Asymmetric Hydroamination

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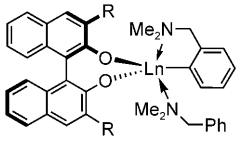
Asymmetric Intermolecular Hydroamination of Unactivated Alkenes with Simple Amines**

*Alexander L. Reznichenko, Hiep N. Nguyen, and Kai C. Hultzsch**

In memory of Herbert Schumann (1935–2010)

The development of efficient methods for the synthesis of nitrogen-containing compounds remains an important goal in contemporary catalysis research because of the central role of this class of compounds in biological systems and pharmaceutical applications.[1] The addition of an amine N–H bond to a carbon–carbon multiple bond, so-called hydroamination,[2] is a reaction with great synthetic potential, as it not only reduces the formation of waste owing to its atom economy, but it utilizes also very simple starting materials. The development of novel catalyst systems for hydroamination has seen significant progress in the last two decades,[2,3] but the intermolecular hydroamination of unactivated alkenes with simple amines remains very challenging.[4] Therefore, it is not too surprising that asymmetric hydroamination reactions[5] have been studied predominantly in intramolecular reactions.[6,7] Intermolecular reactions have been reported only sporadically and all of these studies were limited to the reaction between aniline derivatives and activated alkenes, such as vinyl arenes,[8] 1,3-dienes,[9] and strained bicyclic alkenes.[10] The first enantioselective gold-catalyzed addition of cyclic ureas to unactivated alkenes in up to 78% *ee* was reported recently by Widenhoefer and coworkers.[11] Herein we report the stereoselective addition of simple amines to unactivated alkenes utilizing chiral rare-earth-metal-based catalysts.

Catalyst systems based on rare-earth-metal complexes exhibit high catalytic activity, in particular in intramolecular hydroaminations,[2,3f] whereas intermolecular hydroaminations are significantly more difficult to achieve as a result of the unfavorable competition between weakly coordinating alkenes and strongly coordinating amines.[4a,b,6b,12] We have previously reported on efficient biphenolate and binaphtholate rare-earth-metal catalysts,[6b,13] which can catalyze the intramolecular hydroamination of aminoalkenes with high activity and up to 95% *ee*. Preliminary studies with a corresponding binaphtholate lanthanum complex for the reactions of styrene[6b] and 1,3-cyclohexadiene[14] indicated the potential applicability of these systems in asymmetric intermolecular hydroaminations. As the lanthanum catalyst showed rather low selectivity[14] we decided to utilize the generally more selective yttrium and lutetium catalysts in our study. For the initial catalyst screening we chose the reaction of 1-heptene with benzylamine.



(*R*)-**1**-Ln R = $SiPh_3$
(*R*)-**2**-Ln R = $Si(3,5\text{-}Me_2C_6H_3)_3$
(*R*)-**3**-Ln R = $SiPh_2tBu$
(*R*)-**4**-Ln R = $SiPh_2Cy$
Ln = Y, Lu

Indeed, the addition of benzylamine to 1-heptene can be observed at 150°C in the presence of 5 mol% of the binaphtholate complexes **1**–**4** (Table 1). As expected,[4a,b] the reaction proceeds with high Markovnikov selectivity. The reactions achieve high conversions and no other by-products were observed besides the hydroamination product.[15]

The triphenylsilyl-substituted binaphtholate yttrium complex (*R*)-**1**-Y achieved the highest enantioselectivity, 58% *ee* (Table 1, entry 1).[16] A 15-fold excess of alkene was used in order to accelerate the reaction. Lower alkene/amine ratios led to longer reaction times and lower conversion (Table 1, entry 3), while a greater excess of alkene led to a slight acceleration of the reaction (Table 1, entry 4). The enantiomeric excess was only slightly influenced by the alkene/amine ratio. The *R*-configured binaphtholate catalysts formed the hydroamination product with *R* configuration,[17] which is the opposite selectivity of that observed for intramolecular hydroaminations of aminoalkenes with these catalysts.[6b]

The sterically more shielded tri(xylyl)silyl-substituted binaphtholate complex (*R*)-**2**-Y and the novel *tert*-butyldiphenylsilyl- and cyclohexyldiphenylsilyl-substituted binaphtholate complexes (*R*)-**3**-Y and (*R*)-**4**-Y, respectively, achieve slightly lower selectivities of 44–47% *ee*, with (*R*)-**3**-Y displaying the lowest activity. The smaller ionic radius of lutetium in (*R*)-**1**-Lu results in lower selectivity as well, while the activity remains comparable to that of the yttrium complex (Table 1, entry 6). Therefore, further investigations with a broader range of substrates were conducted predominantly with **1**-Y (Table 2).

[*] A. L. Reznichenko, H. N. Nguyen, Prof. Dr. K. C. Hultzsch
Department of Chemistry and Chemical Biology
Rutgers, The State University of New Jersey
610 Taylor Road, Piscataway, NJ 08854-8087 (USA)
Fax: (+1) 732-445-5312
E-mail: hultzsch@rci.rutgers.edu
Homepage: http://chem.rutgers.edu/~hultzsch/

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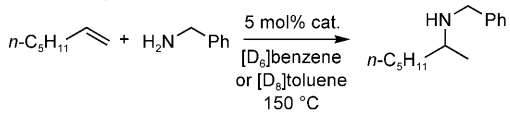
Table 1: Catalyst screening for the intermolecular hydroamination of 1-heptene with benzylamine.[a]



Entry	Cat.	*t* [h]	Conv. [%][b] (yield [%][c])	*ee* [%][d] (config.)
1	(*R*)-**1**-Y	36	90 (65)	58 (*R*)
2	(*R*)-**1**-Y	48	– (78)[e]	58 (*R*)
3	(*R*)-**1**-Y[f]	48	85 (57)	57 (*R*)
4	(*R*)-**1**-Y[g]	18	95 (68)	54 (*R*)
5	(*S*)-**1**-Y[h]	18	95	55 (*S*)
6	(*R*)-**1**-Lu	30	95 (62)	40 (*R*)
7	(*R*)-**2**-Y	24	90 (61)	44 (*R*)
8	(*R*)-**3**-Y	48	85 (59)	46 (*R*)
9	(*R*)-**4**-Y	17	90	47 (*R*)

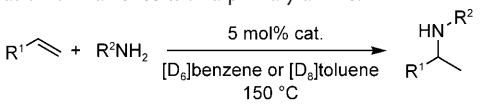
[a] General reaction conditions: 3.0 mmol 1-heptene, 0.2 mmol benzylamine (alkene/amine 15:1), 10 μmol cat. (0.1 mL of a 0.1 M cat. solution in [D_6]benzene or [D_8]toluene). [b] The conversion of the amine was determined by ^{1}H NMR spectroscopic analysis. [c] Yield of isolated product after column chromatography. [d] Determined by ^{19}F NMR spectroscopy of the Mosher amide after removal of the benzyl group. [e] Preparative-scale reaction using 12.0 mmol 1-heptene, 1.0 mmol benzylamine (alkene/amine 12:1). [f] Alkene/amine 7:1. [g] 8 mol% cat., alkene/amine 50:1. [h] 4 mol% cat., 170°C.

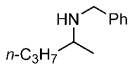
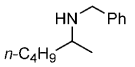
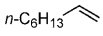
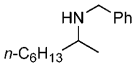
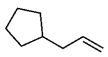
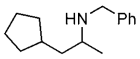
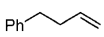
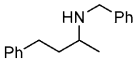
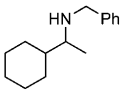
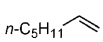
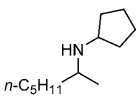
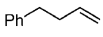
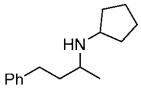
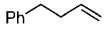
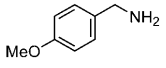
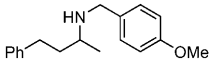
Analogous to 1-heptene, linear and branched 1-alkenes are converted into their respective *N*-benzylalkan-2-amines with good turnover. However, branching in the allylic position, for example in vinylcyclohexane (Table 2, entry 8) leads to significantly diminished reactivity. The highest reactivity was observed for 4-phenyl-1-butene, for which a lower alkene/amine ratio of 10:1 was possible. All reactions with **1**-Y provide similar selectivities in the range of 51–61% *ee*. Reactions with cyclopentanamine proceed with comparable enantioselectivity, but diminished activity (Table 2, entries 9–11). Similar observations were made for *para*-methoxybenzylamine, in which the reduced reactivity can be attributed to a possible deactivation of the catalyst by the methoxy group.

The reaction of 1-heptene with the enantiomerically pure (*R*)-1-phenylethanamine using (*S*)-**1**-Y produces the hydroamination product in 54% yield (75% conversion) and a diastereomeric excess of 73%, while the reaction of the apparent mismatching catalyst (*R*)-**1**-Y led only to traces of the hydroamination product even at elevated reaction temperatures and longer reaction time (Scheme 1).

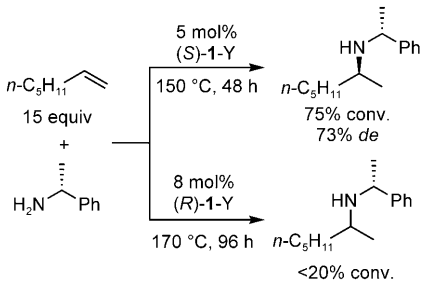
Initial kinetic studies suggest that the reaction is first order with respect to amine, alkene, and catalyst concentration (see the Supporting Information). These preliminary

Table 2: Asymmetric intermolecular hydroamination of 1-alkenes with a primary amine.[a]



Entry	Alkene	Amine	Product	Cat.	Alkene/amine	*t* [h]	Conv. [%][b] (yield [%][c])	*ee* [%] (config.)
1				(*R*)-**1**-Y	14:1	72	90 (70)	61 (*R*)[d]
2				(*S*)-**1**-Y	13:1	72	90 (54)	61 (*S*)[d]
3				(*R*)-**4**-Y[e]	15:1	60	95 (59)	50 (*R*)[d]
4				(*R*)-**1**-Y	15:1	40	97 (72)	57 (*R*)[d]
5				(*R*)-**1**-Lu	15:1	44	95 (70)	44 (*R*)[d]
6				(*S*)-**1**-Y	15:1	19	95 (59)	51 (*S*)[d]
7				(*S*)-**1**-Y[e]	10:1	11	100 (72)	56 (*S*)[d, g]
8				*rac*-**1**[f]	12:1	96	25	–
9				(*S*)-**1**-Y[e]	15:1	60	95 (61)	61[g]
10				(*R*)-**4**-Y[e]	15:1	27	95 (68)	56[g]
11				(*S*)-**1**-Y[e]	9:1	39	90 (68)	54[g]
12				(*S*)-**1**-Y	10:1	48	85 (67)	56 (*S*)[g]
13				(*R*)-**3**-Y	10:1	72	75 (61)	54 (*R*)[g]
14				(*R*)-**4**-Y	10:1	48	80	44 (*R*)[g]

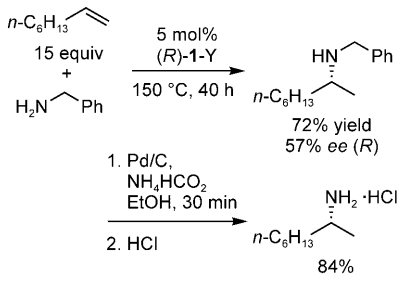
[a] General reaction conditions: 1.8–3.0 mmol 1-alkene (9- to 15-fold excess), 0.2 mmol amine, 10 μmol cat. (0.1 mL of a 0.1 M cat. solution in [D_6]benzene or [D_8]toluene). [b] The conversion of amine was determined by ^{1}H NMR spectroscopic analysis. [c] Yield of isolated product after column chromatography. [d] Determined by ^{19}F NMR spectroscopy of the Mosher amide after removal of the benzyl group by hydrogenation. [e] 4 mol% cat. [f] 8 mol% cat., 170°C. [g] Determined by ^{1}H NMR spectroscopy of the salt of *O*-acetyl mandelic acid.



Scheme 1. Stereoselective addition of (*R*)-1-phenylethanamine to 1-heptene using (*S*)-**1**-Y and (*R*)-**1**-Y.

data suggest the participation of the amine in the catalytic steps leading from the resting state of the catalyst to the presumably rate-determining alkene-insertion step. Although kinetic data for these types of reactions are scarce, it should be noted that a zero-order rate dependence on the amine concentration was observed in the rare-earth-metal-catalyzed intermolecular hydroamination of alkynes.[4b]

In summary, we have studied the first asymmetric intermolecular hydroaminations of unactivated alkenes with simple amines using the binaphtholate catalysts **1**–**4**. Furthermore, benzylamine may be utilized as an ammonia equivalent, because the benzyl group may be removed easily; as a result the corresponding chiral primary 2-aminoalkanes can be obtained directly from the 1-alkenes (Scheme 2).



Scheme 2. Stereoselective synthesis of 2-aminoalkanes (using the example of 2-aminooctane) by means of the asymmetric hydroamination of 1-alkenes.

It is important to note that the binaphtholate catalysts, in contrast to chiral lanthanocenes,[18] seem to be configurationally stable even under the very harsh reaction conditions (150–170 °C). Improvements in the catalyst design (in particular with respect to reactivity and selectivity) will certainly depend on a better understanding of the steric and electronic requirements of the catalyst. Current investigations focus in particular on a broader range of substrates and a larger set of catalysts to probe the scope and limitations of this transformation.

Experimental Section

In the glovebox, a screw-cap NMR tube was charged with an appropriate amine (0.2 mmol), alkene (3 mmol), and a solution of catalyst (0.1 M in [D_6]benzene or [D_8]toluene, 0.1 mL, 10.0 μmol, 5 mol%). The NMR tube was then sealed, removed from the glovebox, and placed into a thermostatted oil bath. Flame-sealed NMR tubes were used for more volatile substrates, such as 1-hexene or 1-pentene. The progress of the reaction was monitored by ^{1}H NMR spectroscopy. After completion of the reaction, the mixture was concentrated in vacuo and purified by column chromatography on a 3 cm thick pad of silica or alumina.

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[14] The addition of *n*-propylamine to 1,3-cyclohexadiene proceeded at 80 °C with 20 % *ee* and a regioselectivity of 1.7:1 when 3 mol % of a tri(xylyl)silyl-substituted binaphtholate lanthanum catalyst was used. See: D. V. Gribkov, Dissertation, University of Erlangen-Nuremberg, **2005**.

[15] However, the yields of isolated products formed in the NMR-scale reactions using 0.2 mmol amine range from 60–70 % after column chromatography owing to the small scale of the reaction and the volatility of the products. A larger 1.0 mmol scale reaction gave a better yield of isolated product (see Table 1, entry 2).

[16] The enantiomeric excess was determined by ^{1}H NMR spectroscopy of the salt of the *O*-acetyl mandelic acid, as well as by ^{19}F NMR spectroscopy of the corresponding Mosher amide after removal of the benzyl group.

[17] The absolute configuration was assigned by comparison of the ^{19}F NMR spectroscopic data of the Mosher amide of the deprotected primary amine with the data of analogous compounds reported in the literature. See the Supporting Information.

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