ORGANIC LETTERS

2006
Vol. 8, No. 24
5657−5660

Reductive Aldol Coupling of Divinyl Ketones via Rhodium-Catalyzed Hydrogenation: *syn*-Diastereoselective Construction of *β*-Hydroxyenones

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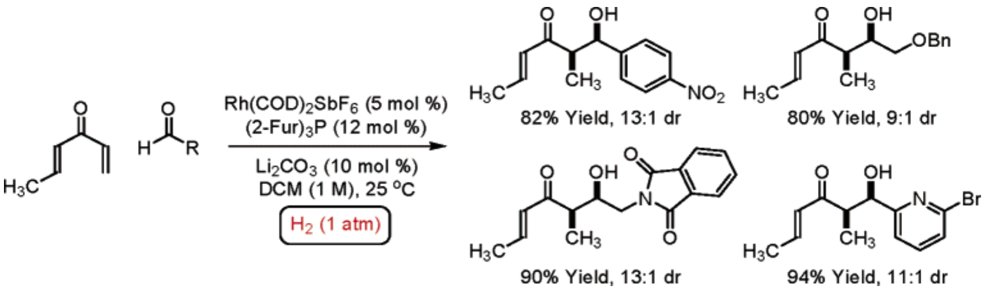
Received September 29, 2006

ABSTRACT



Catalytic hydrogenation of divinyl ketones 1a and 1e in the presence of diverse aldehydes 2a–e at ambient temperature and pressure using cationic rhodium catalysts ligated by tri-2-furyl phosphine enables formation of aldol products 3a–e and 5a–e, respectively, with high levels of syn diastereoselection. Through an assay of counterions ($Rh(COD)_2X$), $Rh(COD)_2SbF_6$ is identified as the optimum precatalyst for reductive aldol couplings of this type. For para-substituted styryl vinyl ketones 1b–e, a progressive increase in isolated yield is observed for electron-releasing para substituents.

Following seminal studies by Revis (1987),[1a] the catalytic reductive coupling of α,*β*-unsaturated carbonyl compounds and aldehydes to form aldol products, termed the “reductive aldol reaction”, has been the subject of intensive investigation. To date, catalysts for reductive aldol coupling based on rhodium,[1,2] cobalt,[3] iridium,[4a] palladium,[4b] copper,[4c−g] and indium[4h] have been described. Further, highly diastereo-[1c,2e,3b−d,4e,h,i] and enantioselective[1d,g,h,4a,f,g] variants have been achieved.

The majority of catalytic systems for reductive aldol coupling employs acrylate pronucleophiles in combination with hydrosilanes as the terminal reductant. We have developed conditions for *hydrogen-mediated* reductive aldol

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(1) For rhodium-catalyzed reductive aldol reaction mediated by silane or other reductants, see: (a) Revis, A.; Hilty, T. K. *Tetrahedron Lett.* **1987**, *28*, 4809−4812. (b) Matsuda, I.; Takahashi, K.; Sata, S. *Tetrahedron Lett.* **1990**, *31*, 5331−5334. (c) Taylor, S. J.; Morken, J. P. *J. Am. Chem. Soc.* **1999**, *121*, 12202−12203. (d) Taylor, S. J.; Duffey, M. O.; Morken, J. P. *J. Am. Chem. Soc.* **2000**, *122*, 4528−4529. (e) Emiabata-Smith, D.; McKillop, A.; Mills, C.; Motherwell, W. B.; Whitehead, A. J. *Synlett* **2001**, 1302−1304. (f) Freiría, M.; Whitehead, A. J.; Tocher, D. A.; Motherwell, W. B. *Tetrahedron* **2004**, *60*, 2673−2692. (g) Fuller, N. O.; Morken, J. P. *Synlett* **2005**, 1459−1461. (h) Nishiyama, H.; Siomi, T.; Tsuchiya, Y.; Matsuda, I. *J. Am. Chem. Soc.* **2005**, *127*, 6972−6973. (i) Willis, M. C.; Woodward, R. L. *J. Am. Chem. Soc.* **2005**, *127*, 18012−18013.

(2) 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*, 15156−15157. (b) Huddleston, R. R.; Krische, M. J. *Org. Lett.* **2003**, *5*, 1143−1146. (c) Koech, P. K.; Krische, M. J. *Org. Lett.* **2004**, *6*, 691−694. (d) Marriner, G. A.; Garner, S. A.; Jang, H.-Y.; Krische, M. J. *J. Org. Chem.* **2004**, *69*, 1380−1382. (e) Jung, C.-K.; Garner, S. A.; Krische, M. J. *Org. Lett.* **2006**, *8*, 519−522.

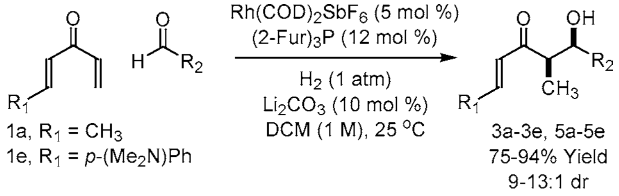
(3) For cobalt-catalyzed reductive aldol reaction, see: (a) Isayama, S.; Mukaiyama, T. *Chem. Lett.* **1989**, 2005−2008. (b) Baik, T.-G.; Luis, A. L.; Wang, L.-C.; Krische, M. J. *J. Am. Chem. Soc.* **2001**, *123*, 5112−5113. (c) Wang, L.-C.; Jang, H.-Y.; Roh, Y.; Lynch, V.; Schultz, A. J.; Wang, X.; Krische, M. J. *J. Am. Chem. Soc.* **2002**, *124*, 9448−9453. (d) Lam, H. W.; Joensuu, P. M.; Murray, G. J.; Fordyce, E. A. F.; Prieto, O.; Luebbers, T. *Org. Lett.* **2006**, *8*, 3729−3732.

10.1021/ol0624023 CCC: $33.50

coupling that are applicable to commercially available methyl and ethyl vinyl ketones (MVK and EVK).[2a,e] Furthermore, upon the use of cationic rhodium catalysts ligated by tri-2-furylphosphine, exceptionally high levels of syn-diastereoselection are observed.[2e,5]

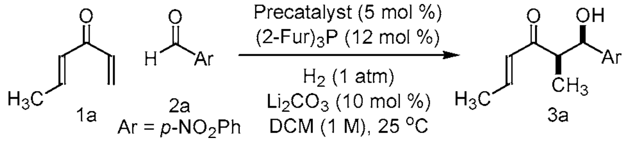
Remarkably, under the conditions of hydrogen-mediated aldol coupling, functional groups borne by the aldehyde that are generally considered "hydrogen labile" (alkynes, alkenes, benzylic ethers, and nitroarenes) remain intact.[2e] These results support the feasibility of couplings involving vinyl ketones that incorporate unsaturated functional groups. Here, we report the first reductive aldol couplings of *divinyl ketones*. Specifically, catalytic hydrogenation of crotyl vinyl ketone **1a** or *para*-(dimethylamino)styryl vinyl ketone **1e** in the presence of assorted aldehydes results in reductive coupling of the less-substituted vinyl moiety to furnish the corresponding *syn*-aldols **3a**−**e** and **5a**−**e**, respectively.[6,7] Additionally, we describe studies of the reductive coupling of various para-substituted styryl vinyl ketones **1b**−**e**, wherein progressive increases in isolated yields are observed for electron-releasing para substituents. These studies offer further insight into the structural and interactional features of the catalytic system required for efficient hydrogen-mediated aldol coupling and provide access to β-hydroxyenones, which are important precursors to dihydropyridinones (Scheme 1).[7]

Scheme 1. Catalytic Reductive Aldol Coupling of Divinyl Ketones Mediated by Hydrogen



Our initial studies focused on the reductive coupling of crotyl vinyl ketone **1a** to *p*-nitrobenzaldehyde. Using our previously developed conditions for syn-selective aldol coupling,[2e] crotyl vinyl ketone **1a** (200 mol %) was subjected to hydrogenation at ambient temperature and pressure in the presence of *p*-nitrobenzaldehyde **2a** (100 mol %) to furnish hydroxyenone **3a** in 72% isolated yield with an 8:1 syn/anti ratio (Table 1, entry 1). In the hope of improving chemical yield and diastereoselectivity, alternate rhodium precatalysts were screened. Upon use of Rh(COD)$_2$BARF (BARF = $\{3,5\text{-}(CF_3)_2C_6H_3\}_4B^{\theta}$), a substantial increase in diastereoselectivity is observed, but the isolated yield of hydroxyenone **3a** is diminished considerably (Table 1, entry 2). Similarly, upon use of Rh(COD)$_2$BF$_4$, a 61% isolated yield of coupling product **3a** is obtained with a 9:1 diastereomeric ratio (Table 1, entry 3). Gratifyingly, upon use of Rh(COD)$_2$SbF$_6$ as the precatalyst, hydroxyenone **3a** is produced in 82% isolated yield with a 13:1 diastereomeric ratio, representing an improvement in both yield and stereoselectivity in comparison to the reaction employing Rh(COD)$_2$OTf as the precatalyst (Table 1, entry 4).

Table 1. Counterion Effects in the Hydrogen-Mediated Reductive Aldol Coupling of Divinyl Ketone **1a** to *p*-Nitrobenzaldehyde **2a** Employing Cationic Rhodium Precatalysts[a]



entry	rhodium precatalyst	yield	dr (syn/anti)
1	Rh(COD)$_2$OTf	72%	8:1
2	Rh(COD)$_2$BARF	55%	17:1
3	Rh(COD)$_2$BF$_4$	61%	9:1
4	Rh(COD)$_2$SbF$_6$	82%	13:1

[a] Cited yields are of material isolated by SiO$_2$ chromatography. Diastereomeric ratios were determined by ^{1}H NMR analysis of the crude reaction mixtures. See Supporting Information for detailed experimental procedures.

Under optimized conditions using Rh(COD)$_2$SbF$_6$ as the precatalyst and (2-Fur)$_3$P as the ligand, the hydrogen-mediated aldol coupling of crotyl vinyl ketone **1a** to diverse aldehydes **2a**−**e** was conducted at ambient temperature and pressure (Figure 1, top). High levels of syn-diastereoselection were observed using aromatic aldehydes (**3a**, 82% yield, 13:1 dr), α-heteroatom-substituted aldehydes (**3b**, 80% yield, 9:1 dr; **3c**, 85% yield, 13:1 dr), heterocyclic aromatic aldehydes (**3d**, 94% yield, 11:1 dr), and α,β-unsaturated aldehydes (**3e**, 75% yield, 12:1 dr). Notably, the unsaturated products **3a**−**e** are not subject to overreduction under the conditions of hydrogen-mediated coupling, presumably due to a diminished rate of conjugate reduction in response to β-substitution of the enone moiety. Generally, reactions are complete within

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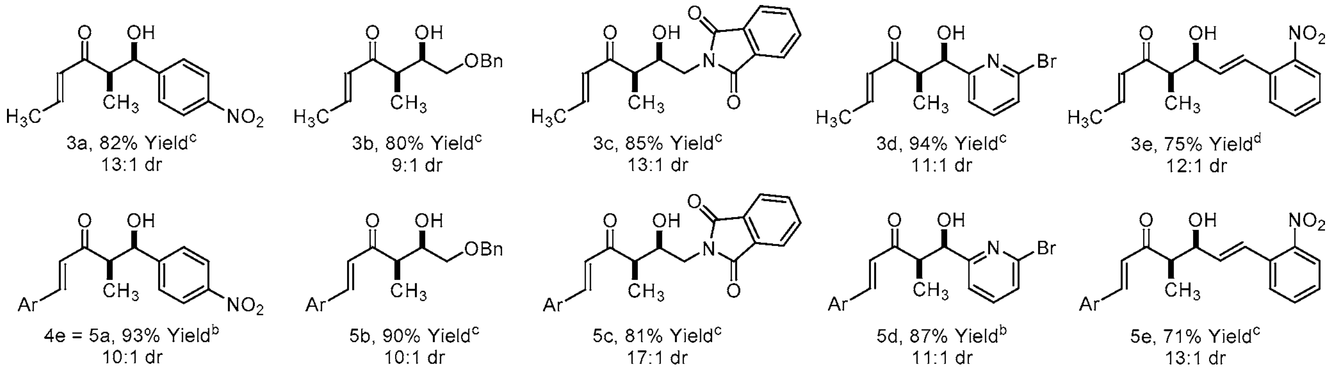
(4) For reductive aldol coupling catalyzed by other metals, see the following. Iridium: (a) Zhao, C.-X.; Duffey, M. O.; Taylor, S. J.; Morken, J. P. *Org. Lett.* **2001**, *3*, 1829−1831. Palladium: (b) Kiyooka, S.; Shimizu, A.; Torii, S. *Tetrahedron Lett.* **1998**, *39*, 5237−5238. Copper: (c) Ooi, T.; Doda, K.; Sakai, D.; Maruoka, K. *Tetrahedron Lett.* **1999**, *40*, 2133−2136. (d) Lam, H.-W.; Joensuu, P. M. *Org. Lett.* **2005**, *7*, 4225−4228. (e) Lam, H.-W.; Murray, G. J.; Firth, J. D. *Org. Lett.* **2005**, *7*, 5743−5746. (f) Zhao, D.; Oisaki, K.; Kanai, M.; Shibasaki, M. *Tetrahedron Lett.* **2006**, *47*, 1403−1407. (g) Deschamp, J.; Chuzel, O.; Hannedouche, J.; Riant, O. *Angew. Chem., Int. Ed.* **2006**, *45*, 1292−1297. Indium: (h) Shibata, I.; Kato, H.; Ishida, T.; Yasuda, M.; Baba, A. *Angew. Chem., Int. Ed.* **2004**, *43*, 711−714. (i) Miura, K.; Yamada, Y.; Tomita, M.; Hosomi, A. *Synlett* **2004**, 1985−1989.

(5) For tri-2-furylphosphine effects in metal-catalyzed reactions, see: (a) Farina, V.; Krishnan, B. *J. Am. Chem. Soc.* **1991**, *113*, 9585−9595. (b) Farina, V. *Pure Appl. Chem.* **1996**, *68*, 73−78. (c) Anderson, N. G.; Keay, B. A. *Chem. Rev.* **2001**, *101*, 997−1030.

(6) To date, a single study of catalyzed aldol additions involving aldol donors incorporating an enone moiety has been reported: Trost, B. M.; Shin, S.; Sclafani, J. A. *J. Am. Chem. Soc.* **2005**, *127*, 8602−8603.

(7) For noncatalyzed aldol additions of preformed enolates derived from methyl enones, see: (a) Patterson, I.; Osborne, S. *Tetrahedron Lett.* **1990**, *31*, 2213−2216. (b) Reiter, M.; Ropp, S.; Gouverneur, V. *Org. Lett.* **2004**, *6*, 91−94. (c) Baker-Glenn, C.; Hodnett, N.; Reiter, M.; Ropp, S.; Ancliff, R.; Gouverneur, V. *J. Am. Chem. Soc.* **2005**, *127*, 1481−1486. (d) Reiter, M.; Turner, H.; Mills-Webb, R.; Gouverneur, V. *J. Org. Chem.* **2005**, *70*, 8478−8485. (e) Gao, B.; Yu, Z.; Fu, Z.; Feng, X. *Tetrahedron Lett.* **2006**, *47*, 1537−1539.



3a, 82% Yield[c] 13:1 dr

3b, 80% Yield[c] 9:1 dr

3c, 85% Yield[c] 13:1 dr

3d, 94% Yield[c] 11:1 dr

3e, 75% Yield[d] 12:1 dr

4e = 5a, 93% Yield[b] 10:1 dr

5b, 90% Yield[c] 10:1 dr

5c, 81% Yield[c] 17:1 dr

5d, 87% Yield[b] 11:1 dr

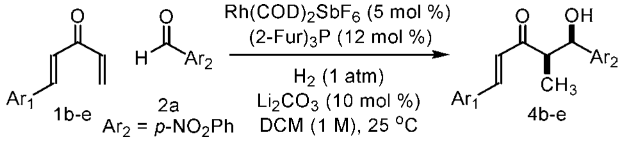
5e, 71% Yield[c] 13:1 dr

Figure 1. Hydrogen-mediated aldol coupling of crotyl vinyl enone **1a** (top) and styryl vinyl enone **5a** (bottom) to assorted aldehydes. Cited yields are of isolated material. Diastereomeric ratios were determined by ^{1}H NMR analysis of the crude reaction mixtures. Ar = *p*-dimethylaminophenyl. [b]Enone loadings of 150 mol % were employed. [c]Enone loadings of 200 mol % were employed. [d]Enone loadings of 300 mol % were employed. See Supporting Information for detailed experimental procedures.

7 h, as determined by consumption of the aldehyde. If the couplings are allowed to continue beyond this point, product overreduction becomes evident. As a control experiment, hex-4-en-3-one and *p*-nitrobenzaldehyde were exposed to standard coupling conditions. The aldol addition product **3a** was not formed. Finally, upon reexposure of aldol addition product **3a** to standard coupling conditions, **3a** may be recovered in high yield without any noticeable erosion in diastereoselectivity. This latter experiment suggests that hydrogen-mediated aldol addition is irreversible.

As one would anticipate, crotyl vinyl ketone **1a** is somewhat unstable with respect to polymerization and must be used immediately upon isolation. Accordingly, crystalline divinyl ketones of enhanced stability were sought, which led to the preparation of para-substituted styryl vinyl enones **1b**−**e**. With the exception of **1c**, these compounds are crystalline materials that may be stored for prolonged periods of time in the dark. To evaluate their reactivity in the reductive aldol coupling, styryl vinyl enones **1b**−**e** (150 mol %) were hydrogenated in the presence of *p*-nitrobenzaldehyde (100 mol %) at ambient temperature and pressure using Rh-$(COD)_2SbF_6$ as the precatalyst (Table 2). As reflected by the isolated yield of aldol coupling products **4b**−**e**, it was found that the reaction responds remarkably to the effect of remote electron-withdrawing or -releasing groups. For example, whereas *para*-nitrostyryl vinyl enone **1b** provides only a 44% isolated yield of aldol coupling product **4b** (Table 2, entry 1), the corresponding *para*-(dimethylamino)styryl vinyl enone **1e** furnishes aldol coupling product **4e** in 93% yield under identical coupling conditions (Table 2, entry 4). These effects may be attributed to modulation of the HOMO energies of the intermediate rhodium enolates, with more reactive rhodium enolates being derived from precursors possessing electron-releasing *p*-styryl substituents. It is also interesting to note that diastereoselectivity decreases with increasing enolate reactivity, presumably due to intervention of boatlike transition structures, or increased isomerization of enolate geometry in advance of aldol coupling. As previously hypothesized,[2e] it is believed that *Z*-(*O*)-enolate formation occurs with high levels of kinetic stereospecificity by way of internal hydride delivery to the enone s-cis conformer through a six-centered transition structure.[8] Addition of the *Z*-(*O*)-enolate to the aldehyde through a Zimmerman−Traxler-type transition structure would then account for the observed syn-diastereoselectivity.[9]

Table 2. Reductive Aldol Coupling of Styryl Vinyl Ketones[a]



entry	styryl vinyl ketone, Ar_1	yield	dr (syn/anti)
1	**1b**, *p*-nitrophenyl	44%	16:1
2	**1c**, phenyl	50%	12:1
3	**1d**, *p*-methoxyphenyl	64%	11:1
4	**1e**, *p*-(dimethylamino)phenyl	93%	10:1

[a] Cited yields are of material isolated by SiO_2 chromatography. Diastereomeric ratios were determined by ^{1}H NMR analysis of the crude reaction mixtures. See Supporting Information for detailed experimental procedures.

Under standard conditions using $Rh(COD)_2SbF_6$ as the catalyst precursor and Fur_3P as the ligand, the hydrogen-mediated aldol coupling of *para*-(dimethylamino)styryl vinyl ketone **1e** to aldehydes **2a**−**e** was conducted at ambient temperature and pressure (Figure 1, bottom). Again, highly syn-diastereoselective coupling is observed for aromatic aldehydes (**5a**, 93% yield, 10:1 dr), α-heteroatom-substituted aldehydes (**5b**, 90% yield, 10:1 dr; **5c**, 81% yield, 17:1 dr), heterocyclic aromatic aldehydes (**5d**, 87% yield, 11:1 dr),

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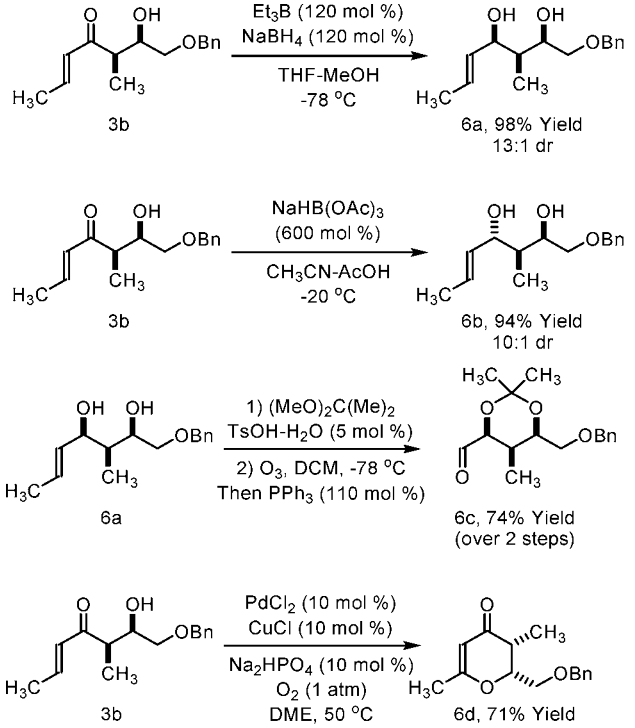
(8) Enones constrained in the s-trans configuration, such as cyclohexenone, do not participate in hydrogen-mediated reductive aldol coupling.

(9) Zimmerman, H. E.; Traxler, M. D. *J. Am. Chem. Soc.* **1957**, *79*, 1920−1923. See also: Evans, D. A.; Nelson, J. V.; Taber, T. R. *Top. Stereochem.* **1982**, *13*, 1−115.

Scheme 2. Elaboration of Aldol Adduct **3b** to Diverse Building Blocks for Polypropionate Construction[a]



[a] Cited yields are of material isolated by SiO_2 chromatography. Diastereomeric ratios were determined by ^1H NMR analysis of the crude reaction mixtures. See the experimental section for detailed procedures.

and α,β-unsaturated aldehydes (**5e**, 71% yield, 13:1 dr). Unlike adducts **3a**−**e**, the *para*-(dimethylamino)styryl-containing adducts **5a**−**e** are far less susceptible to overreduction under the conditions of hydrogen-mediated C−C coupling. Additionally, for couplings that employ **1e**, lower loadings of a pronucleophile may be used.

To illustrate the relevance of this methodology with respect to the synthesis of polypropionate-derived substructures, aldol coupling product **3b** was subjected to several different transformations. Exposure of **3b** to conditions for syn-diastereoselective hydroxy-directed reduction affords the *syn*-1,3-diol containing stereotriad **6a** with a diastereomeric ratio of 13:1.[10] Access to the corresponding *anti*-1,3-diol **6b** is achieved upon treatment of **3b** with $NaHB(OAc)_3$.[11] Here, a diastereomeric ratio of 10:1 is observed. As illustrated by the conversion of **6a** to **6c**, the crotyl residue may serve as a masked aldehyde, enabling entry into higher polyols. Finally, oxidative cyclization catalyzed by palladium permits direct conversion of **3b** to dihydropyranone **6d** (Scheme 2).[7b−d]

In summary, rhodium-catalyzed hydrogenation of divinyl ketones **1a** and **1e** in the presence of aldehydes **2a**−**e** results in highly syn-diastereoselective reductive aldol coupling to afford the α,β-unsaturated coupling products **3a**−**e** and **5a**−**e**, respectively, without overreduction. As revealed by a survey of counterions ($Rh(COD)_2X$, where X = OTf, BF_4, SbF_6, BARF = $\{3,5\text{-}(CF_3)_2C_6H_3\}_4B$), $Rh(COD)_2SbF_6$ is identified as the optimum precatalyst for reductive aldol couplings of this type. Finally, for para-substituted styryl vinyl ketones **1b**−**e**, a progressive increase in isolated yield in response to the presence of electron-releasing para substituents is observed. These studies offer further insight into the structural and interactional features of the catalytic system required for efficient hydrogen-mediated aldol coupling and provide new methods for the construction of natural products that incorporate polypropionate motifs.

Acknowledgment. Acknowledgment is made to the Research Corporation Cottrell Scholar Program, the Sloan Foundation, the Dreyfus Foundation, the Robert A. Welch Foundation, Johnson & Johnson, and the NIH-NIGMS (RO1-GM69445) for partial support of this research.

Supporting Information Available: Spectral data for all new compounds (^1H NMR, ^{13}C NMR, IR, HRMS). This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) (a) Chen, K.-M.; Gunderson, K. G.; Hardtmann, G. E.; Prasad, K.; Repic, O.; Shapiro, M. J. *Chem. Lett.* **1987**, 1923−1926. (b) Song, H. Y.; Joo, J. M.; Kang, J. W.; Kim, D.-S.; Jung, C.-K.; Kwak, H. S.; Park, J. H.; Lee, E.; Hong, C. Y.; Jeong, S. W.; Jeon, K.; Park, J. H. *J. Org. Chem.* **2003**, *68*, 8080−8087.

(11) (a) Evans, D. A.; Chapman, K. T. *Tetrahedron Lett.* **1986**, *27*, 5939−5942. (b) Evans, D. A.; Chapman, K. T.; Carreira, E. M. *J. Am. Chem. Soc.* **1988**, *110*, 3560−3578. (c) White, J. D.; Blakemore, P. R.; Browder, C. C.; Hong, J.; Lincoln, C. M.; Nagornyy, P. A.; Robarge, L. A.; Wardrop, D. J. *J. Am. Chem. Soc.* **2001**, *123*, 8593−8595. (d) Eustache, F.; Dalko, P. I.; Cossy, J. *J. Org. Chem.* **2003**, *68*, 9994−10002.