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Asymmetric Hydroformylation of Vinyl Acetate: Application in the Synthesis of Optically Active Isoxazolines and Imidazoles

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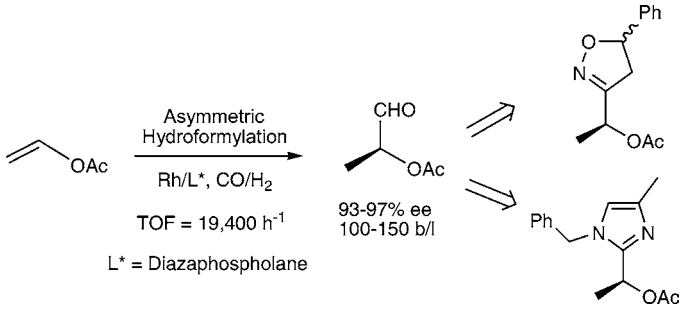
ABSTRACT



(*R*)- and (*S*)-2-(Acetyloxy)-propanal were prepared [93.8% ee, 102 b/l for (*R*), 96.9% ee, 149 b/l for (*S*)] via asymmetric hydroformylation of vinyl acetate on a 150−180 g scale and were used as the starting materials in the synthesis of chiral isoxazoline and imidazole derivatives which proceeded without racemization of the chiral center.

Asymmetric hydroformylation (AHF) is an atom economic, highly chemoselective transformation that allows conversion of olefins into chiral aldehydes in a single catalytic step.[1] Since aldehydes can be easily transformed into a variety of useful chemicals, such as amines, imines, alcohols, and acids, AHF constitutes an attractive entry to chiral intermediates. We recently have identified several highly selective ligands based on bis-phosphacycles for rhodium−catalyzed asymmetric hydroformylation reactions.[2−4] Out of this ligand class, diazaphospholane (*S*,*S*)-**1**[2] and (*R*,*R*)-Ph-BPE (**2**)[3] exhibit remarkable selectivity while maintaining high catalytic activity (Figure 1). For example, (*S*,*S*)-**1** gave 97% ee (branched-to-linear ratio (b/l) = 40) in the AHF of vinyl acetate at 80 °C while **2** led to 94% ee and unprecedented regioselectivity (b/l = 45) in the AHF of styrene at 80 °C. Very high selectivity and hydroformylation rates achieved with (*S*,*S*)-**1** and its diastereoisomer (*R*,*R*)-**3**[5] in AHF of vinyl

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(1) (a) Claver, C., van Leeuwen, P. W. N. M. In *Rhodium Catalyzed Hydroformylation*; Claver, C., van Leeuwen, P. W. N. M., Eds.; Kluwer Academic Publishers: Dordrecht, The Netherlands, 2000; Chapter 5. (b) Claver, C.; Dieguez, M.; Pamies, O.; Castillon, S. *Top. Organomet. Chem.* **2006**, *18*, 35−64.

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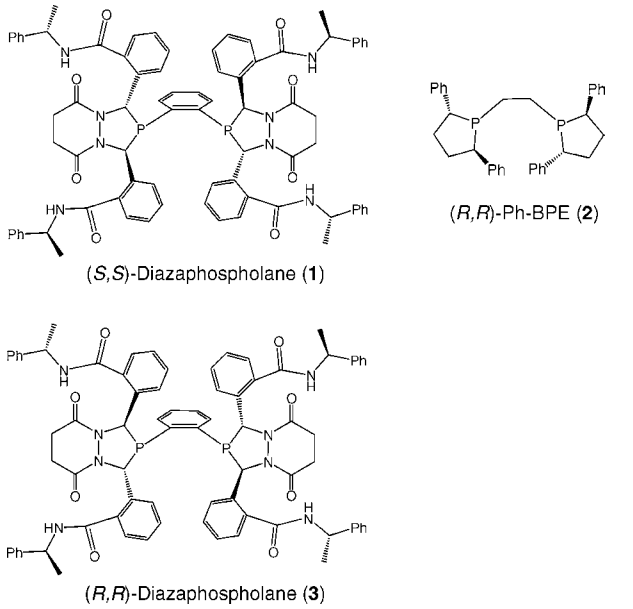
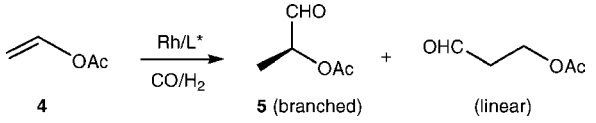


Figure 1. Structures of highly selective ligands in AHF.

acetate (**4**) coupled with a high degree of synthetic functionality offered by its hydroformylation product, 2-(acetyloxy)-propanal (**5**), prompted us to explore the synthesis and utilization of **5** (Scheme 1).

Scheme 1. Asymmetric Hydroformylation of Vinyl Acetate



In this communication, we report the large scale preparation of both enantiomers of **5** (150−180 g scale) by AHF of vinyl acetate using (*S*,*S*)-**1** and (*R*,*R*)-**3** and the application of both enantiomers of **5** in the preparation of various heterocyclic compounds, specifically chiral isoxazoline (**10**−**12**) and imidazole (**15**) derivatives.

Since the previous AHF experiments with (*S*,*S*)-**1** were conducted on a mixture of olefins,[2] it was important to determine catalytic properties of (*S*,*S*)-**1** in AHF of pure vinyl acetate. For this purpose, a series of runs with vinyl acetate were conducted using an Endeavor parallel reactor at 80−100 °C and 50−450 psi syngas pressure with the substrate to a Rh molar ratio varying from 5000 to 150000. We found that even at a Rh to substrate ratio of 100000 and 200 psi syngas pressure, reactions were 97% complete within 5 h, which translates into an average TOF of 19400 h^{-1} (Table 1).

(5) (*S*,*S*)-**1** and (*R*,*R*)-**3** diastereoisomers differ in chirality of the phosphacycle fragment of the ligand which determines absolute configuration of AHF products.

Table 1. AHF of Vinyl Acetate with (*S*,*S*)-**1**[a]

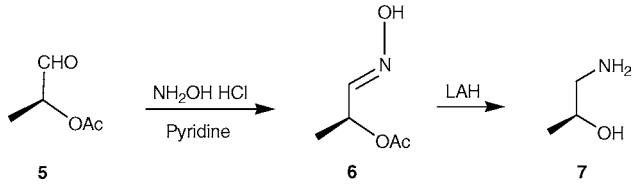
entry	pressure	% conversion	b/l[b]	% ee[c]	TOF (h^{-1})[d]
1	50	14	22.5	91	2800
2	100	72	29.9	95	14400
3	200	97	28.7	95	19400
4	300	97	26.1	96	19400
5	400	94	29.0	96	18800

[a] Conditions: temp = 80 °C, vinyl acetate/Rh molar ratio = 100000, (*S*,*S*)-**1**/Rh = 1.2, 4 mL of vinyl acetate, 5 h reaction time. [b] ratio of branched to linear isomers. [c] % ee = enantiomeric excess of branched isomer. [d] TOF = turnover frequency (average).

Enantio- and regioselectivities were maintained at very high levels (95−96% ee, b/l = 26−30) regardless of the pressure used (within the range of 100−450 psi). With this information in hand, a scale-up of vinyl acetate AHF was undertaken in a 300 mL Parr reactor. Tetraglyme was used (25 g) during the reaction to allow for easy product recovery and catalyst recycling.[6] Vinyl acetate (135 g) was reacted under hydroformylation conditions for 23 h using (*S*,*S*)-**1**/Rh catalyst (VA/Rh = 100000) at 75 °C and 475 psi syngas pressure. This led to 98.9% substrate conversion and clean product formation (96.8% ee and b/l = 46.9). The product (*S*-**5**) was recovered from the reaction mixture by distillation under reduced pressure (155 g, 85.5% yield, 96.8% ee, b/l = 139). Hydroformylation of vinyl acetate with (*R*,*R*)-**3** at 50 °C gave 92.8% yield of *R*-**5** (93.8% ee and b/l = 102) after distillation. Enhanced product regioselectivity upon distillation is due to the lower boiling point of the branched isomer. These experiments demonstrate that diazaphospholanes (*S*,*S*)-**1** and (*R*,*R*)-**3** enable highly efficient and highly enantio- and regioselective hydroformylation of vinyl acetate on a large scale.

Having synthesized large quantities of (*S*)- and (*R*)-2-(acetyloxy)-propanal (**5**), we focused on the application of **5** to the synthesis of chiral intermediates of varying molecular complexity. At the outset, (*S*)-1-amino-2-propanol (**7**) was synthesized as shown in Scheme 2 to ensure that the

Scheme 2. Synthesis of (*S*)-Amino-2-propanol **7**



enantioselectivity established during AHF can be maintained during synthetic transformations (Scheme 2). The aldoxime **6** was obtained as a mixture of *Z* and *E* isomers in 90% yield by treatment of **5** with hydroxylamine hydrochloride in the presence of pyridine. Lithium aluminum hydride

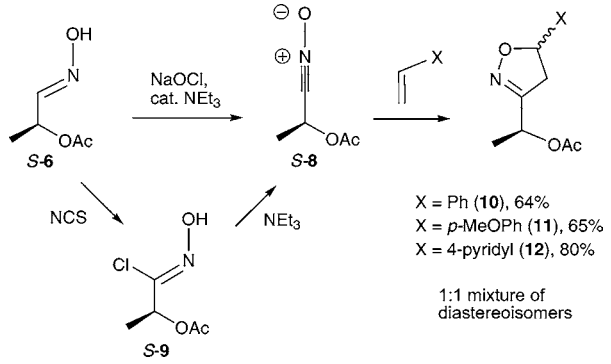
(6) See Supporting Information for more details.

reduction of the aldoxime **6** gave (*S*)-1-amino-2-propanol (**7**) in 70% yield. Optical purity of **7** was found to be the same (94% ee) as that of **5**, thereby establishing the complete retention of the chiral center during aldoxime formation and the subsequent reduction. Interestingly, when triethylamine was used as a base for the preparation of aldoxime, the enantioselectivity of **7** was significantly reduced to 28% ee.

After obtaining the chiral oxime *S*-**6**, its application toward the synthesis of two classes of heterocyclic compounds was explored. Conversion of oxime derivatives to nitrile oxides and subsequent cycloaddition reactions with various dipolarophiles is a well-known method to generate isoxazoline derivatives.[7] Hydrolysis and reduction of the isoxazolines provides entry into hydroxyl ketones and hydroxylamines, respectively.

A broad range of isoxazoline derivatives having a chiral side chain (Scheme 3) can be envisioned from nitrile oxide

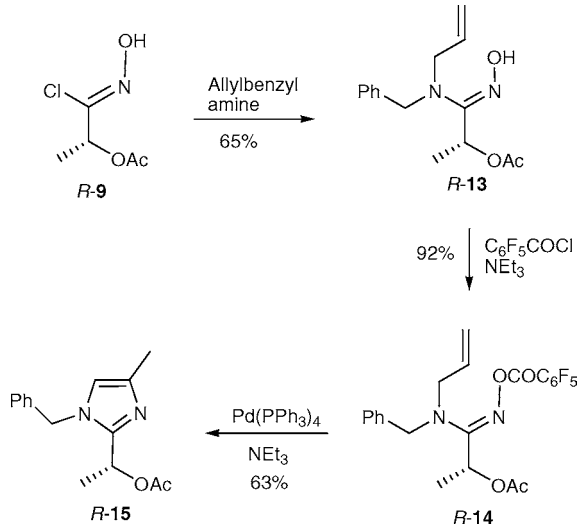
Scheme 3. Synthesis of Chiral Isoxazolines



S-**8** by choosing appropriate dipolarophiles. To demonstrate the generality of this strategy, we synthesized isoxazoline **10**, **11**, and **12**. Nitrile oxide *S*-**8** was prepared in situ from *S*-**6** using aqueous sodium hypochlorite (5% solution) and a catalytic amount of triethylamine in methylene chloride. Reaction of in situ generated *S*-**8** with styrene furnished **10** in 64% yield as diastereomeric mixture (1:1). Similarly, reaction between *S*-**8** and *p*-methoxystyrene led to the formation of **11** in 65% yield. However, reaction of *S*-**8** with 4-vinylpyridine did not give the desired cycloadduct **12** under these conditions. The failure of this reaction was attributed to the instability of 4-vinylpyridine in the presence of hypochlorite. To circumvent this difficulty, an alternative approach to generate nitrile oxide *S*-**8** was employed. For this purpose, hydroximoyl chloride *S*-**9** was prepared in 85% yield from *S*-**6** by chlorination with *N*-chlorosuccinimide.[8] Unlike *S*-**6**, which exists as a mixture of isomers, hydroximoyl chloride *S*-**9** exists as a single isomer (*Z*) as shown by NMR analysis. Reaction of nitrile oxide *S*-**8** with 4-vinylpyridine afforded **12** in 80% yield.

Hydroximoyl chloride **9** with its chlorine moiety provides a useful handle for further elaboration to other heterocyclic compounds. We have utilized this compound to synthesize substituted imidazole derivatives containing a chiral side chain (Scheme 4). The aldoxime *R*-**6** and hydroximoyl

Scheme 4. Synthesis of Chiral Imidazole Derivatives



chloride *R*-**9** were prepared by following the same procedures employed for *S*-**6** and *S*-**9**. In addition to spectroscopic methods, *R*-**9** was characterized by X-ray analysis (vide infra). The critical step in this synthesis is an amino Heck reaction. The key substrate *R*-**14** was prepared from *R*-**9** first by reaction with allylbenzylamine to obtain *R*-**13** followed by its treatment with pentafluorobenzoyl chloride. Both intermediates *R*-**13** and *R*-**14** were obtained as a mixture of *E* and *Z* isomers. The intermediate *R*-**14** was subjected to an amino Heck reaction according to a literature procedure[9] to obtain imidazole derivative *R*-**15** in 63% yield.

To determine the optical purity of *R*-**15**, the other enantiomer, *S*-**15**, was prepared from *S*-**9** following the same reaction sequence presented in Scheme 4. The optical purity of *R*-**15** and *S*-**15** evaluated by Chiral HPLC analysis (Chiralpack AD column) was found to be 94.2% ee and 94.9% ee, respectively. These results clearly demonstrate that no decrease of optical purity has taken place during the synthesis of imidazole derivatives.

Finally, the existence of hydroximoyl chloride *R*-**9** as a solid provided an opportunity to determine unambiguously by X-ray crystallography the absolute configuration of 2-(acetyloxy)-propanal obtained by AHF of vinyl acetate employing bisdiazaphospholane ligands. Our original assignment[2] of the absolute configuration of 2-(acetyloxy)-propanal (**5**), obtained via AHF of vinyl acetate using (*S*,*S*)-**1** and (*R*,*R*)-**3**, was based on the comparison with previously reported AHF data.[10] Accordingly, the absolute configuration of 2-(acetyloxy)-propanal produced by (*S*,*S*)-**1** and (*R*,*R*)-**3** was assigned as *S* and *R*, respectively. Large colorless

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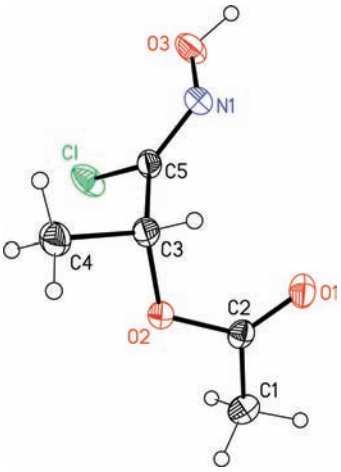

Figure 2. Thermal ellipsoid drawing of (*R*)-**9** shown at 40% probability level.

crystals of **9**, originated from AHF of vinyl acetate with (*R*,*R*)-**3**, were obtained from a THF/hexane mixture at −40 °C. Hydroximoyl chloride (**9**) crystallized in noncentrosymmetric space group $P2_12_12_1$.[11] X-ray analysis (Figure 2) determined the compound to be of *R* configuration[12] thus confirming previous assignment.

In conclusion, we have demonstrated that both enantiomers of 2-(acetyloxy)-propanal (**5**) are easily accessible on a large scale using highly efficient and highly selective asymmetric hydroformylation of vinyl acetate. The turnover frequencies achieved are the highest reported for any ligand or any substrate in rhodium-catalyzed asymmetric hydroformylation. The 2-(acetyloxy)-propanal (**5**) was shown to be a versatile chiral intermediate that can be transformed into various isoxazoline and imidazole derivatives without loss of optical purity. Extension of this approach should allow the synthesis of other chiral substituted imidazoles as well as chiral heterocyclic compounds containing sulfur or oxygen.

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Supporting Information Available: Experimental procedures, NMR spectra for **10**, **11**, **12**, and **15**, and single-crystal X-ray analysis data for (*R*)-**9**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) Structure of (*R*)-**9**. $C_5H_8ClNO_3$, M_w = 165.57, orthorhombic, $P2_12_12_1$, colorless plates (0.24 × 0.18 × 0.11 mm^3), a = 6.1304(6) Å, b = 10.4292(10) Å, c = 11.9236 Å, temp = 173(2) K, Z = 4, V = 762.34(13) Å (3), R1 = 0.0319, 0.0325, wR2 = 0.0787, 0.793 ($I > 2\sigma(I)$, all data), GOF = 1.084.

(12) Since the compound used to grow crystals was not pure enantiomer (94% ee) it was necessary to confirm whether the crystal used for X-ray analysis was indeed the major enantiomer. To accomplish this, single crystal used to supply small crystal for X-ray analysis was later analyzed by chiral HPLC. The analysis showed it to be pure enantiomer of the major isomer.