ORGANIC LETTERS

XXXX
Vol. XX, No. XX
000–000

Rhodium-Catalyzed Highly Regioselective Hydroaminomethylation of Styrenes with Tetraphosphorus Ligands

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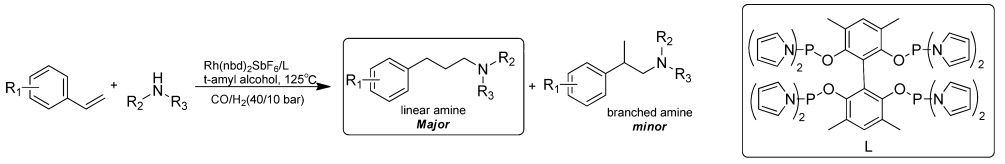
Received May 6, 2013

ABSTRACT



The highly linear-selective hydroaminomethylation of styrenes is very challenging. Herein, an efficient, highly chemoselective, and linear-selective hydroaminomethylation (l/b up to >99:1) of styrenes using $Rh(nbd)_2SbF_6$ with a pyrrole-based 3,3′,5,5′-substituted tetraphosphorus ligand is documented. This is in sharp contrast to other available processes leading to branched amines and provides a novel atom economic approach to 3-arylpropylamines.

Amines are an important class of molecules in bulk as well as fine chemicals. Many amines can serve as versatile building blocks in the synthesis of pharmaceuticals, agrochemicals, natural products, and dyes.[1] Various methods for preparing amines have been developed, including alkylation of ammonia and amines, reduction of imines, and hydrocyanation of alkenes followed by reduction. Making amines directly from inexpensive and readily available alkenes is an attractive approach due to the atom economy. While hydroamination of olefins[2] and reductive hydroamination of alkynes[3] can lead to certain amines, those methods still remain to be developed. Hydroaminomethylation of alkenes, originally discovered by W. Reppe at BASF,[4] is a powerful method and holds great potential for commercial applications.

The hydroaminomethylation consists of a tandem reaction of hydroformylation of an alkene to aldehyde and subsequent condensation with an amine to form enamine or imine, followed by hydrogenation. It is an atom economic and environment benign approach to amines.[5] The challenge

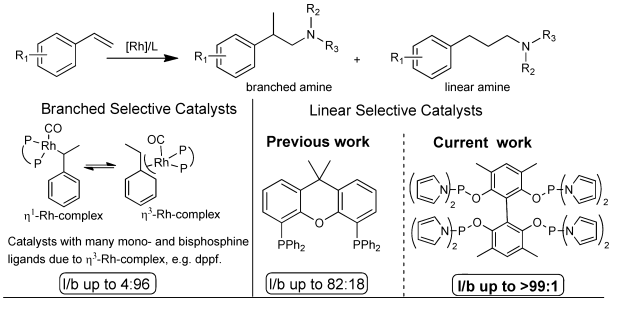


Figure 1. Regioselective hydroaminomethylation of styrenes.

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10.1021/ol4012635 © XXXX American Chemical Society

of this reaction is to combine the highest chemo- and regioselectivity together to efficiently obtain the expected amine. Linear-selective hydroaminomethylation of styrenes is very challenging among the different alkenes due to the intrinsic trend to form branched amines (the highest l/b = 82/18[6]). To the best of our knowledge, there is no general report on the highly linear−selective hydroaminomethylation of styrenes to produce 3-arylpropylamines. Herein, a rhodium catalytic system is presented with a tetraphosphorus ligand, which allows for an efficient and unprecedented linear-selective (l/b up to >99:1) hydroaminomethylation of styrenes (Figure 1).

We envision that the highly linear-selective hydroaminomethylation of styrene and its derivatives is an elegant and powerful tool to synthesize many small molecular phamarceuticals,[7] such as Sensipar, NPS 467, NPS 568, and Strattera (Figure 2). Many catalytic systems have been developed to achieve highly branched-selective hydroaminomethylation of styrenes (the ratio of b/l varies from 59:41 to 96:4), such as the zwitterionic Rh complex developed by Alper (b/l up to 15),[8] Rh/P,N-ligands reported by Kostas group (b/l up to 6.6),[9] Rh/carbene catalyst documented by Beller (b/l = 79:21),[10] and catalytic system of Rh/bidentate phosphine ligands promoted by a Lewis acid disclosed by Beller and Thiel (b/l up to 96:4).[11] Without any phosphine ligand, Rh can catalyze the hydroaminomethylation of styrenes to offer branched products with good selectivity (b/l up to 16).[12] The linear selective hydroaminomethylation of styrenes can be easily achieved with α-substituted styrenes, with the l/b ratio up to >99:1, in either intra-[13] or intermolecular reactions.[10,11a] This high regioselectivity can be attributed to the steric hindrance of the substituents. Selective hydroaminomethylation of styrene to linear amine (l/b = 82/18) in the presence of Xantphos as a ligand was first reported by Beller's group.[6] We believe that the development of new ligands is the key to implementing the highly linear selective hydroaminomethylation of styrenes.

In our continuing efforts to develop novel catalysts for organic synthesis, synthesis and application of novel multiple

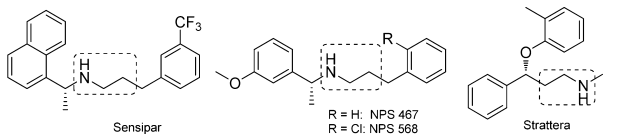

Figure 2. Sensipar, NPS 467, NPS 568, and Strattera.

chelating Tetrabi ligands (Tetrabi = 2,2′,6,6′-tetrakis-((diphenylphosphino)methyl)-1,1′-biphenyl)[14] and BTPP ligands (BTPP = biphenyl-2,2′6,6′-tetrakis(dipyrrolyl phosphoramidite))[15] were reported in hydroformylation. Those two kinds of ligands have found many applications in the highly regioselective hydroformylation of simple terminal alkenes and functionalized alkenes, as well as internal alkenes. The good performance was envisioned to result from the multiple chelating ability and improved local ligand concentration. Among the studied alkenes, styrene has been hydroformylated to the linear aldehyde with surprisingly high linear selectivity (l/b = 22 for styrene, l/b up to >99:1 for its derivatives).[16] The high linear regioselectivity prompted us to assess our ligands further in the hydroaminomethylation of styrenes, since the selectivity in hydroaminomethylation is provided by the initial hydroformylation step.

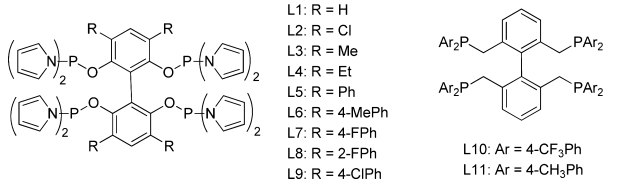

Figure 3. Structures of the tested ligands.

Initially, combinations of $[Rh(nbd)_2BF_4]$ with different tetraphosphorus ligands (Figure 3) were tested in the model reaction of styrene with piperidine. Some representative results are shown in Table 1, regarding the influence of ligands and solvents. Except for L11 (Table 1, entry 11), most Rh complexes give high conversions. It should be noted that, compared with pyrrole-based tetraphosphorus ligands (L1−9), Tetrabi ligands produced more ethylbenzene as a byproduct through direct hydrogenation (Table 1, entries 10 and 11). However, the linear selectivity of Tetrabi ligands is very poor with the branched amines as major products. Although the amines selectivity is not

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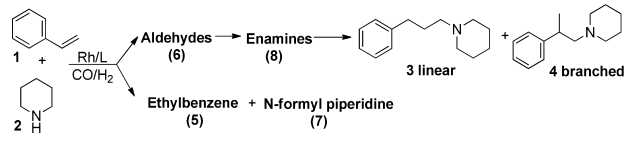
satisfactory, the linear selectivity is promising with the pyrrole-based ligands, with which the production of ethylbenzene is also surpressed (Table 1, entries 1−9).

The chemo- and regioselectivity of hydroaminomethylation is significantly influenced by ligand structure. Compared with ligand L1, the attachment of electron-donating methyl and ethyl groups at the 3,3′,5,5′-positions of the biphenyl backbone results in higher amines selectivity with yields of 56.3% and 55.2% and linear selectivity with an l/b ratio of 4.6 and 4.1, respectively (Table 1, entries 3 and 4). The reverse effect was detected with an electron-withdrawing group (Table 1, entry 2). The linear selectivity is somewhat improved when replaced by a phenyl group (Table 1, entry 5). The effect of the substituents of the phenyl moiety on selectivity is also remarkable (Table 1, entries 5−9). Among the tested ligands, L3 appeared to be the optimal ligand giving good regioselectivity (l/b = 4.52), which is a little different from our previous report on the corresponding hydroformylation where the L6 is the best ligand.[16] It is expected that the presence of amines will influence the l/b selectivity of the initial hydroformylation.

Table 1. Hydroaminomethylation of Styrene with Piperidine with Different Ligands and Solvents[a]



			product distribution (%)[b]					
entry	L	conv (%)	6	7	8	3+4	3[c]	l/b[d]
1	L1	97	4.8	3.1	59.9	32.2	60.0	1.5
2	L2	92	7.8	5.6	56.1	30.4	58.3	1.4
3	L3	100	1.5	1.9	40.2	56.3	82.1	4.6
4	L4	100	3.1	1.9	39.8	55.2	80.4	4.1
5	L5	100	3.9	16.0	41.6	38.1	62.9	1.7
6	L6	100	3.9	13.5	42.7	39.8	64.3	1.8
7	L7	98	5.1	24.1	32.7	38.0	54.5	1.2
8	L8	100	6.1	9.4	57.7	26.8	50.0	1.0
9	L9	100	8.5	10.7	57.4	23.4	47.4	0.9
10	L10	98	5.1	4.5	52.3	34.8	47.4	0.9
11	L11	82	1.7	6.7	21.2	66.3	23.1	0.3
12	L3	100	5.8	2.2	41.4	50.6	77.8	3.5
13	L3	100	0.7	2.3	0	97	11.5	0.13
14	L3	100	0.2	1.4	0	98.4	14.5	0.17
15	L3	100	0.5	1.2	0	98.3	16.0	0.19
16	L3	98	1.9	0.3	51.3	46.5	90.5	9.5
17	L3	99	0.4	2.4	18.0	79.2	52.4	1.1

[a] Unless otherwise mentioned, all reactions were carried out with a $[Rh(nbd)_2]BF_4$/ligand/substrate ratio of 1:4:500, under syngas of CO/H_2 (30 bar/10 bar) at 125 °C for 8 h. Ethylbenzene accounts for the product balance. Solvents used: entries 1−11 (toluene), 12 (xylene), 13 (methanol), 14 (ethanol), 15 (isopropanol), 16 (*tert*-amylalcohol), 17 (*tert*-amyl alcohol/methanol = 1:1). [b] Determined by GC analysis using bis(methoxyethyl) ether as an internal standard. [c] Percentage of linear amine in all amines. [d] The linear/branched ratio was determined on the basis of GC analysis and repeated three times; error is estimated to be <0.2. nbd = 2,5-norbornadiene.

In the survey of solvent effects on the regioselectivity, aromatic solvent xylene was tested first, in which both the yield and linear selectivity were brought down to some extent, although full conversion was achieved (Table 1, entry 12). The reaction proceeds smoothly in more polar solvents (Table 1, entries 13−15), and the yields of amines are excellent; however, the regioselectivity of this reaction was converted to a branched amine. The linear selectivity increased following the trend MeOH < EtOH < iPrOH. It motivated us to test alcohol with more bulky groups and higher pK_a values. Though hydrogenation of the in situ produced enamine is the rate-determining step,[4c] the regioselectivity improved dramatically in *tert*-amyl alcohol with l/b = 9.5.

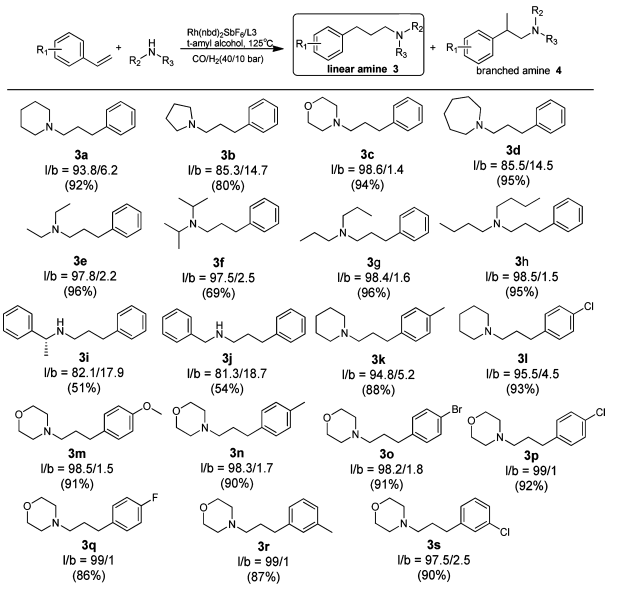
To improve the l/b ratio, other Rh sources with different counterions were screened with L3 in *tert*-amyl alcohol; all the reactions proceeded with almost full conversion, and the formation of *N*-formylpiperidine is also suppressed. Interestingly, a positive impact on regioselectivity was observed when the BF_4^- counterion was replaced by SbF_6^- (Table 2, entry 5, l/b = 15.5). Further optimizations demonstrated that increasing the partial pressure of CO and doubling the reaction time raised the proportion of amines up to 92.4% and suppressed the formation of enamine thoroughly when one more equivalent of styrene was added (Table 2, entry 10). The ligand/Rh ratio can be reduced from 4 to 1, without an obvious decline in conversion and the yield of amines (Table 2, entry 11). The consumption of ligands decreased compared with the available bisphosphorus and monophosphorus ligands in the hydroaminomethylation. This can be explained by the enhanced chelating ability of the ligand through multiple

Table 2. Hydroaminomethylation of Styrene with Piperidine with Different Metal Sources and Pressures[a]

			distribution(%)[b]			
entry	L/Rh	CO/H_2 (bar)	8	3+4	3[c]	l/b[d]
1	4	30/10	33.6	62.4	87.2	6.8
2	4	30/10	44.8	48.9	91.1	10.2
3	4	30/10	32.9	61.1	91.9	11.4
4	4	30/10	34.4	60.3	92.8	12.8
5[e]	4	30/10	50.3	44.2	93.9	15.5
6[e]	4	20/10	53.7	42.3	93.4	14.1
7[e]	4	20/20	44.2	46.3	93.2	13.6
8[e]	4	10/30	42.1	50.6	91.8	11.2
9[f]	4	40/10	–	92.2	93.5	14.4
10[f]	2	40/10	–	92.4	93.8	15.1
11[f]	1	40/10	7.1	91.1	92.8	12.9
12[f,g]	2	40/10	45.4	54.4	91.4	10.6

[a] Rh/substrate = 1:500, styrene/piperidine = 1:1, *tert*-amyl alcohol, 125 °C, 8 h. Full conversion was achieved based on piperidine. Ethylbenzene and aldehydes account for the product balance. Entry 1 ($[Rh(cod)Cl]_2$), 2 ($Rh(cod)_2BF_4$), 3 ($Rh(acac)(CO)_2$), 4 ($Rh(acac)(C_2H_4)_2$), entries 5−12 ($Rh(nbd)_2SbF_6$). [b] See Table 1 footnote b. [c] See Table 1 footnote c. [d] See Table 1 footnote d. [e] Trace of *N*-formylpiperidine was detected. [f] Styrene/piperidine = 2, 16 h. [g] Rh/substrate = 1:1000. cod = 1, 5-cyclooctadiene, acac = acetyl acetonate, nbd = 2,5-norbornadiene.

Scheme 1. Hydroaminomethylation of Styrenes and Amines[a]



[a] Conditions: $Rh(nbd)_2SbF_6$/L3/styrenes/amine = 0.2:0.4:200:100, CO/H_2 (40 bar/10 bar), 125 °C,16 h. Full conversion was achieved based on the amines. Yields (data in parentheses) of the total amines were determined by GC analysis using bis(methoxyethyl) ether as an internal standard. l/b = linear amine (%)/branched amine (%), determined on the basis of GC analysis and repeated three times; error is estimated to be <0.2.

chelating modes.[15,16] Both the conversion and amines selectivity decreased when the catalyst loading was $<0.2\%$ (Table 2, entry 12). The optimized conditions were set as styrene/amine = 2:1, 0.2% Rh (L/Rh = 2), CO/H_2 (40 bar/10 bar), at 125 °C for 16 h.

The compatibility of our protocol in the hydroaminomethylation of styrenes with various amines was tested. As shown in Scheme 1, styrene was hydroaminomethylated smoothly with a series of aliphatic secondary amines in full conversion, including both cyclic amines (**3a**−**3d**) and chain amines (**3e**−**3h**). Compared with cyclic amines without a heteroatom, the chain amines produced better regioselectivity with l/b > 95:5, and the linear selectivity followed the trend Ethyl < *n*-Propyl < *n*-Butyl (**3e**, **3g**, **3h**). Compared with piperidine (**3a**), azepane afforded a higher yield of amine (95%, **3d**), although the linear selectivity is somewhat decreased. The erosion of both total amines and regioselectivity was detected in the hydroaminomethylation of pyrrolidine (yield of 80%, l/b = 85.3/14.7, **3b**), in which trace aldol product was also detected. The hydroaminomethylation of styrene with morpholine proceeded with excellent regioselectivity (l/b = 98.6/1.4) to give 94% of the desired amines (**3c**). The primary amines were also investigated in this reaction (**3i** and **3j**). Although the yield and selectivity were not satisfactory (bishydroaminomethylation and carbonylation of amines were detected), it demonstrated the feasibility of using primary amines. Ammonia was also tested, but no promising result was achieved. Hydroaminomethylation of *para*-substituted styrenes with piperidine gave higher linear selectivities, regardless of the electronic effects of the substituents (**3k** and **3l**). Both the high yield of amines and good linear selectivity were obtained from the reaction of substituted styrenes with morpholine (**3m**−**3s**), among which *p*-chloro, *p*-fluoro, and *m*-methyl styrenes furnished excellent linear selectivity with l/b up to 99/1 (**3p**−**3r**).

In conclusion, a highly chemo- and regioselective hydroaminomethylation of styrene and its derivatives to linear amines using $Rh(nbd)_2SbF_6$ with pyrrole-based 3,3′,5,5′-substituted tetraphosphorus ligands was disclosed. Those ligands are highly stable at rt and can be easily handled in air. The highest linear selectivity was reported for the hydroaminomethylation of styrene and its derivatives. Based on ealier reports on the effect of bite angle and the electronic property of the ligand on the regioselectivity of hydroformylation,[17] the performance of the present system can be accounted for by the electron-withdrawing property of the pyrrole moiety and the steric interactions between the more bulky tetraphosphorus ligands and the substrates. This creates an obstacle for the formation of an η^3-Rh-complex that favors the branched product in the initial step. This protocol is in sharp contrast to other available processes leading to branched amines and provides a novel atom economic approach to 3-arylpropylamines. Further studies are in progress with the aim of exploring the mechanism and optimizing the ligands to develop more efficient, selective catalytic systems.

Acknowledgment. This research was supported by the National Institutes of Health (GM58832), China Scholarship Council, and The National Key S&T Research Foundation of China (2010CB126105). Scholarship Award for Excellent Doctoral Student granted by Ministry of Education for S.L.

Supporting Information Available. Experimental procedures and analytic data (NMR, GC traces). This material is available free of charge via the Internet at http://pubs.acs.org.

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The authors declare no competing financial interest.