ORGANIC LETTERS

2011
Vol. 13, No. 1
164−167

Regioselective Rhodium-Catalyzed Hydroformylation of 1,3-Dienes to Highly Enantioenriched β,γ-Unsaturated Aldehyes with Diazaphospholane Ligands

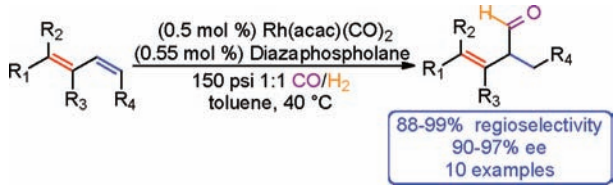
Avery L. Watkins and Clark R. Landis*

Department of Chemistry, University of Wisconsin−Madison, 1101 University Avenue, Madison, Wisconsin 53706, United States

landis@chem.wisc.edu

Received November 17, 2010

ABSTRACT



Regioselective and enantioselective rhodium-catalyzed hydroformylation of 1,3-dienes with chiral bisdiazaphospholane ligands yields β,γ-unsaturated aldehydes that retain a C=C functionality for further conversion. The reaction conditions are mild, featuring low catalyst loadings (0.5 mol %), pressures readily obtained in glass bottles, and convenient reaction times (1.5−12 h). Optimized reaction conditions produce high enantioselectivity (>90% ee), regioselectivity (88−99%), and conversion to β,γ-unsaturated aldehydes (99%) for ten 1,3-dienes encompassing a variety of substitution patterns.

Asymmetric hydroformylation (AHF) of alkenes is a catalytic, atom economical route to enantioenriched aldehydes under mild reaction conditions.[1,2] Chiral diazaphospholane ligands yield particularly fast and selective rhodium catalysts for the AHF of simple alkenes.[3] The AHF of 1,3-dienes provides convenient access to β,γ-unsaturated aldehyde intermediates in natural product syntheses,[4] as demonstrated by Jacobsen and Liu's synthesis of (+)-ambruticin.[5a] Although considered to be "especially challenging",[5a] Takaya, Nozaki, et al.[4b,c] demonstrated effective hydroformylation (78−94% regioselectivity and 80−97% ee) for three diene substrates with rhodium catalysts modified by the (*R*,*S*)-BINAPHOS ligand. However, the procedure requires 1−3 day reaction times, high-pressure autoclaves, and excess ligand. In this contribution, we report the synthesis of α-chiral β,γ-unsaturated aldehydes by regio- (88−99%) and enantioselective (90−97% ee) rhodium-catalyzed AHF of ten 1,3-diene substrates in the presence of chiral diazaphos-

(1) For a recent review on enantioselective hydroformylation see: Breit, B.; Seiche, W. *Synthesis* **2001**, 1.

(2) See for example: Sakai, N.; Mano, S.; Nozaki, K.; Takaya, H. *J. Am. Chem. Soc.* **1993**, *115*, 7033. Dieguez, M.; Pamies, O.; Ruiz, A.; Claver, C. *New J. Chem.* **2002**, *26*, 827. Cobley, C. J.; Klosin, J.; Qin, C.; Whiteker, G. T. *Org. Lett.* **2004**, *6*, 3277. Cobley, C. J.; Gardner, K.; Klosin, J.; Praquin, C.; Hill, C.; Whiteker, G. T.; Zanotti-Gerosa, A.; Petersen, J. L.; Abboud, K. A. *J. Org. Chem.* **2004**, *69*, 4031. Yan, Y. J.; Zhang, X. M. *J. Am. Chem. Soc.* **2006**, *128*, 7198.

(3) (a) Clark, T. P.; Landis, C. R.; Freed, S. L.; Klosin, J.; Abboud, K. A. *J. Am. Chem. Soc.* **2005**, *127*, 5040. (b) Klosin, J.; Landis, C. R. *Acc. Chem. Res.* **2007**, *40*, 1251. (c) Thomas, P. J.; Axtell, A. T.; Klosin, J.; Peng, W.; Rand, C. L.; Clark, T. P.; Landis, C. R.; Abboud, K. A. *Org. Lett.* **2007**, *9*, 2665. (d) Watkins, A. L.; Hashiguchi, B. G.; Landis, C. R. *Org. Lett.* **2008**, *10*, 4553.

(4) See for example (+)-Ambruticin: (a) Liu, P.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2001**, *123*, 1072. (b) Amphidinolixe, X.; Furstner, A.; Kattnig, E.; Lepage, O. *J. Am. Chem. Soc.* **2006**, *128*, 9194. (c) Discodermolide, L. E.; Poree, F.; Bourin, A.; Barbion, J.; Agouridas, E.; Lannou, M.; Commercon, A.; Betzer, J.; Pancrazi, A.; Ardisson, J. *Chem.—Eur. J.* **2008**, *14*, 11092.

10.1021/ol102797t © 2011 American Chemical Society
Published on Web 12/06/2010

pholane ligands (Figure 1) using glass bottle reactors, 1−12 h reaction times, and 1.1 equiv of ligand.

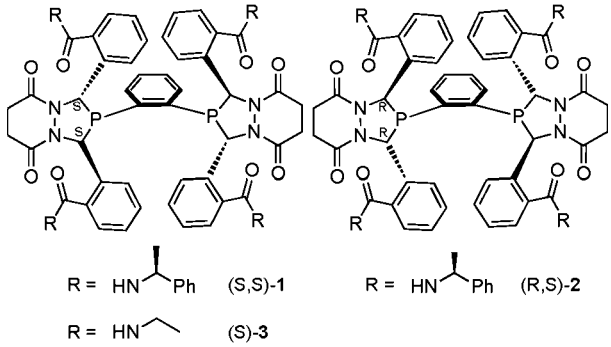
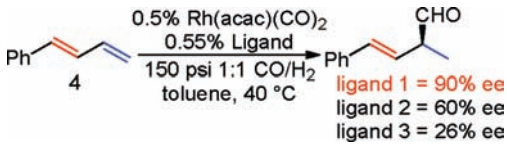


Figure 1. Diazaphospholane ligand structures.

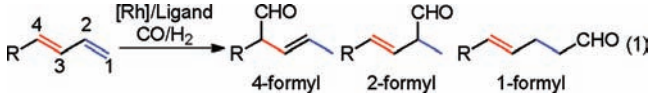
One approach to non-AHF, direct synthesis of chiral β,γ-unsaturated aldehydes involves the asymmetric organocatalytic addition of vinyl triflourborate salts to "SOMO" activated nascent enamines as reported by MacMillan and Kim.[6] Hydroformylation of dienes presents many opportunities for the synthesis of both fine and commodity chemicals.[7] AHF of dienes to yield chiral β,γ-unsaturated aldehydes intrinsically are advantaged due to the mild temperatures and essentially neutral pH, so long as the stereoselectivity of the double bond, along with regioselectivity and enantioselectivity of formylation, are controlled. For the dienes examined herein, 2-formyl products are preferred (see eq 1 for the numbering scheme used for all products and reactants).

We initiated our studies by evaluating the hydroformylation of (*E*)-1-phenyl-1,3-butadiene (**4**) under conditions of 150 psi synthesis gas (1:1 $CO:H_2$) using 0.5 mol % of $Rh(acac)(CO)_2$ and 0.55 mol % of ligands **1**−**3**[8] at 40 °C (Scheme 1). The reactions were complete within 4 h,

Scheme 1. Ligand Influence on Enantioselectivity

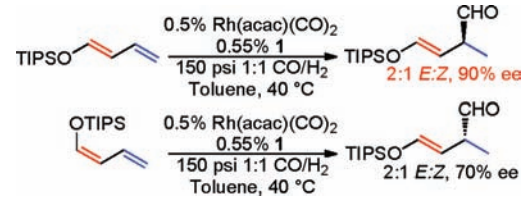


producing the β,γ-unsaturated 2-formyl regioisomer as the sole product in each case. Although excellent enantioselectivity (90% ee) was observed with use of ligand **1**, only modest enantioselectivities of 60% ee and 26% ee were obtained with ligands **2** and **3**, respectively. All three ligands yielded (*E*) alkene stereochemistry, exclusively.



During the course of our studies, we were unable to achieve high enantioselectivities for 1,3-dienes that comprise (*E*) and (*Z*) stereoisomer mixtures. This suggests that the enantioselectivity of the reaction depends on the 1,3-diene stereochemistry. For example, subjecting (*E*)-1-trisisopropylsilyoxy-1,3-diene to AHF yielded the 2-formyl aldehyde 2.5:1 ratio of the (*E*)- and (*Z*)-stereoisomers (Scheme 2) and

Scheme 2. Substrate Stereochemistry Effect



with 90% enantiomeric excess for the (*Z*)-product (we were unable to determine the ee of the (*E*)-product). On the other hand, AHF of the (*Z*)-stereoisomer gives the 2-formyl aldehyde with identical 2:1 *E*:*Z* ratio and, for the (*Z*)-product, the *opposite* sense of chirality in only 70% enantiomeric excess. Thus, we focused our attention primarily on 1,3-dienes that could be obtained as pure samples of the (*E*)-stereoisomer.

AHF of monosubstituted 1,3-dienes bearing aromatic and heteroaromatic substituents (entries 1 and 2) gives excellent enantioselectivities (91% ee and 97% ee, respectively) and exclusive formation of the (*E*)-stereoisomer. AHF of dienyl ethers produces 2-formyl aldehydes with high levels of enatioselectivity (90−94% ee). However, these aldehydes exist as a 1:1 mixture of (*E*)- and (*Z*)-stereoisomers, with somewhat reduced enantioselectivity observed for the (*Z*)-isomer. Attempts to increase the stereoselectivity by incorporating a sterically demanding TIPS group (entry 5) provided only a small increase in stereoselectivity (2.5:1 *E*:*Z*) while maintaining excellent enantioselectivity. Dienyl ethers are interesting substrates for AHF because reduction of both the aldehyde and alkene provides a straightforward route to monoprotected chiral 1,4-butanediols. Highly selective AHF extends to carboethoxy-1,3-pentadiene (Table 1, entry 6). AHF of this 1,1-disubstituted diene completes in only 1.5 h yielding exclusively the (*E*)-stereoisomer of the β,γ-unsaturated, 2-formyl aldehyde in 91% enantiomeric excess.

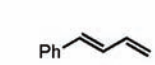
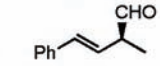
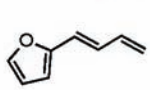
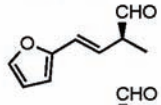
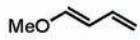
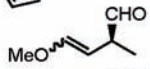
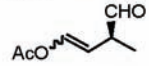
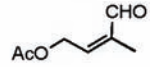
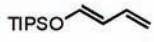
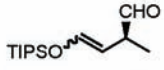
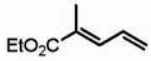
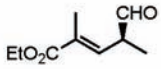
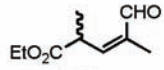
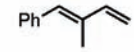
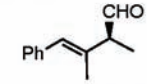
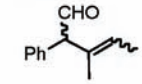
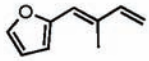
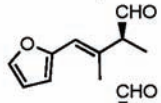
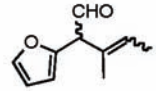
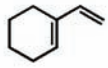
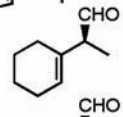
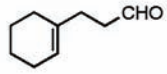
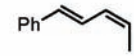
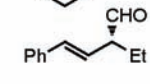
(5) (a) Smejkal, T.; Han, H.; Breit, B.; Krische, M. J. *J. Am. Chem. Soc.* **2009**, *131*, 10036. (b) Horiuchi, T.; Ohta, T.; Nozaki, K.; Takaya, H. *Chem. Commun.* **1996**, 155. (c) Horiuchi, T.; Ohta, T.; Shirakawa, E.; Nozaki, K.; Takaya, H. *Tetrahedron* **1997**, *53*, 7795.

(6) Kim, H.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2008**, *130*, 398.

(7) (a) Clement, W. H.; Orchin, M. *Ind. Eng. Chem. Prod. Res. Dev.* **1965**, *4*, 283. (b) Fell, B.; Bahrmann, H. *J. Mol. Catal.* **1977**, *2*, 211. (c) Bahrmann, H.; Fell, B. *J. Mol. Catal.* **1980**, *8*, 329. (d) Botteghi, C.; Branca, M.; Saba, A. *J. Organomet. Chem.* **1980**, *184*, C17. (e) van Leeuwen, P. W. N. M.; Roobeek, C. F. *J. Mol. Catal.* **1985**, *31*, 345. (f) Chalchat, J. C.; Garry, R. P.; Lecomte, E.; Michet, A. *Flavour Fragrance J.* **1991**, *6*, 178. (g) Bertozzi, S.; Campigli, N.; Vitulli, G.; Lazzaroni, R.; Salvadori, P. *J. Organomet. Chem.* **1995**, *487*, 41. (h) Barros, H. J. V.; Hanson, B. E.; dos Santos, E. N.; Gusevskaya, E. V. *Appl. Catal., A* **2004**, *278*, 57. (i) Barros, H. J. V.; da Silva, J. G.; Guimaraes, C. C.; dos Santos, E. N.; Gusevskaya, E. V. *Organometallics* **2008**, *27*, 4523.

(8) Ligands **1** and **2** are commercially available from Sigma Aldrich.

Table 1. Substrate Scope for the Asymmetric Hydroformylation 1,3-Dienes with Ligands **1**−**3**[a]

entry	1,3 diene	2-formyl	percent[b]	other	percent[b]	ligand	time (h)	% conv[b]	E:Z[b]	% ee (*E*,*Z*)[c]
1			99	---	---	1	4	99	>99:1	91
2			99	---	---	1	4	99	>99:1	97
3			99	---	---	1	4	99	1:1	94, 67[e]
4			60		40	1	1.5	99	1:1	91, 88[e]
5			99	---	---	1	4	99	2.5:1	90, nd[e]
6			95		5	1	1.5	99	>99:1	91
7[d]			88		12	3	4	99	>99:1	93
8[d]			98		2	3	4	99	>99:1	93
9[d]			88		12	3	4	99	>99:1	92
10			99	---	---	2	12	99	>99:1	91

[a] Reaction conditions unless otherwise noted: [alkene] = 1.2 M, [Rh] = 0.006 M, [ligand] = 0.0066 M, 150 psi 1:1 CO/H_2, 40 °C in toluene. [b] Determined via ^1H NMR spectroscopy. [c] Determined by chiral GC or chiral SFC chromatography (see the Supporting Information). [d] Reaction performed with 120 psi CO, 40 psi H_2, 50 °C. [e] Values for % ee are listed as (*E*-isomer, *Z*-isomer); *E*- and *Z*-isomers have opposite absolute configurations.

The successful hydroformylation of carboethoxy-1,3-pentadiene is noteworthy, as evidenced by Fürstner et al.'s recent use of the same aldehyde in the total synthesis of Iejimalide B.[9] Their route to the chiral aldehyde involved 6 steps starting from enantiopure Roche ester (methyl 3-hydroxy-2-methylpropionate). In contrast, *catalytic* AHF of the *achiral* 1,3-diene substrate provides this aldehyde in *one step*.

AHF of 1,2-disubstituted dienes (Table 1, entries 7−9) is more challenging. The combination of the less sterically hindered ligand **3** and a slightly elevated partial pressure of CO (120 psi CO, 40 psi H_2) were necessary to achieve good selectivity. From ligand screening results (see the Supporting Information), it appears that the steric parameter of the ligand affects the regioselectivity. Increasing the carbon monoxide partial pressure suppresses formation of 1-formyl aldehydes and increases enantioselectivity for the formation of 2-formyl aldehydes. AHF of 1-phenyl-2-methyl-1,3-butadiene with ligand **3** at 50 °C with 120 psi CO, 40 psi H_2 (entry 7) is complete within 4 h, yielding 2-formyl (88%) and 4-formyl aldehydes (12%). Interestingly, both regiosomers are β,γ-unsaturated aldehydes. Despite the reduced regioselectivity, the 2-formyl aldehyde was observed with exclusive (*E*) stereochemistry and 93% enantiomeric excess. Greater selectivity is observed when the phenyl group is replaced with the less bulky and more electron rich furyl group (entry 8). AHF of 1-(2-furyl)-2-methyl-1,3-butadiene gives 2-formyl aldehydes regioselectively (98%) as a single (*E*)-stereoisomer with 93% enantiomeric excess. The more rigid vinyl cyclohexene (entry 9) substrate proceeds with reduced regioselectivity (88% 2-formyl and 12% achiral 1-formyl) but with 92% ee.

AHF of internal alkenes is especially challenging, nevertheless 1-phenyl-1(*E*),3(*Z*)-diene yields high selectivity with ligand **2** (Table 1, entry 10). Complete consumption of the 1,3-diene is observed in 12 h, yielding the (*E*)-2-formyl aldehyde as the sole reaction product with excellent enantioselectivity (90% ee).

It is interesting that diazaphospholane-based AHF of (*E*)-1,3-dienes yields mixed (*E*)- and (*Z*)-stereoisomers with opposite absolute senses of stereochemistry (i. e., 2(*R*),3(*E*) and 2(S),3(*Z*)-2-formyl aldehydes) for entries 3−5 (Table 1). Analysis of the reaction mixtures at partial substrate conversion revealed no evidence for *E*−*Z* interconversion of the parent diene. This suggests that *E*−*Z* interconversion occurs "on" the cycle without dissociation of isomerized

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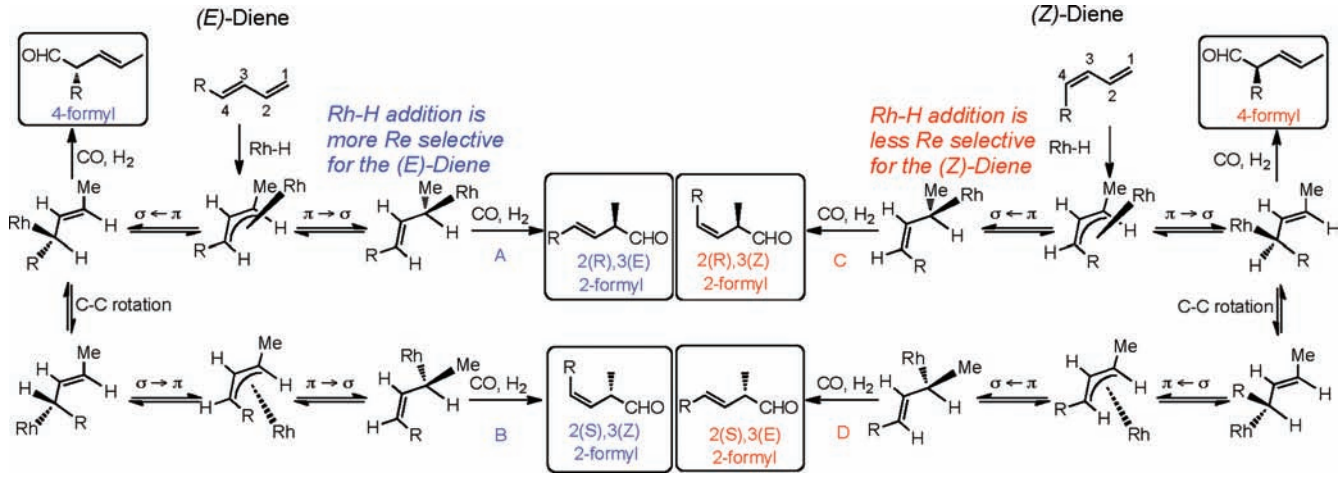
Scheme 3. Proposed Mechanism for the AHF of 1,3-Dienes



diene. The left side of Scheme 3 provides a plausible rationalization: the initial insertion of the vinyl group into the Rh−H bond is highly selective for the *re* enantioface but *E*−*Z* isomerization necessarily inverts the stereochemistry at the 2-position. Similar π-allyl complexes have been previously suggested as intermediates in the hydroformylation of 1,3-dienes[7a,i,4b] and the sequence of $\sigma-\pi$ allyl interchanges and C−C bond rotations have well-documented precedent in π-allylpalladium complexes.[10] Ultimately the *E*:*Z* ratio is controlled by the flux through points A and B of Scheme 3.

Further insight into stereocontrol is provided by the stereochemical outcome of the hydroformylation of (*Z*)-TIPS dienyl ether (Scheme 2). As illustrated on the right side of Scheme 3, addition of Rh−H to the diene is *re* selective but less so than for the (*E*) diene. Rapid $\sigma-\pi$ exchanges and C−C rotations establish Curtin−Hammet conditions with the *E*:*Z* ratio controlled by the relative fluxes through points D and C. Because the ultimate product regioselectivity is independent of the initial diene stereochemistry, this model requires that $\text{flux}^{A}/\text{flux}^{B} = \text{flux}^{D}/\text{flux}^{C} \approx 2.5$. For the R = OAc, OMe substituents, $\text{flux}^{A}/\text{flux}^{B} \approx 1$. For substrates that give 2-formyl aldehydes with exclusively (*E*)-alkene stereochemistry, it is likely that rotation about the C_4-C_3 bond is prevented for steric reasons.

The significance of successful diene AHF to organic synthesis lies in the simultaneous extension of the carbon scaffold, introduction of a chiral branching point, and installation of a versatile aldehyde group while retaining an alkene functionality for further transformation in an atom efficient catalytic process. The resulting β,γ-unsaturated aldehydes may be subjected to alkene metathesis, reduced and subjected to Sharpless epoxidation, hydrogenated to the corresponding alkanes and/or alcohols, etc. Although one must take caution in comparing catalysts' performance because conditions may not be optimized, the diazaphospholane ligands appear to give significantly (at least 10-fold) higher rates and somewhat higher selectivities under milder conditions than prior reports.[4b,c]

Acknowledgment. This research was supported by a grant from the National Science Foundation (NSF-CHE-0715491). We are grateful to Dow Chemical for their generous donation of $Rh(acac)(CO)_2$ and assistance with large-scale ligand preparation. We also would like to thank Prof. Tehshik Yoon and co-workers of the University of Wisconsin−Madison for access to SFC instrumentation.

Supporting Information Available: Experimental details, characterization data, and conditions for the determination of enantiomeric excess. This material is available free of charge via the Internet at http://pubs.acs.org.

OL102797T

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