Asymmetric Synthesis

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Iterative Asymmetric Hydroformylation/Wittig Olefination Sequence**

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Rhodium-catalyzed hydroformylation is an atom-economic, commodity-scale process for the production of linear aldehydes.[1] Asymmetric hydroformylation (AHF) is underutilized because of the limited availability of chiral ligands which demonstrate useful selectivity and activity.[2] Hydroformylation constitutes a potentially powerful method for synthesizing enantiopure aldehydes from readily accessible reagents.[3] Such chiral aldehydes are valuable intermediates in the synthesis of pharmaceuticals and other complex organic molecules. We[4] and others[5] have demonstrated effective enantioselective hydroformylation of alkenes. Previously we have reported that the bis(diazaphospholane) **1** (Figure 1)

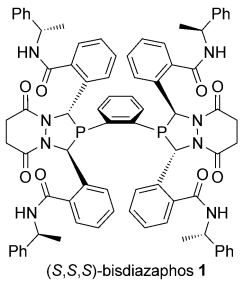
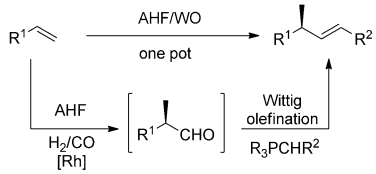


Figure 1. The chiral ligand **1** used in this study.

enables highly active, regio- and enantioselective rhodium-catalyzed hydroformylation of aryl alkenes,[4b] 1,3-dienes,[4d] vinylic and allylic amines, and alcohols.[4c] For example, AHF of allyl ethers using **1** and rhodium catalysts yield Roche-aldehyde derivatives with high enantiomeric excess.[4c,6] One of the many applications of the Roche aldehyde concerns olefination[7] to form γ-chiral α,β-unsaturated carbonyl intermediates. A generalized and efficient AHF/olefination protocol would enhance emerging hydroformylation technology.

There have been a few reports of one-pot hydroformylation/Wittig olefination sequences. Breit and co-workers described the diastereoselective hydroformylation/Wittig olefination/hydrogenation of 1,1-disubstituted allylic alcohols, in which the alcohol is tethered to a phosphorus ligand to induce a diastereoselective linear hydroformylation.[8] Helmchen and co-workers have recently reported the procedure using chiral homoallylic amines to produce substituted proline analogues using a hydroformylation/Wittig olefination/aza-Michael addition sequence.[9] Risi and Burke have demonstrated the synthesis of (+)-patulolide C[10] and the Prelog–Djerassi lactone[11] using hydroformylation reactions. Herein we demonstrate general, efficient, and enantioselective one-pot AHF/Wittig olefination (AHF/WO) sequences in the presence of rhodium complexes of **1** to produce γ-chiral α,β-unsaturated carbonyl compounds (Scheme 1).



Scheme 1. General one-pot AHF/WO sequence with stabilized Wittig ylides resulting in γ-chiral α,β-unsaturated carbonyl products.

The enantioselective hydroformylation of vinyl acetate was conducted in the presence of various stabilized Wittig ylides (Table 1) in glass pressure bottles with simultaneous addition of vinyl acetate and a Wittig reagent.[12] Hydroformylation of vinyl acetate with the carboethoxy-substituted Wittig ylide results in 79% yield of an α,β-unsaturated ester in 99% *ee* (**2a**, entry 1). Analogues of **2** have been used in organic synthesis.[13] The AHF/WO of vinyl acetate and the Wittig ylide bearing a carbobenzyloxy group yielded **2b** (entry 2) with a high enantioselectivity (99% *ee*) and in modest yield (46%). Interestingly, **2b** was the only product observed to undergo a second hydroformylation/Wittig olefination transformation. Subsequent isomerization yielded **2b′** [Eq. (1)]. As shown in Table 1, stabilized Wittig reagents based on α-substituted esters (entries 3 and 5) and ketones (entry 4) are effective in the AHF/WO sequence. In all examples, high *E*/*Z* selectivity (>95:5), high regioselectivity, and little erosion of enantioselectivity was observed.

Sequential AHF/WO, in which AHF is performed first in the absence of the Wittig reagent, has been used for alkenes of several types (Scheme 2). The AHF/WO of *N*-vinylphthalimide, 6-methoxy-2-vinylnaphthalene, CBZ-protected 3-pyr-

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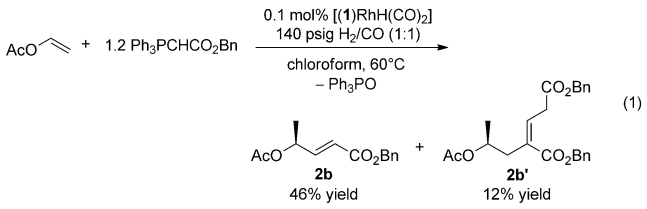
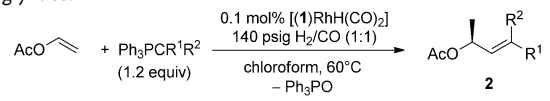
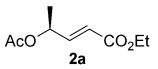
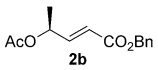
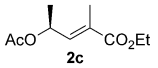
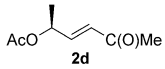
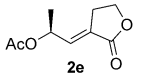


Table 1: One-pot AHF/WO of vinyl acetate in the presence stabilized Wittig ylides.[a]

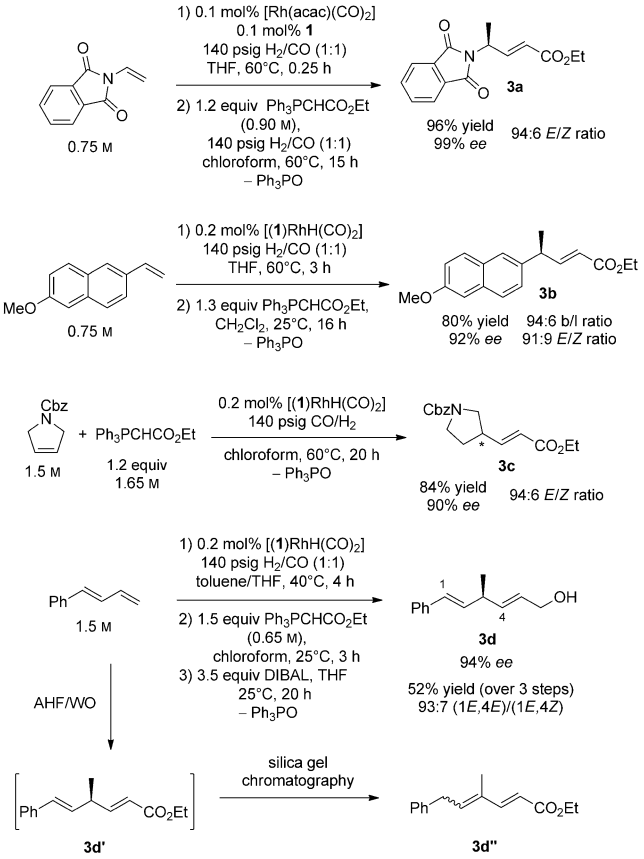


Entry	Product	*t* [h]	*E*/*Z*[b]	Yield [%]	*ee* [%][c]
1	 **2a**	18	>95:5	79	99
2	 **2b**	15	>95:5	46	99
3	 **2c**	18	>95:5	68	90
4	 **2d**	21	>95:5	71	97
5	 **2e**	18	>95:5	67	98

[a] Reaction conditions: Pre-activation of [Rh(acac)(CO)$_2$] and **1** with 140 psig (1:1) H_2/CO for 0.5 hour at 40 °C with subsequent injection of the vinyl acetate/Wittig ylide solution ([vinyl acetate] = 1.5 M, [Wittig ylide] = 1.8 M) in chloroform. [b] Measured by ^{1}H NMR spectroscopy. [c] See the Supporting Information for determination of the enantiomeric excess. acac = acetylacetonate.

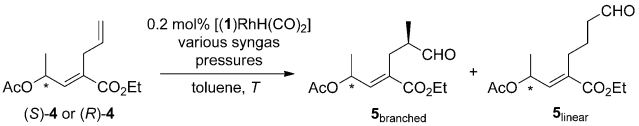
roline, and phenyl-1,3-butadiene proceed with good yields and selectivities. Please note that the procedures for the vinylnaphthalene and diene involve different temperatures for the AHF and WO steps compared to those used for the reactions listed in Table 1. Also note that the AHF/WO of the CBZ-protected 3-pyrroline was performed with simultaneous addition of substrate and ylide. The one-pot sequential procedure for *N*-vinylnaphthalene provided approximately a 10% higher *ee* value than the tandem process, presumably because the sensitive aldehydes epimerize faster in the presence of an ylide at the higher temperature. Also note that **3d′** is susceptible to isomerization, thus yielding **3d″**. This problem can be circumvented by reduction of the ester to the alcohol **3d**.

Wittig olefination with an allyl-substituted ylide yields a 1,4-diene which can undergo subsequent hydroformylation (Table 2). AHF of enantiomerically enriched samples of **4** using four different combinations of syngas (1:1 H_2/CO) pressure and temperature reveals dramatically different regioselectivities. At 140 psig of syngas and a temperature of 40 °C, the branched aldehyde was favored [86% $\mathbf{5}_{branched}$ for (*S*)-**4** and 79% $\mathbf{5}_{branched}$ for (*R*)-**4**], whereas the branched isomer is the minor product [23% **5** (branched) for (*S*)-**4** and 17% $\mathbf{5}_{branched}$ for (*R*)-**4**] at 15 psig of syngas and 100 °C. The



Scheme 2. Sequential AHF/WO reactions of different alkenes.

Table 2: AHF of **4** at various syngas pressures and temperatures.[a]



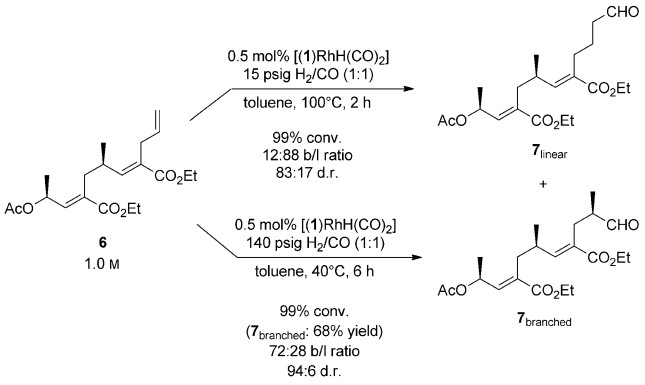
	(*S*)-**4**		(*R*)-**4**	
	140 psig	15 psig	140 psig	15 psig
40 °C, 3 h	conv. 99[b]	conv. 99[b]	conv. 92[b]	conv. 99[b]
	b/l 86:14[c]	b/l 75:25[c]	b/l 79:21[c]	b/l 69:31[c]
	d.r. 93:7[d]	d.r. 93:7[d]	d.r. 4:96[d]	d.r. 6:94[d]
100 °C, 1 h	conv. 99[b]	conv. 99[b]	conv. 99[b]	conv. 99[b]
	b/l 63:37[c]	b/l 23:77[c]	b/l 52:48[c]	b/l 17:83[c]
	d.r. 95:5[d]	d.r. 89:11[d]	d.r. 6:94[d]	d.r. 13:87[d]

[a] [Alkene] = 1.5 M and 1:1 H_2:CO. [b] Percent conversion. [c] $\mathbf{5}_{branched}$/$\mathbf{5}_{linear}$ ratio. [d] The d.r. value for $\mathbf{5}_{branched}$.

combination of high pressure and high temperature (100 °C and 140 psig) results in almost equal amounts of the branched and linear regioisomers [63% $\mathbf{5}_{branched}$ for (*S*)-**4** and 52% $\mathbf{5}_{branched}$ for (*R*)-**4**]. The low temperature and pressure (40 °C and 15 psig) combination produces modest branched isomer selectivity [75% $\mathbf{5}_{branched}$ for (*S*)-**4** and 69% $\mathbf{5}_{branched}$ for (*R*)-**4**]. Different regioselectivities for different enantiomers indicate a match/mismatch effect with the enantiopure catalyst. For all eight experiments in Table 2, high diastereomeric ratios for the branched product (≥87% major diastereomer) with

either enantiomer of the substrate **4** indicates that the catalyst chirality controls the stereoselectivity. The internal trisubstituted alkene remains unreacted in all of these experiments. Previously, interesting effects of the CO pressure on the regio- and enantioselectivity have been observed for the AHF of conjugated alkenes (styrene and 1,3-dienes) with rhodium/diazaphospholane catalysts.[4d,14] Kollár and co-workers, van Leeuwen et al., and Casey et al. observed pressure and temperature effects in the hydroformylation of styrene using rhodium[15] and platinum.[16]

Complex materials containing multiple stereocenters and various functionalities can be synthesized by sequential AHF/WO procedures. For example, olefination of the aldehyde $\mathbf{5}_{branched}$ with the allyl carboethoxy-substituted Wittig ylide yielded the 1,4,8-triene **6** (Scheme 3). Hydroformylation of **6**

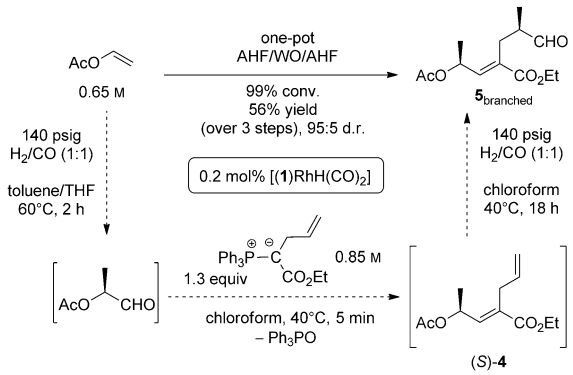


Scheme 3. Hydroformylation of the 1,4,8-triene **6** to yield the products $\mathbf{7}_{branched}$ and $\mathbf{7}_{linear}$.

at 15 psig of syngas and 100 °C gave linear ($\mathbf{7}_{linear}$) and branched ($\mathbf{7}_{branched}$) isomers with $\mathbf{7}_{linear}$ being the major product (12 % $\mathbf{7}_{branched}$). At 140 psig of syngas and 40 °C the reaction is branched selective (72 % $\mathbf{7}_{branched}$). By using silica gel chromatography, each of these regioisomers can be isolated. The branched isomer $\mathbf{7}_{branched}$, which contains ester, acetoxy, and aldehyde functional groups, two C=C double bonds, and three stereocenters, is obtained with high diastereometric ratio (94:6).

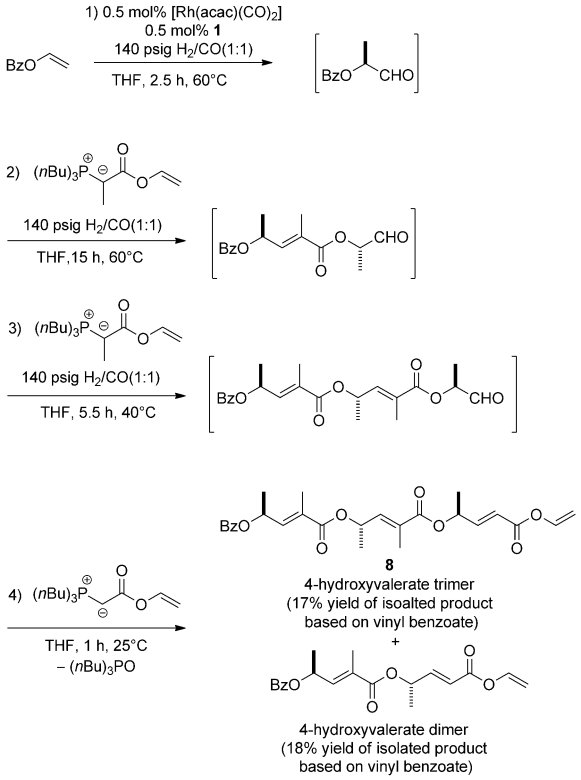
Multiple one-pot iterative AHF/WO sequences can be accomplished with a single catalyst loading (Schemes 4). For example, a pressure bottle charged with vinyl acetate, [Rh(acac)(CO)$_2$] (0.2 %), the ligand **1**, and syngas generated a branched aldehyde in two hours. Subsequent depressurization and injection of the allyl-substituted Wittig ylide gave the 1,4-diene (*S*)-**4**. This sequence was required because the allyl-substituted Wittig ylide is also capable of undergoing hydroformylation and subsequent intramolecular olefination, thus yielding ethyl 1-cyclopentene-1-carboxylate as the major product. Repressurization with 140 psig of H$_2$/CO (1:1) at 40 °C effected AHF of (*S*)-**4** to give the aldehyde $\mathbf{5}_{branched}$ in modest isolated yield (56 %) with a high d.r. value (95:5).

One-pot AHF/WO sequences with multiple iterations yield vinylogous ester oligomers with a single loading of the rhodium/bis-3,4-diazaphospholane catalyst. For example, AHF/WO/AHF/WO/AHF/WO produced a substituted unsa-



Scheme 4. Net one-pot AHF/WO/AHF reaction of vinyl acetate with an allyl-substituted Wittig ylide (AHF and WO transformations are shown with dashed arrows).

turated trimer of 4-hydroxyvalerate (Scheme 5).[17] Asymmetric hydroformylation of vinyl benzoate was followed by depressurization and the first addition of a vinyl-ester-substituted Wittig reagent. Repressurization with syngas, hydroformylation, and depressurization was followed by injection of the second ylide. A final AHF/WO cycle yielded the trimer **8** with three unique stereocenters in a 17 % isolated yield. Synthesis of a monodisperse oligomer requires precise control of stoichiometric amounts of the Wittig ylide for each iteration step.[18] Separation of the trimer from smaller and larger oligomers was accomplished by using silica gel chromatography. NMR spectroscopy (^{1}H, ^{13}C, COSY,



Scheme 5. One-pot AHF/WO/AHF/WO/AHF/WO using a single catalyst loading. Bz = benzoyl.

HSQC) confirmed the connectivity of the trimer product, apparently with one diasteromer predominating. Mass spectrometry confirmed the presence of **8**, along with trace amounts of the dimer and tetramer.[19] The yield and purity of the trimer appears to be limited more by the difficulty of measuring stoichiometric amounts of the ylide and isolation of the product from tributylphosphine oxide, rather than by hydroformylation or olefination conversion and selectivity.,[18,20]

Iterative $(AHF/WO)_n$ sequences constitute a powerful one-pot approach to the sequence-specific construction of oligomers in which multiple stereocenters are introduced by a single loading of a chiral catalyst. The success of the examples shown here rests on the remarkable activity and robustness of the rhodium/bis(diazaphospholane) catalysts, their high selectivity for a variety of alkene substrates, and the ability of stabilized ylides to generate olefins of α-chiral aldehydes without racemization. In addition this work demonstrates that a simple change in the hydroformylation temperature and pressure can tweak the catalyst to be either linear or branched selective. The α,β-unsaturated carbonyl groups resulting from olefination provide sites for additional functionalization and the creation of stereocenters.

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[1] C. Claver, P. W. N. M. van Leeuwen, *Rhodium Catalyzed Hydroformylation*, Kluwer Academic Publishers, Dordrecht, The Netherlands, **2000**.

[2] a) J. Klosin, C. R. Landis, *Acc. Chem. Res.* **2007**, *40*, 1251 – 1259; b) A. Gual, C. Godard, S. Castillón, C. Claver, *Tetrahedron: Asymmetry* **2010**, *21*, 1135 – 1146.

[3] a) P. Eilbracht, L. Bärfacker, C. Buss, C. Hollmann, B. E. Kitsos-Rzychon, C. L. Kranemann, T. Rische, R. Roggenbuck, A. Schmidt, *Chem. Rev.* **1999**, *99*, 3329 – 3366; b) B. Breit, W. Seiche, *Synthesis* **2001**, 1 – 36; c) B. Breit, *Metal Catalyzed Reductive C-C Bond Formation*, *Vol. 279* (Ed.: M. Krische), Springer, Berlin, **2007**, pp. 139 – 172.

[4] a) T. P. Clark, C. R. Landis, S. L. Freed, J. Klosin, K. A. Abboud, *J. Am. Chem. Soc.* **2005**, *127*, 5040 – 5042; b) A. L. Watkins, B. G. Hashiguchi, C. R. Landis, *Org. Lett.* **2008**, *10*, 4553 – 4556; c) R. I. McDonald, G. W. Wong, R. P. Neupane, S. S. Stahl, C. R. Landis, *J. Am. Chem. Soc.* **2010**, *132*, 14027 – 14029; d) A. L. Watkins, C. R. Landis, *Org. Lett.* **2011**, *13*, 164 – 167.

[5] a) A. T. Axtell, C. J. Cobley, J. Klosin, G. T. Whiteker, A. Zanotti-Gerosa, K. A. Abboud, *Angew. Chem.* **2005**, *117*, 5984 – 5988; *Angew. Chem. Int. Ed.* **2005**, *44*, 5834 – 5838; b) Y. Yan, X. Zhang, *J. Am. Chem. Soc.* **2006**, *128*, 7198 – 7202; c) P. J. Thomas, A. T. Axtell, J. Klosin, W. Peng, C. L. Rand, T. P. Clark, C. R. Landis, K. A. Abboud, *Org. Lett.* **2007**, *9*, 2665 – 2668; d) A. D. Worthy, C. L. Joe, T. E. Lightburn, K. L. Tan, *J. Am. Chem. Soc.* **2010**, *132*, 14757 – 14759; e) X. Zhang, B. Cao, S. Yu, X. Zhang, *Angew. Chem.* **2010**, *122*, 4141 – 4144; *Angew. Chem. Int. Ed.* **2010**, *49*, 4047 – 4050; f) C. L. Joe, K. L. Tan, *J. Org. Chem.* **2011**, *76*, 7590 – 7596; g) X. Wang, S. L. Buchwald, *J. Am. Chem. Soc.* **2011**, *133*, 19080 – 19083; h) S. H. Chikkali, R. Bellini, B. de Bruin, J. I. van der Vlugt, J. N. H. Reek, *J. Am. Chem. Soc.* **2012**, *134*, 6607 – 6616; i) A. J. L. Clemens, S. D. Burke, *J. Org. Chem.* **2012**, *77*, 2983 – 2985; j) G. M. Noonan, J. A. Fuentes, C. J. Cobley, M. L. Clarke, *Angew. Chem.* **2012**, *124*, 2527 – 2530; *Angew. Chem. Int. Ed.* **2012**, *51*, 2477 – 2480; k) R. Franke, D. Selent, A. Börner, *Chem. Rev.* **2012**, *112*, 5675 – 5732; l) T. Gadzikwa, R. Bellini, H. L. Dekker, J. N. H. Reek, *J. Am. Chem. Soc.* **2012**, *134*, 2860 – 2863.

[6] G. W. Wong, T. A. Adint, C. R. Landis, *Org. Synth.* **2012**, *89*, 243 – 254.

[7] a) J. A. Marshall, M. M. Yanik, *J. Org. Chem.* **2001**, *66*, 1373 – 1379; b) G. Ehrlich, M. Kalesse, *Synlett* **2005**, 655 – 657; c) S. Canova, V. r. Bellosta, A. Bigot, P. Mailliet, S. Mignani, J. Cossy, *Org. Lett.* **2007**, *9*, 145 – 148; d) S. Chandrasekhar, S. R. Yaragorla, L. Sreelakshmi, C. R. Reddy, *Tetrahedron* **2008**, *64*, 5174 – 5183; e) J. R. Dunetz, L. D. Julian, J. S. Newcom, W. R. Roush, *J. Am. Chem. Soc.* **2008**, *130*, 16407 – 16416.

[8] a) B. Breit, S. K. Zahn, *Angew. Chem.* **1999**, *111*, 1022 – 1024; *Angew. Chem. Int. Ed.* **1999**, *38*, 969 – 971; b) B. Breit, S. K. Zahn, *Tetrahedron* **2005**, *61*, 6171 – 6179.

[9] A. Farwick, G. Helmchen, *Adv. Synth. Catal.* **2010**, *352*, 1023 – 1032.

[10] R. M. Risi, S. D. Burke, *Org. Lett.* **2012**, *14*, 1180 – 1182.

[11] R. M. Risi, S. D. Burke, *Org. Lett.* **2012**, *14*, 2572 – 2575.

[12] One-pot AHF/Wittig olefination experiments in which the reagents, catalyst precursor, and diazaphospholane were combined in a pressure bottle followed by pressurization, yielded partial hydrogenation of the α,β-unsaturated ester C=C bond and lower *ee* values. However, preformation of $[Rh(\mathbf{1})H(CO)_2]$ with subsequent addition of the hydroformylation substrate, Wittig reagent, and synthesis gas led to high *ee* values and no hydrogenation of the olefination product.

[13] a) B. M. Trost, J.-P. Surivet, F. D. Toste, *J. Am. Chem. Soc.* **2004**, *126*, 15592 – 15602; b) J. R. Duvall, F. Wu, B. B. Snider, *J. Org. Chem.* **2006**, *71*, 8579 – 8590; c) I. López, S. Rodríguez, J. Izquierdo, F. V. Gonzáez, *J. Org. Chem.* **2007**, *72*, 6614 – 6617; d) M. T. Crimmins, D. L. Jacobs, *Org. Lett.* **2009**, *11*, 2695 – 2698; e) Y. Ichikawa, Y. Matsuda, K. Okumura, M. Nakamura, T. Masuda, H. Kotsuki, K. Nakano, *Org. Lett.* **2011**, *13*, 2520 – 2523.

[14] A. L. Watkins, C. R. Landis, *J. Am. Chem. Soc.* **2010**, *132*, 10306 – 10317.

[15] A. van Rooy, E. N. Orij, P. C. J. Kamer, P. W. N. M. van Leeuwen, *Organometallics* **1995**, *14*, 34 – 43.

[16] a) L. Kollár, J. Bakos, I. Tóth, B. Heil, *J. Organomet. Chem.* **1988**, *350*, 277 – 284; b) C. P. Casey, S. C. Martins, M. A. Fagan, *J. Am. Chem. Soc.* **2004**, *126*, 5585 – 5592.

[17] Vinyl-ester-substituted Wittig ylides were accessed from tributylphosphine and an α-halogenated vinyl ester (synthesized from palladium-catalyzed transvinylation with various substituted bromoacetic acids; see the Supporting Information).

[18] The experiment was performed with 1.3 mmol (0.2 g) of vinyl benzoate. Because the tributylphosphine ylides are viscous oils, addition of precise stoichiometric amounts was difficult. It is anticipated that larger scale experiments would improved polydispersity.

[19] See the Supporting Information for ^1H, ^{13}C, COSY, HSQC NMR spectra, and ESI-MS and HRMS results.

[20] At the end of the third hydroformylation, the complete consumption of vinyl protons and appearance of a major aldehyde formyl resonances were observed by ^1H NMR spectroscopy.

