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Hydrogen-Mediated Aldol Reductive Coupling of Vinyl Ketones Catalyzed by Rhodium: High *Syn*-Selectivity through the Effect of Tri-2-furylphosphine

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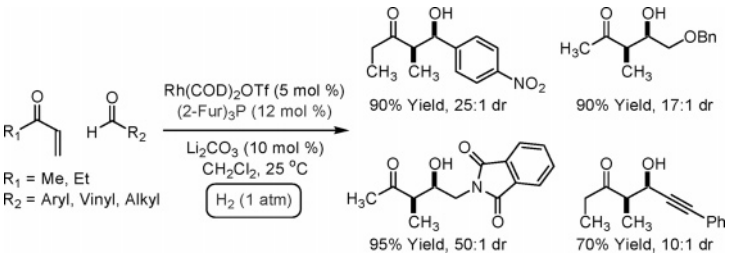
ABSTRACT



Catalytic hydrogenation of methyl vinyl ketone (MVK) and ethyl vinyl ketone (EVK) in the presence of diverse aldehydes at ambient temperature and pressure using tri-2-furylphosphine-ligated rhodium catalysts enables formation of aldol products with high levels of *syn*-diastereoselectivity. A progressive increase in diastereoselectivity is observed upon sequential replacement of phenyl residues for 2-furyl residues (Ph_3P, $FurPh_2P$, Fur_2PhP, Fur_3P). Hydrogen-labile functional groups, including alkynes, alkenes, benzylic ethers, and nitroarenes, remain intact under the coupling conditions.

The aldol reaction has been known for over a century.[1] Stimulated by the observation that *Z*- and *E*-enolates may react stereospecifically to provide *syn*- and *anti*-addition products,[2] several catalyzed aldol additions have been developed that address relative and absolute stereocontrol.[3] Much less attention has been devoted to catalytic systems that attend to regio- and stereoselective *enolization* in aldol additions involving ketones as nucleophilic partners.[4] As first demonstrated by Stork, regiospecific enolate formation may be achieved through stoichiometric enone reduction,[5] enabling generation of enolate isomers that cannot be formed exclusively through acid−base-mediated enolization. Subsequently, the direct metal-catalyzed reductive coupling of enones to aldehydes was achieved, termed the "reductive aldol reaction."[6] To date, catalysts for reductive aldol coupling based on cobalt,[7] rhodium,[8,9] iridium,[10a] palladium,[10b] copper,[10c,d] and indium[10e] have been reported. In two cases,

(1) Though largely attributed to Würtz, the aldol reaction was reported first by Borodin: (a) von Richter, V. *Ber. Deut. Chem. Ges.* **1869**, *2*, 552 (Borodin's earliest results are cited in this article). (b) Würtz, A. *Bull. Soc. Chim. Fr.* **1872**, *17*, 436.

(2) (a) Dubois, J.-E.; Dubois, M. *Tetrahedron Lett.* **1967**, *8*, 4215. (b) Dubois, J.-E.; Fort, J.-F. *Tetrahedron* **1972**, *28*, 1653. (c) Dubois, J.-E.; Fort, J.-F. *Tetrahedron* **1972**, *28*, 1665.

(3) For selected reviews on stereoselective aldol additions, see: (a) Heathcock, C. H. *Science* **1981**, *214*, 395. (b) Heathcock, C. H. *ACS Symp. Ser.* **1982**, *185*, 55. (c) Evans, D. A.; Nelson, J. V.; Taber, T. R. *Top. Stereochem.* **1982**, *13*, 1. (d) Machajewski, T. D.; Wong, C.-H. *Angew. Chem., Int. Ed.* **2000**, *39*, 1352. (e) Palomo, C.; Oiarbide, M.; García, J. M. *Chem. Soc. Rev.* **2004**, *33*, 65.

(4) A classical example of the subtle factors governing regioselective enolization of nonsymmetric ketones involves the deprotonation of steroidal ketones. Whereas cholesteran-3-one exhibits a thermodynamic preference for formation of the Δ_3-enolate, with little kinetic selectivity for formation of Δ_2-enolate, introduction of 7,8-unsaturation results in a thermodynamic preference for formation of the Δ_2-enolate, with little kinetic selectivity for formation of Δ_3-enolate. (a) Velluz, L.; Valls, J.; Nomine, G. *Angew. Chem., Int. Ed. Engl.* **1965**, *4*, 181. (b) Corey, E. J.; Sneen, R. A. *J. Am. Chem. Soc.* **1955**, *77*, 2505. (c) Berkoz, B.; Chavez, E. P.; Djerassi, C. *J. Chem. Soc.* **1962**, 1323. (d) Mazur, Y.; Sondheimer, F. *J. Am. Chem. Soc.* **1958**, *80*, 6296.

(5) Stork, G.; Rosen, P.; Goldman, N. L. *J. Am. Chem. Soc.* **1961**, *83*, 2965. (b) Stork, G.; Rosen, P.; Goldman, N.; Coombs, R. V.; Tsuji, J. *J. Am. Chem. Soc.* **1965**, *87*, 275.

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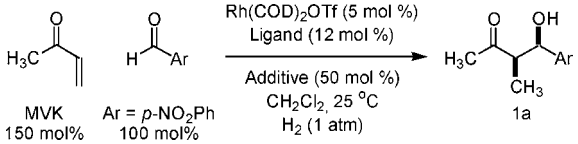
wherein acrylates are used as nucleophilic partners and hydrosilanes serve as terminal reductant, diastereo- and enantioselective aldolization has been achieved.[8c,d,h]

Here, using *elemental hydrogen* as terminal reductant, we disclose the first highly diastereoselective reductive aldol couplings of *vinyl ketones*, which are achieved by virtue of the unique properties of tri-2-furylphosphine.[11] Specifically, hydrogenation of methyl or ethyl vinyl ketone (MVK or EVK) in the presence of structurally diverse aldehydes using tri-2-furylphosphine-modified rhodium catalysts results in reductive coupling to afford aldol products with exceptionally high levels of *syn*-diastereoselection. Notably, the diastereoselectivities observed in the present hydrogen-mediated aldol additions, which are conducted at ambient temperature and pressure, are comparable to and in many instances rival those observed in related low-temperature aldol additions of preformed lithium enolates.[3a−c,12]

It was reasoned that a diastereoselective variant of the rhodium-catalyzed hydrogen-mediated reductive aldol coupling[9a] might be attained through use of the weakly coordinating, π-acidic ligand tri-2-furylphosphine.[11] This ligand may render the rhodium center more Lewis acidic by virtue of its π-acidity, thus conferring heightened levels of stereocontrol by "tightening" the Zimmerman−Traxler-type transition structure.[3] Alternatively, Fur_3P may dissociate to promote formation of enolate haptomers that embody enyl ($\sigma + \pi$) character, which may influence the stereochemical outcome of addition (vide supra).[13] In the event, whereas poor diastereoselectivity is observed in the reductive coupling of MVK with *p*-nitrobenzaldehyde using triphenylphosphine as ligand (Table 1, entry 1), the use of tri-2-furylphosphine under otherwise identical conditions provides the aldol product **1a** in 74% yield with a remarkable 19:1 *syn*/*anti* ratio (Table 1, entry 4). Systematic replacement of phenyl moieties with 2-furyl residues (Ph_3P, $FurPh_2P$, Fur_2PhP, Fur_3P) results in a progressive increase in yield and stereoselectivity (Table 1, entries 1−4). In the absence of Li_2CO_3, coupling performed with the tri-2-furylphosphine ligated rhodium catalyst retains the 19:1 *syn*/*anti* ratio (Table 1, entry 6), revealing the tri-2-furylphosphine effect does not involve transmetalation to lithium. Indeed, the weakly coordinating, π-acidic ligand triphenylarsine also promotes enhanced stereocontrol (Table 1, entry 5). Finally, it was found that a modest increase in concentration enables acquisition of **1a** in 91% yield with a 16:1 *syn*/*anti* ratio at only 10 mol % loadings of Li_2CO_3 (Table 1, entries 7 and 8).

Table 1. Optimization of the Diastereoselective Hydrogen-Mediated Reductive Aldol Coupling To Afford **1a**[a,b]



entry	ligand	additive	[DCM], M	yield, %	dr
1	PPh_3	Li_2CO_3	0.1	31	3:1
2	$(2\text{-Fur})Ph_2P$	Li_2CO_3	0.1	24	6:1
3	$(2\text{-Fur})_2PhP$	Li_2CO_3	0.1	52	15:1
4	$(2\text{-Fur})_3P$	Li_2CO_3	0.1	74	19:1
5	$AsPh_3$	Li_2CO_3	0.1	17	7:1
6	$(2\text{-Fur})_3P$		0.1	63	19:1
7	$(2\text{-Fur})_3P$	Li_2CO_3	0.3	88	16:1
→ 8	**$(2\text{-Fur})_3P$**	**Li_2CO_3 (10%)**	**0.3**	**91**	**16:1**

[a] **Optimized Procedure.** To a 13 mm × 100 mm test tube charged with Li_2CO_3 (5 mg, 0.066 mmol, 10 mol %), Fur_3P (18 mg, 0.079 mmol, 12 mol %), $Rh(COD)_2OTf$ (16 mg, 0.033 mmol, 5 mol %), and aldehyde (100 mg, 0.66 mmol, 100 mol %) was added dichloromethane (1.0 M). The test tube was sealed, and the reaction mixture was sparged with Ar(g) followed by H_2(g) for 20 s each. The reaction was placed under one atmosphere of hydrogen using a balloon, and MVK (81 μL, 0.99 mmol, 150 mol %) was added. The reaction mixture was allowed to stir until consumption of aldehyde was observed, as revealed by TLC analysis. The reaction mixture was evaporated onto silica, and the aldol product **1a** was isolated by flash chromatography (SiO_2: EtOAc/hexane). [b] The cited yields are of isolated material and represent the average of two runs.

Using commercially available MVK and EVK as pronucleophiles, these optimized conditions were applied across a diverse set of aldehydes. High levels of *syn*-diastereoselection were observed using aromatic aldehydes, α,β-unsaturated aldehydes, acetylenic aldehydes, and aliphatic aldehydes. Aldol additions involving EVK occur with higher levels of diastereoselection, presumably due to an enhanced kinetic and thermodynamic preference for formation of the

(6) For reviews encompassing catalytic reductive aldol coupling, see: (a) Motherwell, W. B. *Pure Appl. Chem.* **2002**, *74*, 135. (b) Huddleston, R. R.; Krische, M. J. *Synlett* **2003**, 12. (c) Jang, H.-Y.; Huddleston, R. R.; Krische, M. J. *Chemtracts* **2003**, *16*, 554. (d) Jang, H.-Y.; Krische, M. J. *Eur. J. Org. Chem.* **2004**, 3953. (e) Jang, H.-Y.; Krische, M. J. *Acc. Chem. Res.* **2004**, *37*, 653. (f) Chiu, P. *Synthesis* **2004**, 2210.

(7) For cobalt catalyzed reductive aldol couplings, see: (a) 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.

(8) For rhodium catalyzed reductive aldol couplings mediated by silane, see: (a) Revis, A.; Hilty, T. K. *Tetrahedron Lett.* **1987**, *28*, 4809. (b) Matsuda, I.; Takahashi, K.; Sata, 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) Emiabata-Smith, D.; McKillop, A.; Mills, C.; Motherwell, W. B.; Whitehead, A. J. *Synlett* **2001**, 1302. (f) Freiría, M.; Whitehead, A. J.; Tocher, D. A.; Motherwell, W. B. *Tetrahedron* **2004**, *60*, 2673. (g) Fuller, N. O.; Morken, J. P. *Synlett* **2005**, 1459. (h) Nishiyama, H.; Siomi, T.; Tsuchiya, Y.; Matsuda, I. *J. Am. Chem. Soc.* **2005**, *127*, 6972.

(9) For rhodium catalyzed reductive aldol couplings 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.

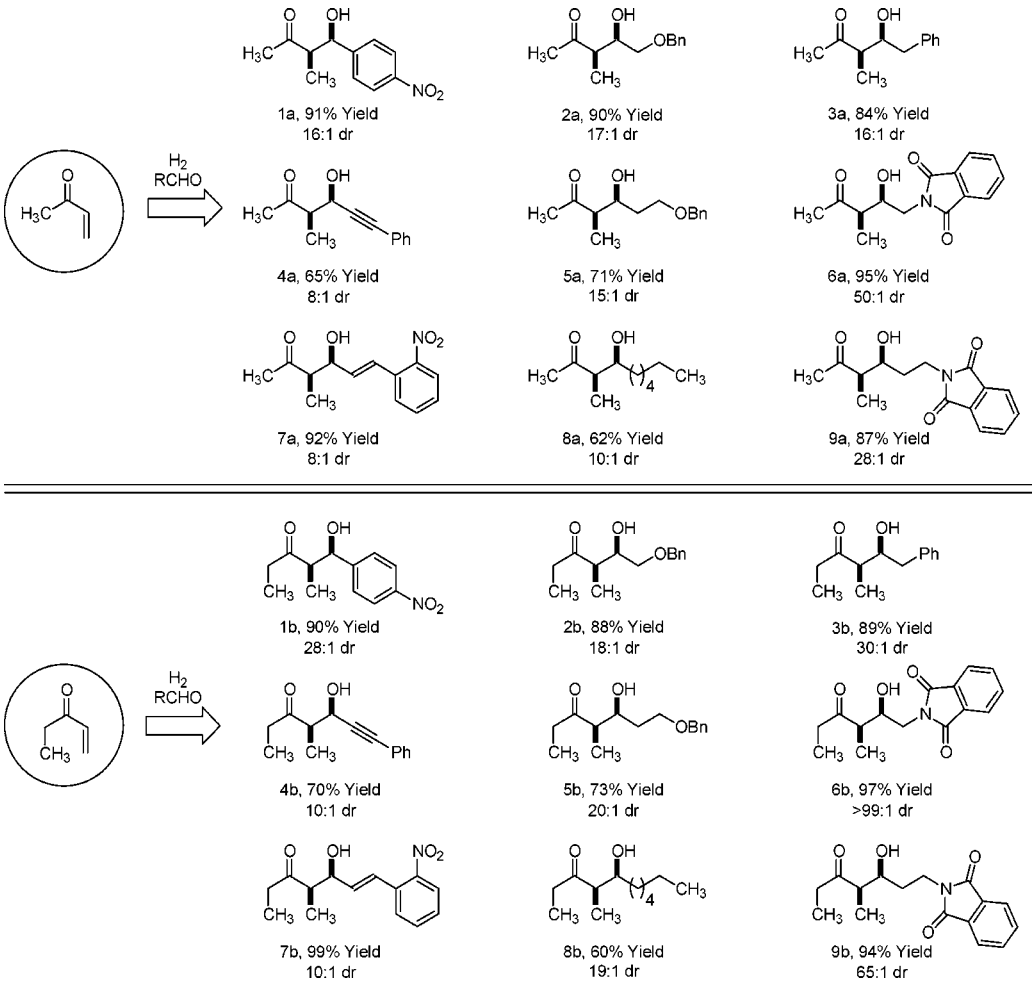
(10) For reductive aldol couplings catalyzed by other metals, see the following references. (a) Iridium: Zhao, C.-X.; Duffey, M. O.; Taylor, S. J.; Morken, J. P. *Org. Lett.* **2001**, *3*, 1829. (b) Palladium: Kiyooka, S.; Shimizu, A.; Torii, S. *Tetrahedron Lett.* **1998**, *39*, 5237. (c) Copper: Ooi, T.; Doda, K.; Sakai, D.; Maruoka, K. *Tetrahedron Lett.* **1999**, *40*, 2133. (d) Lam, H.-W.; Joensuu, P. M. *Org. Lett.* **2005**, *7*, 4225. (e) Indium: Miura, K.; Yamada, Y.; Tomita, M.; Hosomi, A. *Synlett* **2004**, 1985.

(11) (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.

(12) As a point of reference, the lithium *Z*(O)-enolate of 3-pentanone aldolizes with benzaldehyde under kinetically controlled conditions to provide a 9:1 *syn*/*anti*-ratio. Upon equilibration, a 44:56 *syn*/*anti* ratio results. For further examples, see ref 3a−c.

(13) Evans, P. A.; Nelson, J. D. *J. Am. Chem. Soc.* **1998**, *120*, 5581 and references therein.

Table 2. Diastereoselective Hydrogen-Mediated Reductive Aldol Coupling of MVK/EVK to Assorted Aldehydes[a−c]



[a] Reductive couplings were performed at ambient temperature and pressure in 13 × 100 mL test tubes in accordance with the procedure described in Table 1. The following transformations employed slightly different conditions. For aldols **1a**,**b**, the reaction was conducted at 0.3 M concentration using 150 mol % of enone. For entries **2a**,**b**, **3a**,**b**, **5a**,**b**−**7a**,**b**, and **9a**,**b**, the reaction was conducted at 1.0 M concentration using 300 mol % of enone. For compounds **4a**,**b**, the reaction was conducted using 4 mol % of Li_2CO_3, 4.8 mol % of Fur_3P, 2 mol % of $Rh(COD)_2OTf$, and 500 mol % of enone. Finally, for entry **8a**,**b**, the reaction was conducted using 20 mol % of Li_2CO_3, 24 mol % of Fur_3P, and 10 mol % of $Rh(COD)_2OTf$. [b] The cited yields are of isolated material and represent the average of two runs. [c] Diastereomeric ratios were established by ^1H NMR or HPLC analysis.

Z(*O*)-enolate due to increased $A_{1,2}$-strain. Additionally, for lithium *Z*(*O*)-enolates, it has been observed that diastereoselection increases with increasing size of the acyl substituent.[3] The chemoselectivity of this catalytic system is underscored by the formation of **7a**,**b** and **4a**,**b**, which embody alkene and alkyne functionality, yet are not subject to "over-hydrogenation" under the reductive coupling conditions. Further, hydrogen labile functional groups such as benzylic ethers and nitroarenes remain intact, as demonstrated by the formation of **2ab**/**5ab** and **1ab**/**7ab**, respectively (Table 2).

It is well established that additions of *Z*(O)-enolates to α-chiral aldehydes proceeding through Zimmerman−Traxler-type transition structures may exhibit *anti*-Felkin-Anh selectivity, thus avoiding *syn*-pentane interactions evident in the alternate Felkin-Anh mode of approach.[14] Hence, it is noteworthy that the hydrogen-mediated coupling to form **10a** occurs with a distinct *anti*-Felkin preference accompanied by high levels of *syn*-diastereoselection.[15] While chelation controlled addition cannot be ruled out, this result does suggest intervention of *Z*(O)-enolates and Zimmerman−Traxler-type transition structures in the present rhodium catalyzed reductive aldol additions (Scheme 1).

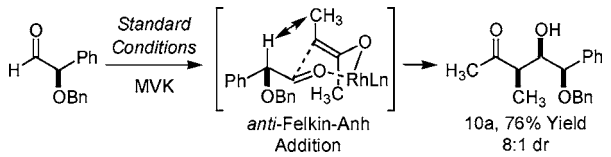
The collective results suggest the following features of the catalytic mechanism: (a) high kinetic selectivity for *Z*(*O*)-enolate formation, likely by means of internal hydride delivery to the enone *s-cis* conformer,[16] (b) high kinetic selectivity for *syn*-aldolization through addition of the *Z*-

(14) Roush, W. R. *J. Org. Chem.* **1991**, *56*, 4151.

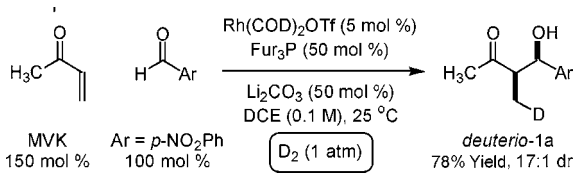
(15) The stereochemical assignment of **10a** is based upon single crystal X-ray diffraction analysis of the corresponding 3,5-dinitrobenzoate. The 8:1 diastereomeric ratio refers to the major isomer versus all other isomers combined.

(16) Enones constrained in the *s-trans* configuration, such as cyclohexenone, do not participate in reductive coupling.

Scheme 1. Diastereoselective Addition of MVK to an α-Chiral Aldehyde



Scheme 2. Reductive Coupling under a Deuterium Atmosphere[a]



(O)-enolate to the aldehyde through a Zimmerman−Traxler-type transition structure, and (c) preservation of kinetic *syn*-selectivity via irreversible enolization and aldolization.[17] The dissociation of Fur_3P to form enolate haptomers that embody enyl ($\sigma + \pi$) character may assist in preserving the kinetic selectivity of enolization by retarding haptomeric equilibria, as observed in related regio- and stereoretentive rhodium catalyzed allylic substitutions.[13]

To gain further insight into the reaction mechanism, the reductive coupling of MVK and *p*-nitrobenzaldehyde was performed using elemental deuterium. The coupling product *deuterio*-**1a** incorporates a single deuterium atom at the former enone β-position. Deuterium incorporation at the α-carbon of the product is not observed, excluding Morita−Baylis−Hillman pathways en route to product. The strict incorporation of a single deuterium atom is consistent with irreversible enolization via enone hydrometalation (Scheme 2).

More than half of the chiral compounds produced industrially from prochiral substrates are made via asymmetric hydrogenation. This suggests an equally powerful approach to *reductive C−C bond formation* mediated by elemental hydrogen. Inspired by this prospect, hydrogen-mediated C−C bond formation has become the focus of research in our laboratory.[6e,9] The present hydrogen-mediated couplings represent the first diastereoselective reductive aldol additions involving vinyl ketones and provide regio- and stereoselectivities rivaling those obtained through the low-temperature reaction of preformed lithium enolates. Future studies will focus on the development of enantioselective variants of the transformations reported herein and the discovery of new "C−C bond forming hydrogenations".

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Supporting Information Available: Spectral data for all new compounds, including single-crystal X-ray diffraction data for **6a** and the dinitrobenzoate of **10a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(17) High levels of diastereoselectivity do not preclude reversible aldolization, provided aldolization proceeds with sufficiently high levels of kinetic stereoselectivity.