ORGANIC LETTERS

2005
Vol. 7, No. 22
4795−4798

Synthesis of Biologically Active Amines via Rhodium–Bisphosphite-Catalyzed Hydroaminomethylation

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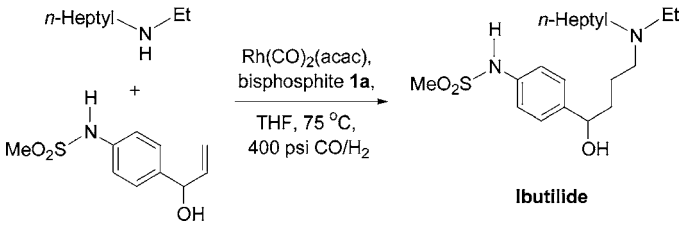
Received April 18, 2005 *(Revised Manuscript Received July 8, 2005)*

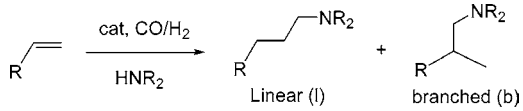
ABSTRACT



We report the use of a highly regioselective rhodium–bisphosphite catalyst for olefin hydroaminomethylation. This catalyst system was successfully applied in the synthesis of two biologically active tertiary amines, ibutilide and aripiprazole.

Rhodium-catalyzed olefin hydroformylation is an industrially practiced transformation for the synthesis of aldehydes and their derivatives.[1] A number of tandem reactions, which employ hydroformylation, have been developed that further extend the synthetic utility of the hydroformylation reaction.[2] In particular, hydroaminomethylation (tandem olefin hydroformylation followed by reductive amination) is an attractive transformation that allows for the synthesis of secondary and tertiary amines from readily available olefins (Scheme 1).[2,3]

Scheme 1. Hydroaminomethylation Reaction



Recent applications of rhodium-catalyzed hydroaminomethylation have predominantly employed phosphine ligands.[2−4] Several of these studies have concluded that phosphite ligands are unsuitable for this reaction and lead to low yields of amine products.[4,5] The inability of rhodium−phosphite catalysts to promote hydroaminomethylation was attributed to hydrolytic instability of the ligand under the reaction conditions. However, a few reports describing successful application of bisphosphite ligands in hydroaminomethylation have also appeared.[6] Bisphosphite ligands such as **1a** form highly regio-[7] and chemoselective[8] rhodium-based hydroformylation catalysts. Additionally, these bisphosphites are very active and lead to hydroformylation rates which are significantly higher than those observed with

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10.1021/ol050848y CCC: $30.25
Published on Web 09/27/2005

bisphosphine ligands. These attributes make pursuit of hydroaminomethylation reactions with bisphosphite ligands attractive. Herein, we report our initial results on the nature of rhodium-phosphite catalyst systems along with their application in the synthesis of two pharmacologically active amines using olefin hydroaminomethylation.

To evaluate the utility of rhodium-phosphite catalysts in hydroaminomethylation reactions, we first attempted the reaction of 1-pentene and piperidine in the presence of 1:2 CO/H_2 (Table 1). Reactions were performed in THF using

Table 1. Hydroaminomethylation of 1-Pentene with Piperidine[a]

ligand	L/Rh	% conv	% amine	l/b[b]
1a	1.0	96.6	8	40.0
1a	0.9	97.0	92	12.1
1a	0.8	97.3	100	6.4
1b	2.4	100	100	1.5

[a] Conditions: 90 °C, 400 psi 1:2 CO/H_2, 0.2 mol % Rh, 18 h, decane internal standard. [b] l/b = linear/branched ratio of amines (1-hexylpiperidine/1-(2-methylpentyl)piperidine).

0.2 mol % $Rh(CO)_2(acac)$ and either bisphosphite **1a** or phosphite **1b** (Figure 1).[9] GC and NMR analysis of reaction

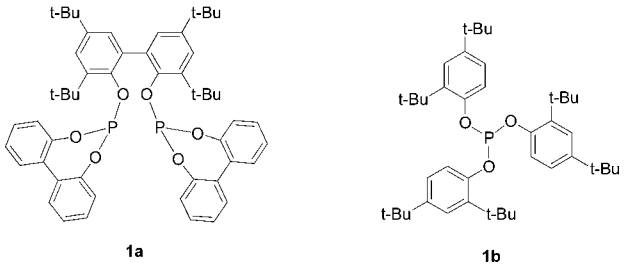


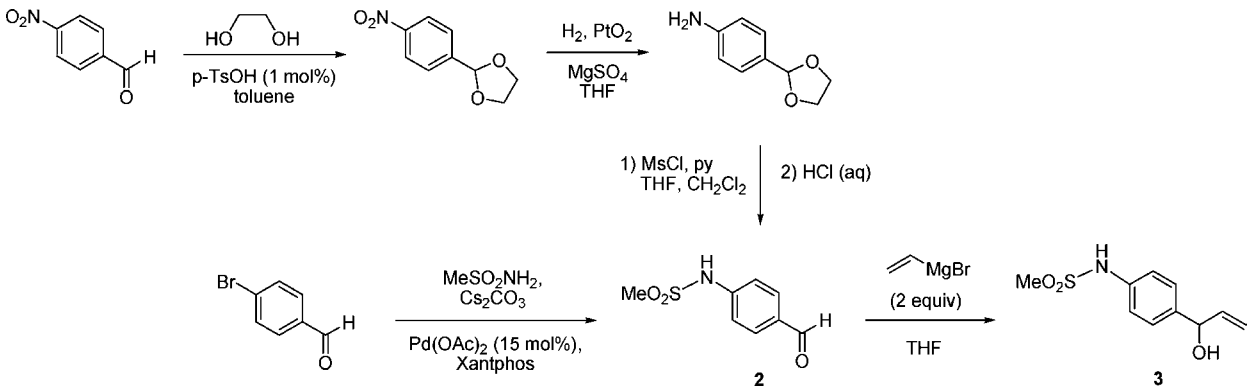
Figure 1. Phosphite ligands used in this study.

mixtures revealed that these catalysts are very effective in promoting hydroaminomethylation. The monodentate phosphite **1b** led to clean formation of amine products with marginal regioselectivity for the linear isomer (l/b = 1.5:1). Neither aldehyde nor enamine intermediates were detectable. The regioselectivity of the amine products was identical to that of the aldehydes produced by 1-pentene hydroformylation in the absence of piperidine.

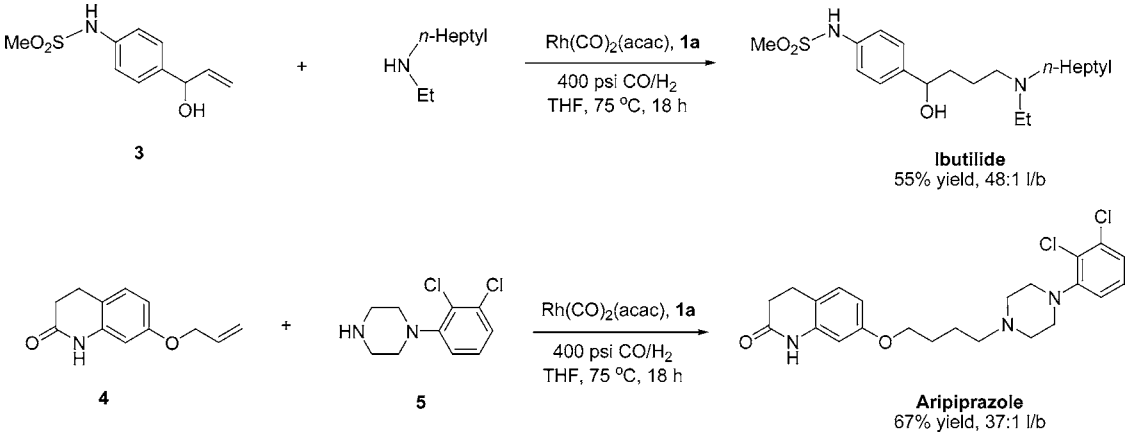
Hydroaminomethylation of 1-pentene with piperidine using bisphosphite **1a** gave amine products, but the selectivity of this reaction was initially irreproducible. A detailed study of the effect of reaction conditions was performed. The rate of amine formation was reduced at lower H_2/CO pressures where hydroformylation readily occurs. These studies also revealed a strong effect of **1a**/Rh ratio on the selectivity of this reaction. When the reaction was performed using equimolar amounts of **1a** and $Rh(CO)_2(acac)$, *N*-hexylpiperidine was formed with high selectivity toward the linear isomer (l/b = 40:1), consistent with the high linear regioselectivity observed for this catalyst in hydroformylation. Enamine and aldol impurities were observable by GC, and the yield of this reaction was lower than that obtained using the monodentate phosphite. As the ratio of **1a** to rhodium was decreased below the stoichiometric level, the yield of amine increased but was accompanied by a concurrent decrease in the linear:branched ratio. These results suggest that enamine hydrogenation using the catalyst system formed by reaction of **1a** with $Rh(CO)_2(acac)$ occurs predominantly by a catalyst which does not contain phosphite ligand. At sub-stoichiometric ratios of **1a** relative to rhodium, enamine hydrogenation becomes faster, but hydroformylation by a phosphite-free species derived from excess $Rh(CO)_2(acac)$ reduces the regioselectivity of the reaction.

Rhodium complexes of bulky monodentate phosphite ligands such as **1b** are in equilibrium with unligated Rh−carbonyl complexes and require very large concentrations of phosphite to bind all available Rh centers.[10] Under the conditions used in our hydroaminomethylation reactions with **1b**, a sufficient concentration of unligated rhodium is present to efficiently hydrogenate the enamine intermediate. Garland has reported that $Rh(CO)_4H$ is a highly active, unselective hydroformylation catalyst which is also capable of hydrogenating olefins.[11] This species is presumably responsible

Scheme 2. Synthesis of Olefin Precursor to Ibutilide



Scheme 3. Synthesis of Ibutilide and Aripiprazole via Hydroaminomethylation



for the enamine hydrogenation observed with phosphite ligands **1a** and **1b**.

Given the successful use of rhodium−phosphite catalysts, we next applied hydroaminomethylation to the synthesis of the anti-arrhythmia drug ibutilide.[12] The required allylic alcohol **3** was synthesized from *N*-(4-formylphenyl)-methanesulfonamide **2**, which was prepared via two different routes (Scheme 2).[13] The 1,3-dioxolane of 4-nitrobenzaldehyde was reduced with hydrogen using PtO_2 catalyst.[14] It was found that the presence of $MgSO_4$ was required to remove water formed during reduction of the nitro functional group. Reductions performed without efficient removal of water led to formation of a bright orange insoluble material, presumably resulting from condensation polymerization of 4-aminobenzaldehyde formed by hydrolysis of the acetal protecting group. Introduction of the sulfonamide group followed by deprotection of the acetal gave *N*-(4-formylphenyl)-methanesulfonamide, **2**. An alternate one-step synthesis of **2** was also developed and employed Pd/Xantphos-catalyzed coupling of 4-bromobenzaldehyde with $MeSO_2NH_2$.[15] Addition of 2 equivalents[16] of vinyl Grignard reagent led to the allylic alcohol precursor (**3**) of Ibutilide. The amine coupling partner, *N*-ethyl-1-heptanamine, was synthesized by $LiAlH_4$ reduction of *n*-heptylacetamide.[17] Reaction of **3** with *N*-ethylheptylamine using 1 mol% $Rh(CO)_2(acac)$ and bisphosphite **1a** (Rh:**1a** = 1:1.1) in THF at 75 °C under 400 psi 1:1 CO/H_2 gave Ibutilide in 55% yield with 48:1 regioselectivity in favor of the desired linear isomer (Scheme 3).[18] A slight excess of bisphosphite **1a** was utilized in this reaction to maximize the regioselectivity at the expense of product yield.

The ^1H NMR spectrum of Ibutilide prepared via hydroaminomethylation (Scheme 3) was identical to that previously reported.[19] Notably, protection of the alcohol moiety in **3** was found to be unnecessary. Although the intermediate hydroxy aldehyde produced from hydroformylation of **3** could cyclize to form a lactol,[20] this potential side reaction did not impact the reductive amination step of the hydroaminomethylation reaction.

The second target studied for application of hydroaminomethylation was the antidepressant aripiprazole.[21] The amine and olefin coupling partners required for synthesis of aripiprazole were prepared following published procedures. The olefinic substrate, 7-(allyloxy)-3,4-dihydro-2(1*H*)-quinoline, **4**, was synthesized by reaction of 3-aminophenol with 3-chloropropionyl chloride followed by *O*-allylation with allyl bromide.[22] The arylpiperazine **5** was prepared by palladium-catalyzed amination using excess piperazine to minimize formation of diarylated product.[23] Hydroaminomethylation of allyl ether **4** with **5** led to aripiprazole in 67% yield with high regioselectivity (l/b = 37:1) using a 1:1.3 ratio of $Rh(CO)_2(acac)$ and bisphosphite **1a** (Scheme 3). The ^1H NMR spectrum of the product, after acidic workup, was identical to NMR data of aripiprazole reported by Oshiro et

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al.[24] Notably, the rhodium−bisphosphite catalyst was tolerant of aryl chloride functionality and exhibited chemoselective reaction of the arylpiperazine N−H bond[25] in the presence of the secondary amide moiety.

The bisphosphite **1a** leads to highly regioselective rhodium-catalyzed intermolecular hydroaminomethylation. Catalyst studies indicate that hydrogenation of the intermediate enamine occurs by a rhodium species which is not coordinated by phosphite ligands. Hydroaminomethylation using ligand **1a** requires significantly lower reaction temperature (70−90 °C) than bisphosphine ligands[4b] (>110 °C). Ligand **1a** leads to high linear regioselectivity and tolerates a variety of functional groups in both the amine and olefin, making this a useful catalyst for synthesis of complex amines via intermolecular hydroaminomethylation reaction. Experiments aimed at further optimization of rhodium−bisphosphite catalysts for hydroaminomethylation reactions are underway. The use of alternative heterogeneous enamine hydrogenation catalysts with these highly selective homogeneous hydroformylation catalysts is currently under investigation.

Acknowledgment. Cynthia Rand of Dowpharma is gratefully acknowledged for her encouragement and support of this work. Tia Jackson is thanked for performing preliminary experiments.

Supporting Information Available: Experimental procedures and spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

OL050848Y

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