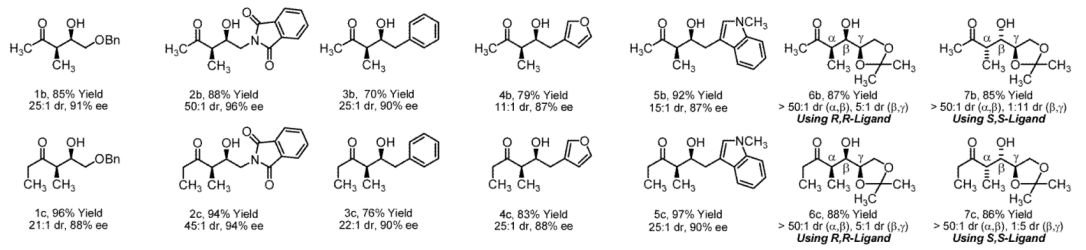
Ligand	RCHO	Yield (dr)
L, R_1 = R_2 = Me, Ar = 2-Fur	2a	90 (>30:1)
M, R_1 = R_2 = Me, Ar = Ph	2a	20 (>30:1)
N, R_1 = R_2 = Me, Ar = 1-[3,5-$(CF_3)_2$Ph]	2a	30 (>30:1)
O, R_1 = R_2 = Me, Ar = 2-[5-Me-Fur]	2a	52 (>30:1)
P, R_1 = R_2 = Me, Ar = 2-Benzofuryl	2a	64 (>30:1)
Q, R_1 = R_2 = Me, Ar = 2-Benzothienyl	2a	65 (>30:1)
R, R_1 = Me, R_2 = Et, Ar = 2-Benzofuryl	2a	32 (>30:1)
S, R_1 = Me, R_2 = Ph, Ar = 2-Benzofuryl	2a	15 (>30:1)
T, R_1 = Et, R_2 = Me, Ar = 2-Benzofuryl	2a	75 (>30:1)
U, R_1 = $(CH_2)_5$, R_2 = Me, Ar = 2-Benzofuryl	2a	90 (>30:1)
V, R_1 = *i*-Pr, R_2 = Me, Ar = 2-Benzofuryl	2a	76 (>30:1)
W, R_1 = Et, R_2 = Me, Ar = 2-Benzothienyl	**2a**	**90 (>30:1)**
W, R_1 = Et, R_2 = Me, Ar = 2-Benzothienyl	**2a**	**94 (>30:1)**
W, R_1 = Et, R_2 = Me, Ar = 2-Benzothienyl	**1a**	**91 (11:1)**
W, R_1 = Et, R_2 = Me, Ar = 2-Benzothienyl	**1a**	**85 (25:1)**

[a]Cited yields are of isolated material. Enantioselectivities were determined by chiral stationary phase HPLC analyses made in comparison to racemic diastereomeric mixtures prepared *via* hydrogenation of the corresponding Morita-Baylis-Hillman adducts. See Supporting Information for detailed experimental procedures.

[b]Reaction was conducted at 0 °C.

Table 2

Diastereo- and enantioselective reductive aldol coupling of MVK and EVK to assorted aldehydes using ligand-**W**[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 prepared *via* hydrogenation of the corresponding Morita-Baylis-Hillman adducts. All reactions were performed at 0 °C using the preformed complex [Rh(COD)(Ligand-W)$_2$]OTf. See Supporting Information for detailed experimental procedures.