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Cascade Synthesis of Fenpiprane and Related Pharmaceuticals via Rhodium-Catalyzed Hydroaminomethylation

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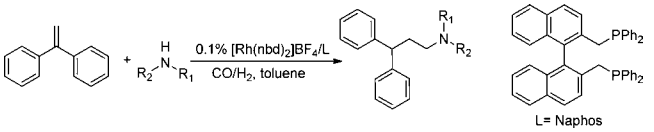
ABSTRACT



A novel rhodium catalytic system with Naphos as ligand was developed for an efficient hydroaminomethylation of 1,1-diphenylethene under relatively mild conditions. This will allow for an atom-economic and environmentally benign synthesis of fenpiprane and related pharmaceuticals.

With a staggering production of up to 20 billion kilograms per year,[1] amines are an important class of molecules in bulk as well as fine chemicals. Many amines can serve as versatile scaffolds for the synthesis of drugs or drug candidates, agrochemicals, natural products, and dyes.[2] Among the different amines, 3, 3-diarylpropylamines are of significant importance as they represent a well-known first-generation family of H_1 antihistaminic agents.[3] A tiny variation of this scaffold either in the amine core or the aryl group will lead to a number of different pharmaceuticals,[4] such as antiallergic agents drixoral, pheniramine, fenpiprane, tussionex;[4e] choleretic agents diisoproamine, prozapine; coronardilatic agent fendiline, and antimuscarinic agent Detrol LA[4e] (Figure 1).

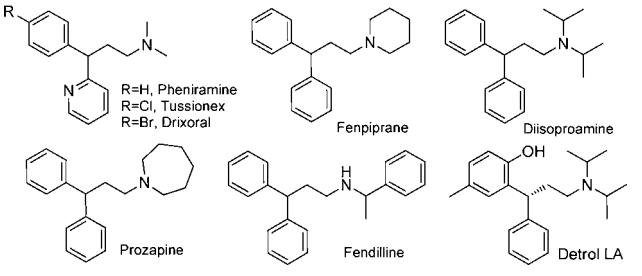


Figure 1. Representative drugs.

The synthesis of 3,3-diarylpropylamine has attracted immense interest, and various methods have been developed. Usually they are prepared via a multistep process not

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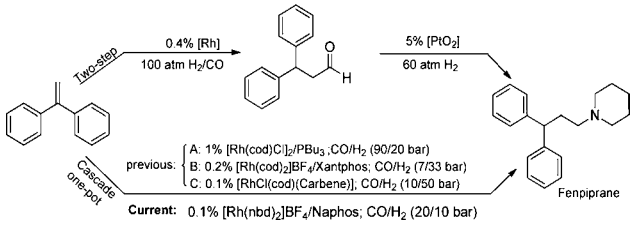
involving transition-metal catalysis.[5] Most known synthetic strategies proceed with the nucleophilic substitution of the corresponding 3,3-diarylpropylhalide.[6]

Superacid-catalyzed electrophilic aromatic substitution has also been developed.[7] In view of today's criterion for atom economy and green chemistry, the so-called hydroaminomethylation seems to hold great potential for industrial applications.

Scheme 1. Synthesis of Fenpiprane through Hydroaminomethylation



Originally discovered by Reppe at BASF,[8] the hydroaminomethylation consists of a cascade reaction of hydroformylation of an alkene to aldehyde and subsequent condensation with an amine to form enamine or imine followed by hydrogenation. This one-pot cascade synthetic strategy is very powerful as it can furnish amines directly from inexpensive alkenes.[1a,9] The synthesis of 3,3-diphenylpropylamine using a hydroformylation−reductive amination sequence was first reported by Botteghi et al.;[5,10] while the overall yields range between 60 and 70% through a two-step approach, the yield for fenpiprane in a one-pot reaction was only 20%. Eilbracht documented a more efficient one-pot synthesis of 3,3-diphenylpropylamines via PBu_3/[Rh(cod)Cl]$_2$ (1% Rh, L/Rh = 16) catalyzed hydroaminomethylation, and the yield of fenpiprane was improved to 72%. Recently, Beller's group developed several elegant methods toward the synthesis of 3,3-diphenylpropylamines through Rh-catalyzed hydroaminomethylation with Xantphos[11] or carbene[3b,12] as ligands. Herein, we present a rhodium catalytic system with Naphos[13] as ligand (0.1% Rh, L/Rh = 4), which allows for an efficient hydroaminomethylation of 1,1-diphenylethene under relatively mild conditions (CO/H_2 = 20/10 bar) to furnish 3,3-diphenylpropylamines (Scheme 1).

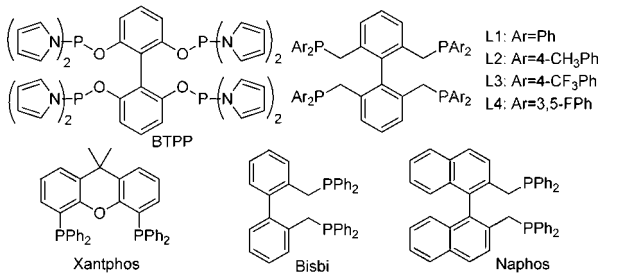


Figure 2. Structures of the tested ligands.

The challenge of hydroaminomethylation is to combine the highest chemo- and regioselectivity together to efficiently obtain the expected amines. In view of 1, 1-diphenylethene, the regioselectivity is unworthy of mentioning due to the steric hindrance, while the chemoselectivity and the activity are the major problems. In order to achieve a more convenient cascade approach to 3, 3-diphenylpropylamines, the attempt was carried out in the hydroaminomethylation of 1, 1-diphenylethene with piperidine to optimize the reaction parameters. Some representative results were given in Table 1; to the best of our knowledge, this is the first detailed discussion on the product distribution of the hydroaminomethylation of 1,1-diphenylethene. Similar to the earlier reports,[5,10] the major byproduct is 1,l-diarylethane from the direct hydrogenation of the olefin double bond.

Different ligands (Figure 2) including monodentate, bidentate, and multidentate phosphorus ligands were tested with $Rh(cod)_2BF_4$ as metal precursor. As a reference, PPh_3 was employed in this model reaction; only 36% conversion and 23% of desired amine were achieved even with the L/Rh ratio of up to 15 (Table 1, entry 1). The conversion was improved up to 83% with Xantphos, while the undesired byproducts (up to 66%) became predominant (Table 1, entry 2). Multiple chelating tetraphosphorus ligands were synthesized by our group and have found wide application in catalysis.[14] Among them, the BTPP ligands were used successfully in the highly linear-selective hydroformylation[14d] and hydroaminomethylation of styrene,[14e] while the activity in this model reaction is not satisfactory (Table 1, entry 3); this can be reconciled with the more electron-withdrawing property of the pyrrole moiety and the steric interactions between the more hindric tetraphosphorus ligands and the bulky alkene. More promising results were got when the Tetrabi ligands were applied, both the chemoselectivity and the activity of hydroaminomethylation to

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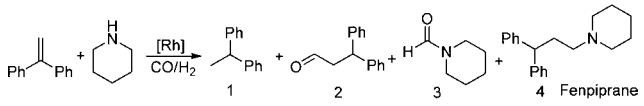
Table 1. Hydroaminomethylation of 1,1-Diphenylethene and Piperidine with Different Catalysts and Solvents[a]



				distribution[b] (%)				
entry	ligand	Rh	conv[b] (%)	1	2	3	4	yield[c] (%)
1[d]	PPh3	$Rh(cod)_2BF_4$	36	34.7	0	2.9	62.4	23
2	Xantphos	$Rh(cod)_2BF_4$	83	40.2	22.4	3.4	34	29
3	BTPP	$Rh(cod)_2BF_4$	11	0	0	53.3	46.7	10
4	L1	$Rh(cod)_2BF_4$	29	44.1	23.5	11.8	20.6	7
5	L2	$Rh(cod)_2BF_4$	49	48	26.5	7.1	18.4	10
6	L3	$Rh(cod)_2BF_4$	47	18.6	10.2	8.5	62.7	32
7	L4	$Rh(cod)_2BF_4$	69	13.1	10.6	10.2	66.1	47
8	Bisbi	$Rh(cod)_2BF_4$	65	73.4	0.1	7.6	18.9	14
9	Naphos	$Rh(cod)_2BF_4$	99	11.7	6.7	2.5	79.2	81
10	Naphos	$Rh(cod)_2BF_4$	>99	17.7	1.2	8.7	72.4	79
11	Naphos	$Rh(nbd)_2BF_4$	>99	13.8	0.1	5.6	80.5	85
12	Naphos	$Rh(acac)(C_2H_4)_2$	>99	26.4	0.2	9.7	63.7	71
13	Naphos	$Rh(acac)(CO)_2$	>99	27.7	0.1	11.9	60.3	69
14	Naphos	$[Rh(COD)Cl]_2$	>99	22.9	0.1	9.3	67.7	75
15[e]	Naphos	$Rh(nbd)_2BF_4$	>99	40	0	22.1	37.9	48
16[f]	Naphos	$Rh(nbd)_2BF_4$	92	35.3	0	4.8	59.9	58
17[g]	Naphos	$Rh(nbd)_2BF_4$	>99	34.4	0	3.8	61.8	64

[a] Unless otherwise mentioned, all reactions were carried out under a syngas of CO/H_2 (25 bar/25 bar) at 125 °C for 60 h in toluene with Rh/ligand/1,1-diphenylethene/piperidine ratio of 1:4:500:500 for entries 2−9, 1:4:250:250 for entries 10−18. [b] Conversion, product distribution, and the yield of amine were determined by GC analysis using bis(methoxyethyl) ether as an internal standard. [c] Yield of the fenpiprane. [d] The ratio of Rh/PPh_3/substrate is 1:15:500. [e] In methanol. [f] In 2-propanol. [g] In ethyl acetate.

amine are promoted when more electron-withdrawing substituents were introduced (Table 1, entries 4−7). The yields of fenpiprane followed the trend L2 < L3 < L4, and the hydrogenation of alkene was suppressed in the same order. Comparably, its biphosphine analogue Bisbi was also tested, to our disappointment, amine was overwhelmed by the production of alkane. However, we were inspired by the promising results from the ligands with the biphenyl backbone (Table 1, entries 3−8) and tested the corresponding biphosphine analogue with binaphthyl skeleton. To our delight, when Naphos was tested in the model reaction, 81% of fenpiprane was achieved with full conversion.

A survey of the effect of Rh precursor demonstrated that $Rh(nbd)_2BF_4$ gave the best result with full conversion and 85% yield of amine (Table 1, entry 11). We found that a higher loading of catalyst was unfavorable for fenpiprane (Table 1, entry 9 vs 10). This reaction proceeded smoothly in all of the solvents tested; however, the constitution of byproducts is enhanced in more polar solvents. For example, in methanol, up to 22.1% of *N*-formylpiperidine and 40% of alkane were formed through direct carbonylation of piperidine and hydrogenation of alkene, respectively (Table 1, entry 15). Toluene was chosen as the best solvent as it can slow down both the carbonylation of piperidine and the hydrogenation of alkene due to its ability to coordinate to the Rh center. It is noteworthy that in the presence of 0.05 mol % of catalyst, still 92% conversion was achieved with up to 86% of fenpiprane (Table 2, entry 3). A shorter

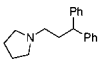
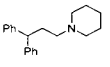
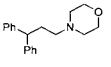
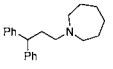
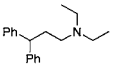
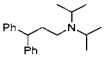
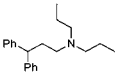
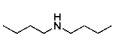
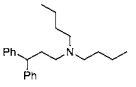
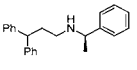
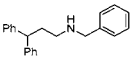
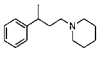
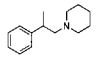
Table 2. Further Optimization of Hydroaminomethylation[a]

entry	Rh loading (%)	CO/H_2 (bar)	temp (°C)	time (h)	conv[b] (%)	yield[c] (%)
1	0.2	25/25	125	60	>99	90
2	0.1	25/25	125	60	>99	93
3	0.05	25/25	125	60	92	86
4	0.2	25/25	125	30	93	84
5	0.2	25/25	100	60	67	55
6	0.2	15/15	125	60	99	89
7	0.1	10/20	125	60	99	90
8	0.1	20/10	125	60	>99	94
9	0.1	25/5	125	60	98	92
10	0.1	5/25	125	60	97	90

[a] Unless otherwise mentioned, all reactions were carried out with a 1,1-diphenylethene/piperidine ratio of 1:1 in toluene. 1,1-Diphenylethane accounts for the product balance based on the consumed 1,1-diphenylethene. [b] See Table 1. [c] See Table 1.

reduction time suppressed the conversion slightly, while lower temperature led to a significantly slower reaction rate (Table 2, entries 4 and 5). A satisfying result was also achieved when the pressure of CO/H_2 was reduced from 25/25 bar to 15/15 bar (Table 2, entry 6). Optimizing the partial pressures of hydrogen and carbon monoxide demonstrated that full conversion and excellent yield (up to 94%) was attained at 125 °C with 0.1% $Rh(nbd)_2BF_4$ under a syngas of CO/H_2 (20 bar/10 bar).

Table 3. Hydroaminomethylation of 1,1-Diphenylethene with Different Amines[a]

entry	alkene	amine	major product	conv [b] (%)	yield [c] (%)
1				94	90(84)
2				99	94(88)
3				94	93(88)
4				98	96(90)
5				99	90(83)
6				98	85(76)
7				99	92(84)
8				99	95(87)
9				96	86(77)
10				91	82(71)
11[d]				99	96(91)
12[d]				99	91(85)[e]

[a] Unless otherwise mentioned, all reactions were carried out with a $[Rh(nbd)_2]BF_4$/Naphos/1,1-diphenylethene/amine of 0.1:0.4:100:100 under a syngas of CO/H_2(20 bar/10 bar) at 125 °C for 60 h. [b] See Table 1. [c] Unless otherwise mentioned, the yield is referred to that of the major product shown in this table. Data in parentheses are the isolated yields. [d] 125 °C for 60 h. [e] Yield of total amines.

To further explore the efficiency and tolerance of this protocol, a series of amines were subjected to hydroaminomethylation with 1,1-diphenylethene. Except for styrene (Table 3, entry 12), all of the other alkenes gave preferentially linear amine products due to the steric hindrance. As shown in Table 3, 1,1-diphenylethene was hydroaminomethylated smoothly with a series of aliphatic secondary amines with excellent conversion, including both cyclic amines (Table 3, entries 1−4) and chain amines (Table 3, entries 5−8). The yields of amines increased with the molecular weight of the starting material and followed the trend pyrrolidine < piperidine < azepane (Table 3, entries 1, 2, and 4) and ethylamine < *n*-propylamine < *n*-butylamine (Table 3, entries 5, 7, and 8), respectively. The reaction of 1,1-diphenylethylene with diisopropylamine afforded only 85% of amines, *although* the conversion is excellent. That may be account for by the more hindric effect of the diisopropylamine, compared with the other chain amines. We were gratified to find that the compatibility of the primary amines in this reaction. Both the (*R*)-α-methylbenzylamine and benzylamine were hydroaminomethylated smoothly to furnish the desired amines (Table 3, entries 9 and 10). Hydroaminomethylation of α-methylstyrene with piperidine proceeded well (> 99% conversion) to afford the amine in up to 96% yield (Table 3, entry 11).

In conclusion, we have disclosed a novel rhodium catalytic system with Naphos as ligand in the hydroaminomethylation of 1,1-diphenylethylene. Compared with the previous reported procedures, this protocol was efficient and carried out under relatively mild conditions. This cascade approach will allow for a convenient, atom-economic, and environmentally benign synthesis of fenpiprane and related pharmaceuticals from inexpensive materials in a one-pot process.

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Supporting Information Available. Experimental procedure, NMR data, and representative GC traces for the synthesized amines. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.