Metal-Hydride Mediated Hydroamination Reactions: Powerful Methods to Chiral Amines

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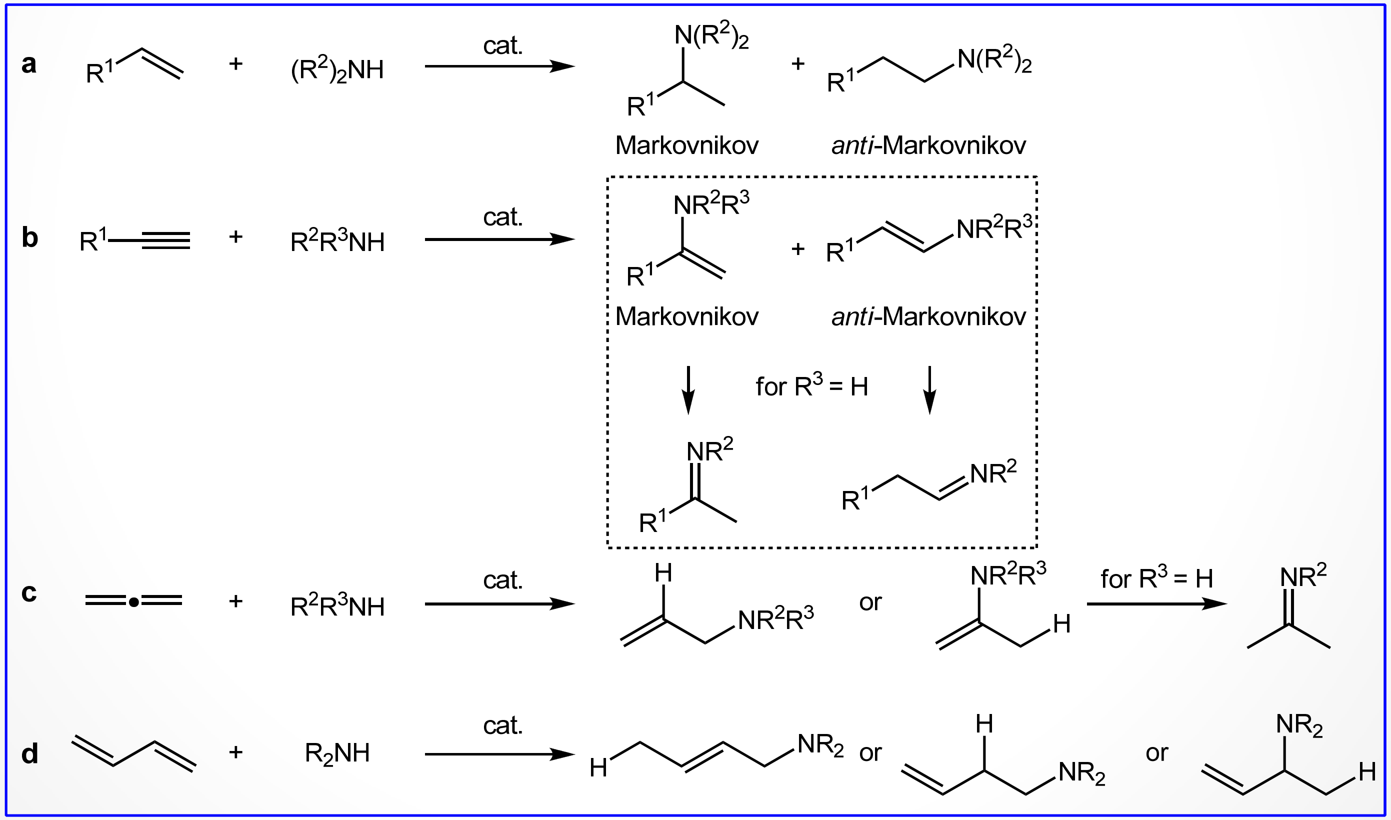
Dong, V. M. *et al.*
J. Am. Chem. Soc. **2015**, *137*, 8392−8395.

Hydroamination Reactions

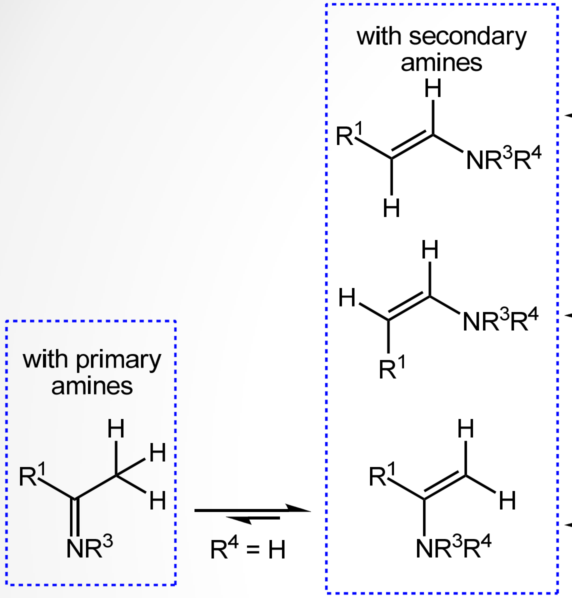
A hydroamination is a reaction in which an N−H unit of a nucleophilic primary/secondary amine or ammonia is added across a C−C multiple bond with cleavage of the N−H bond and formation of a C−N and a C−H bond.



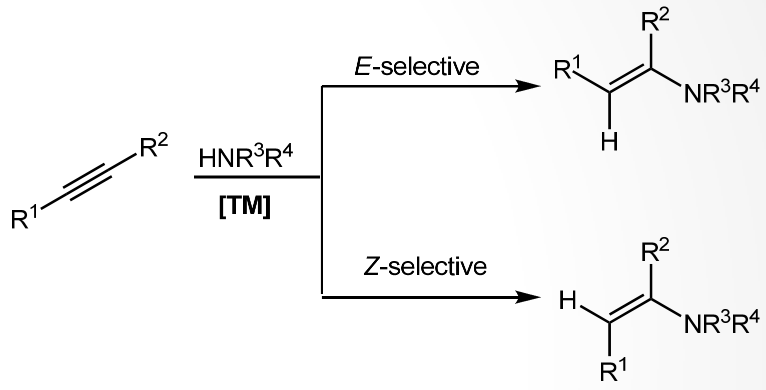
Reznichenko, A. L. *et al. Top. Curr. Chem.* **2014**, *343,* 191–260.

Regioselectivity of Hydroamination Reactions

a) Hydroamination of terminal alkynes

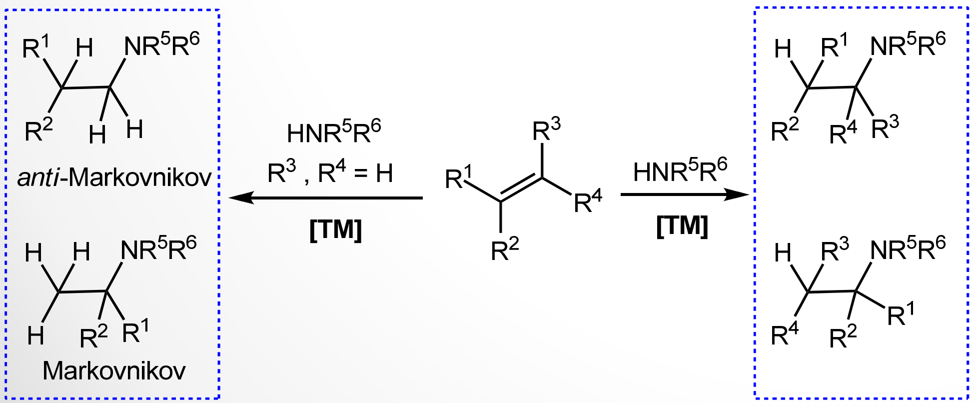


b) Hydroamination of internal alkynes

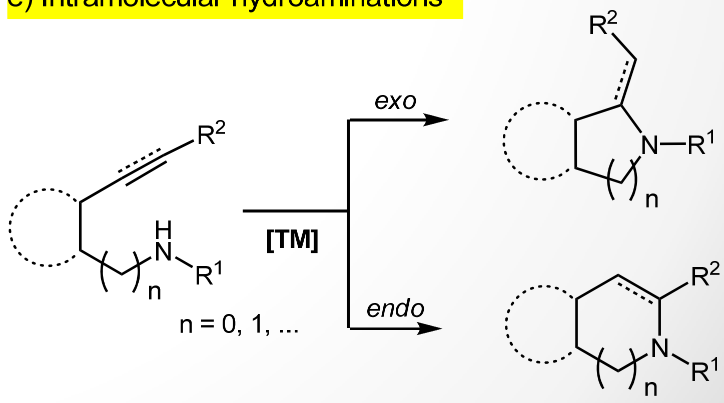


c) Hydroamination of terminal alkenes

d) Hydroamination of internal alkenes

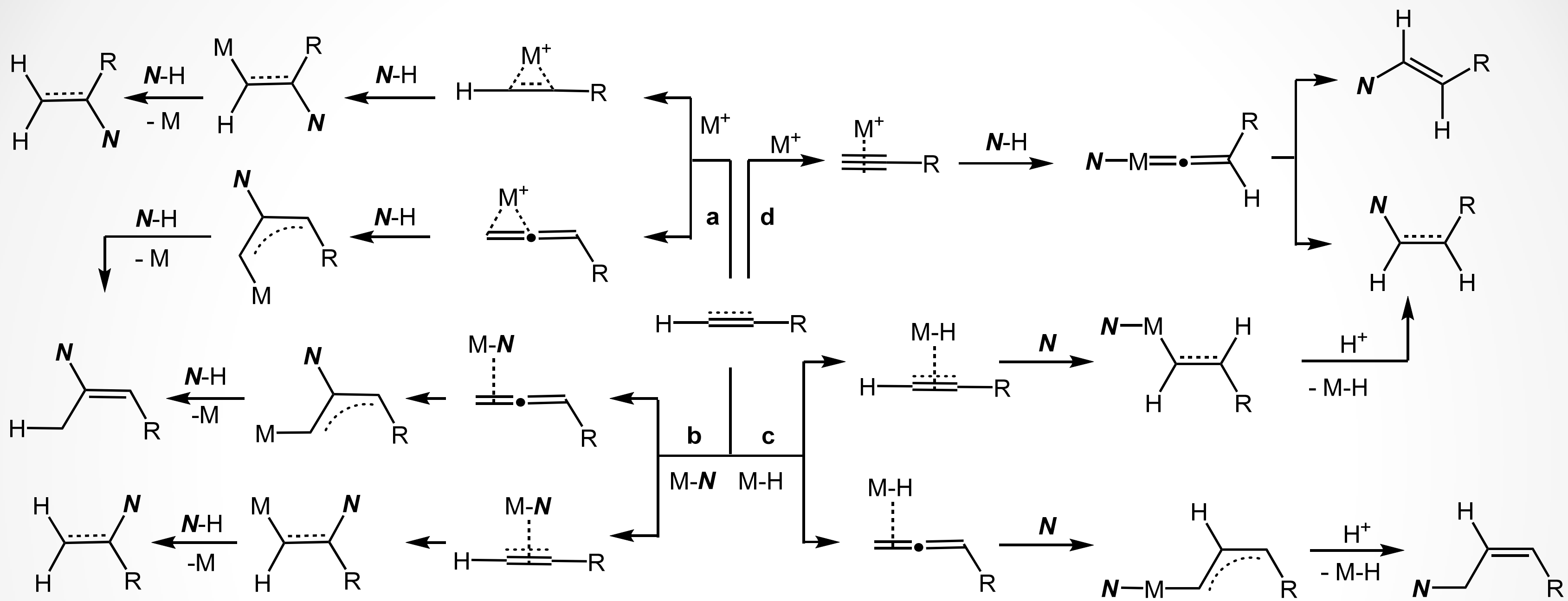


e) Intramolecular hydroaminations



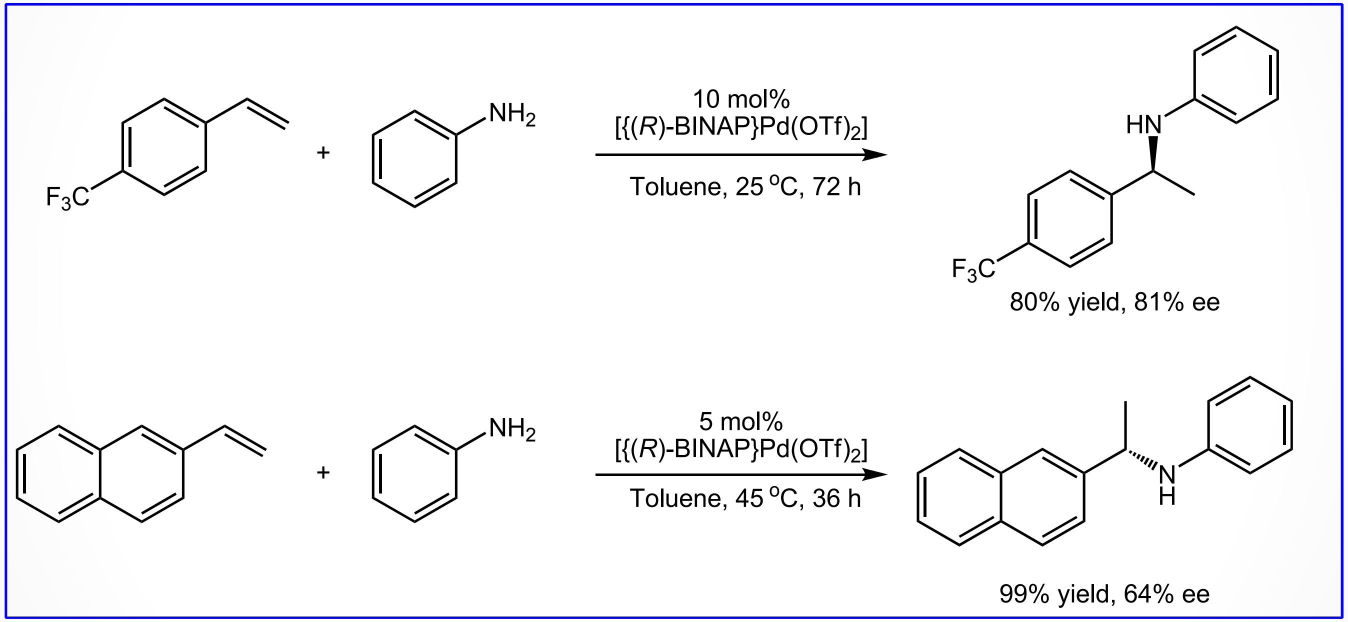
Gooßen, L. J. *et al. Chem. Rev.* **2015**, *115*, 2596−2697.

Four Typical Mechanisms of Hydroamination Reactions



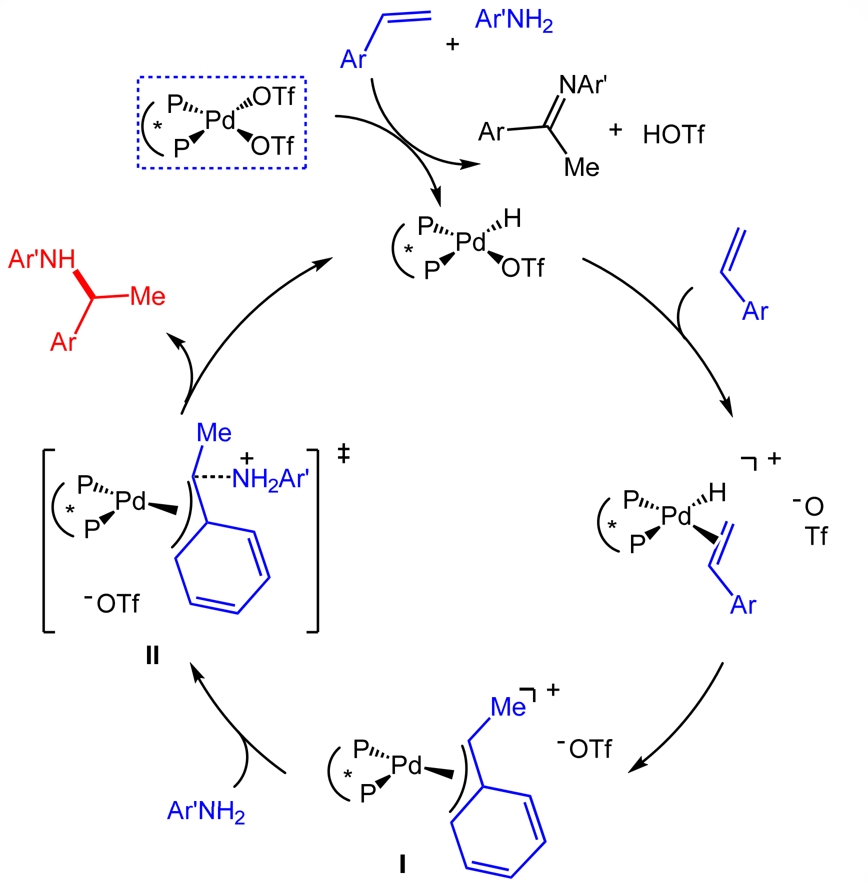
(a) Activation of the C−C multiple bond by π-coordination of a Lewis-acidic metal complex, followed by nucleophilic addition of the N-nucleophile;
(b) Initial formation of a metal−nitrogen bond, followed by insertion of the alkene/alkyne into the M−N bond;
(c) Initial formation of a metal−hydride, and migratory insertion of the alkene/alkyne into the M−H bond;
(d) Rearrangement of initially formed η^2-alkyne−metal species into vinylidene complexes, which are then attacked by the N-nucleophile.

Pd-Catalyzed Hydroamination of Alkenes



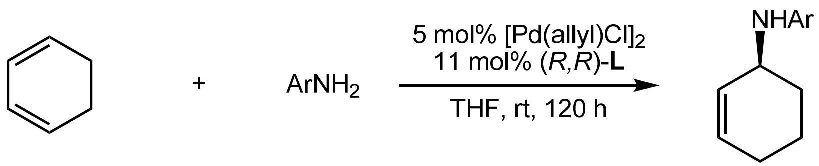
Hartwig, J. F. *et al. J. Am. Chem. Soc.* **2000**, *122*, 9546–9547.

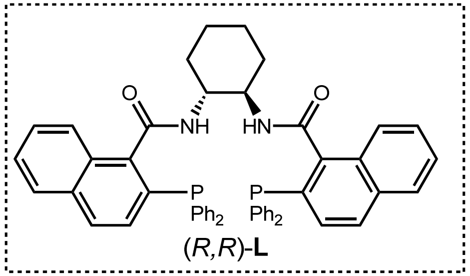
Pd-Catalyzed Hydroamination of Alkenes



Hartwig, J. F. *et al. J. Am. Chem. Soc.* **2006**, *128*, 1828–1839.

Pd-Catalyzed Hydroamination of Alkenes

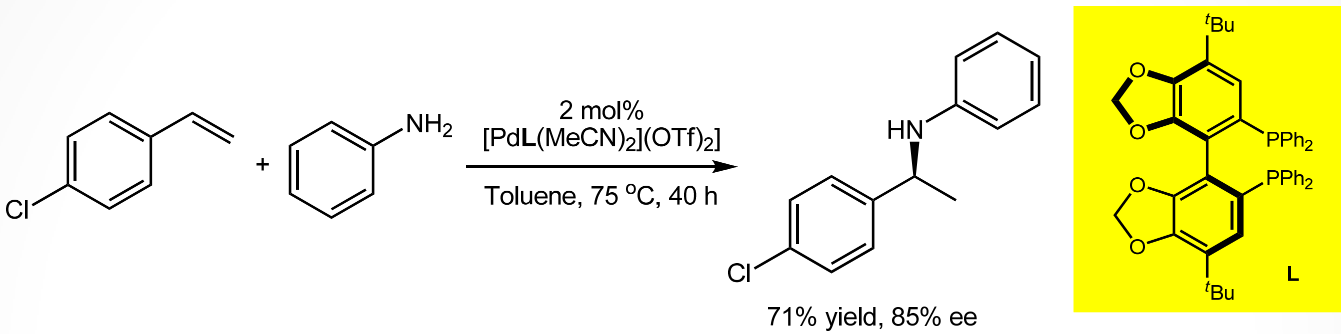




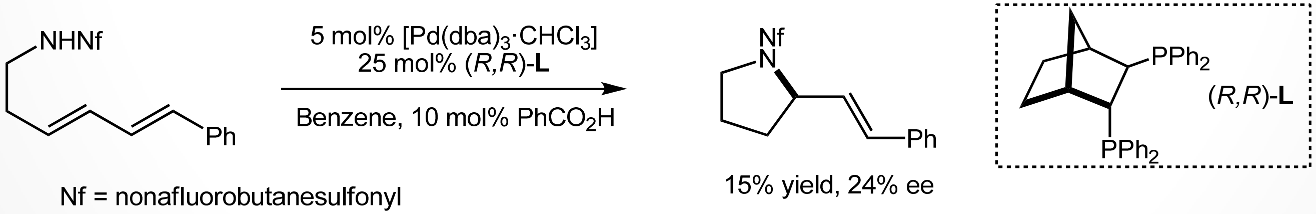
Ar	% yield	% ee
Ph	63	92
4-MeC_6H_4	78	86
2-MeC_6H_4	59	90
4-$EtO_2CC_6H_4$	83	95
4-$CF_3C_6H_4$	73	95

Hartwig, J. F. *et al*. *J. Am. Chem. Soc.* **2001**, *123*, 4366–4367.

Pd-Catalyzed Hydroamination of Alkenes

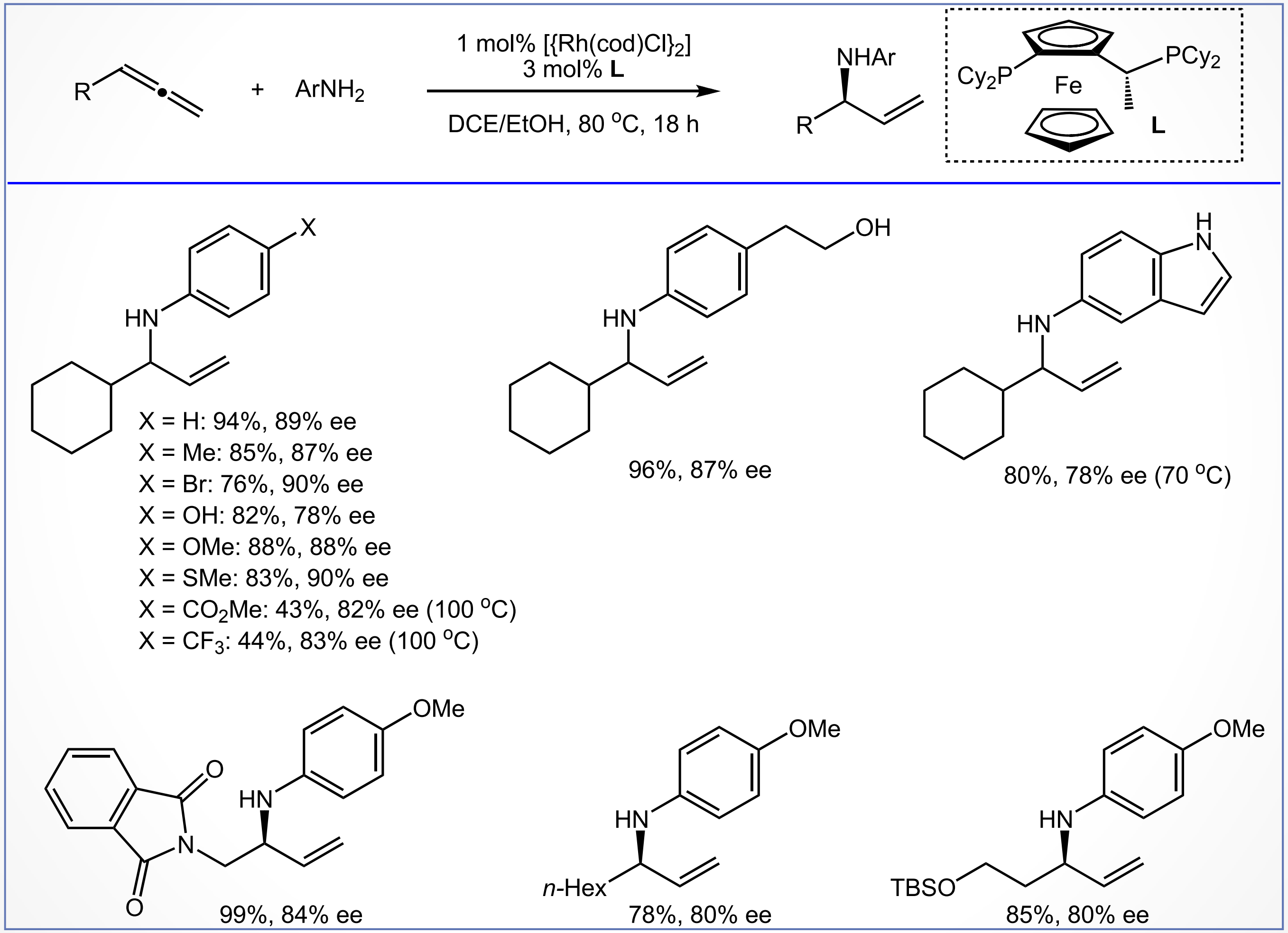


Lin, W. *et al. Adv. Synth. Cat.* **2006**, *348*, 2051–2056.



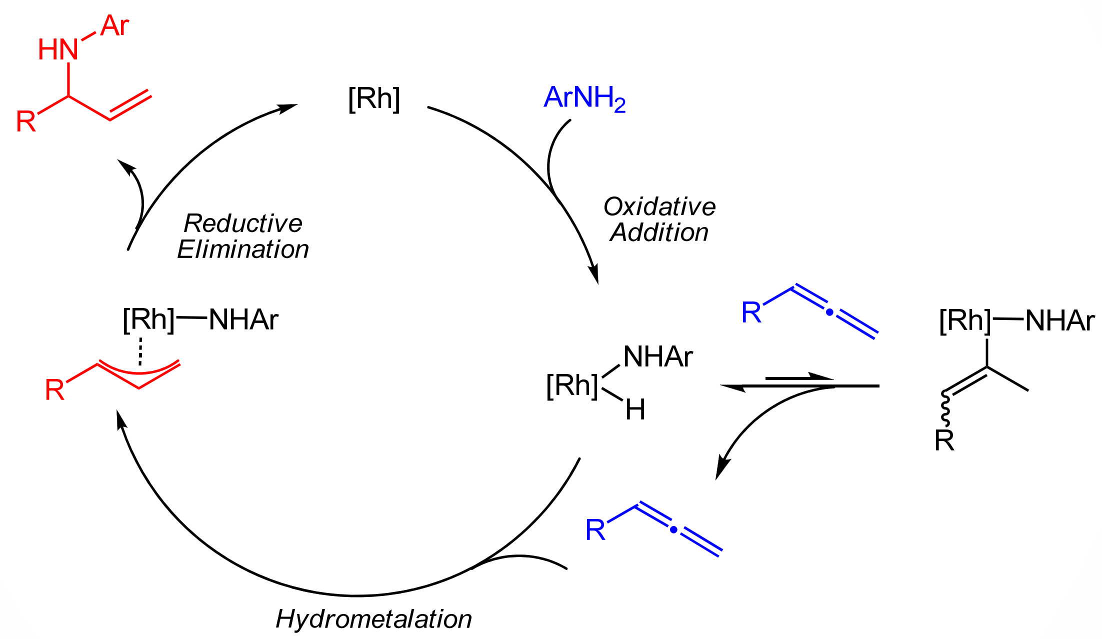
Yamamoto, Y. *et al. J. Am. Chem. Soc.* **2004**, *126*, 1622–1623.

Rh-Catalyzed Hydroamination of Allenes

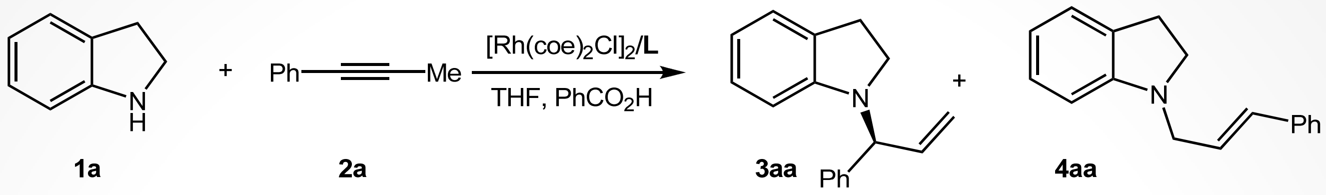


Breit, B. *et al. Angew. Chem. Int. Ed.* **2012**, *51*, 10876–10879.

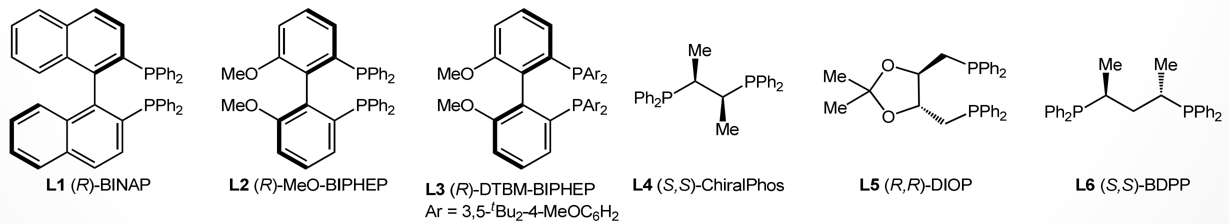
Rh-Catalyzed Hydroamination of Allenes



Rh-Catalyzed Hydroamination of Alkynes



Entry[a]	Ligand	3aa/4aa	Yield of 3aa (%)[b]	Ee of 3aa (%)[c]
1	**L1**	>20:1	4	ND
2	**L2**	19:1	18	55
3	**L3**	>20:1	64	47
4	**L4**	5:1	2	ND
5	**L5**	4:1	57	47
6	**L6**	>20:1	62	87
7[d]	**L6**	>20:1	80[e]	90



[a] **1a** (0.10 mmol), **2a** (0.12 mmol), $[Rh(coe)_2Cl]_2$ (2 mol %), **Ligand** (4.4 mol %), $PhCO_2H$ (30 mol %), THF (0.25 mL), 70 °C, 18 h. [b] Determined by ^1H NMR or GC-FID with 1,3,5-trimethoxybenzene as the internal standard; ND = not determined. [c] Determined by chiral SFC. [d] **1a** (0.20 mmol), **2a** (0.30 mmol), $[Rh(coe)_2Cl]_2$ (4 mol %), (*S*,*S*)-BDPP (8.8 mol %), *m*-xylylic acid (15 mol %). [e] Isolated yield.

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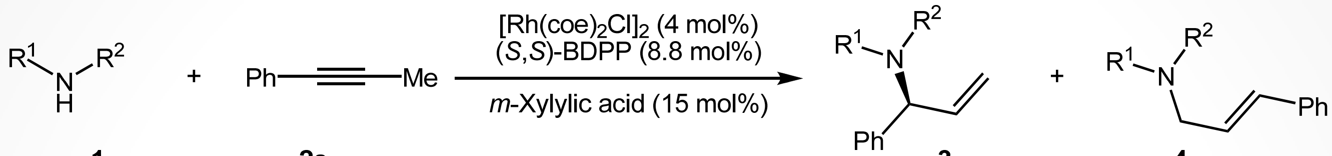
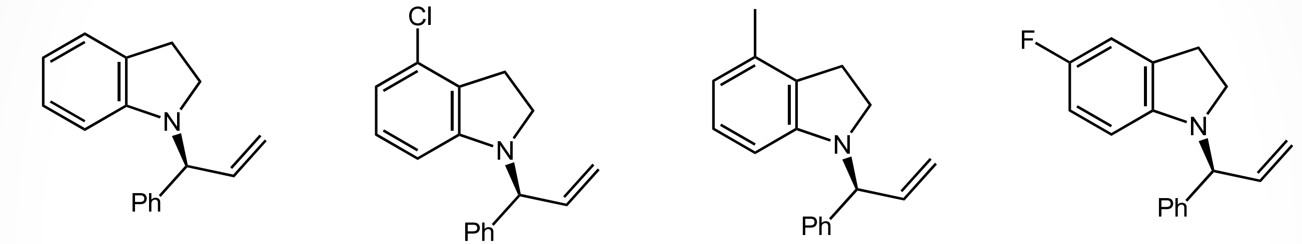
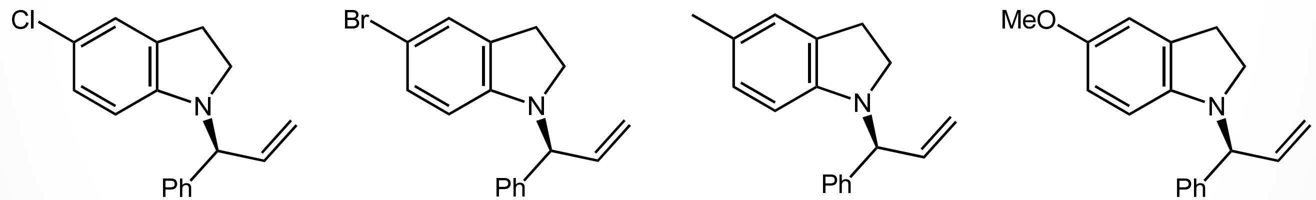
Rh-Catalyzed Hydroamination of Alkynes

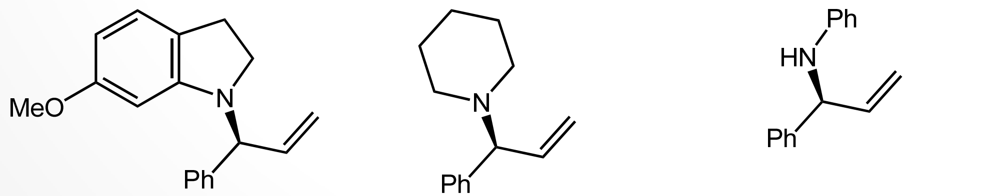




3aa: >20:1, 80%, 90% ee
3ba: >20:1, 72%, 90% ee
3ca: 18:1, 81%, 90% ee
3da: >20:1, 82%, 89% ee

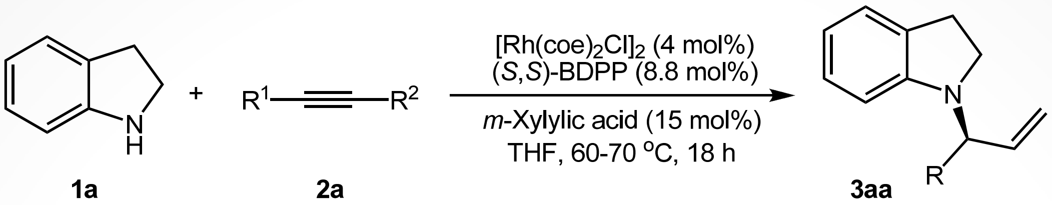


3ea: >20:1, 78%, 90% ee
3fa: 17:1, 85%, 88% ee
3ga: 20:1, 83%, 89% ee
3ha: 12:1, 80%, 77% ee



3ia: 15:1, 84%, 83% ee
3ja: 18:1, 47%, 26% ee
3ka: >20:1, 32%, 76% ee

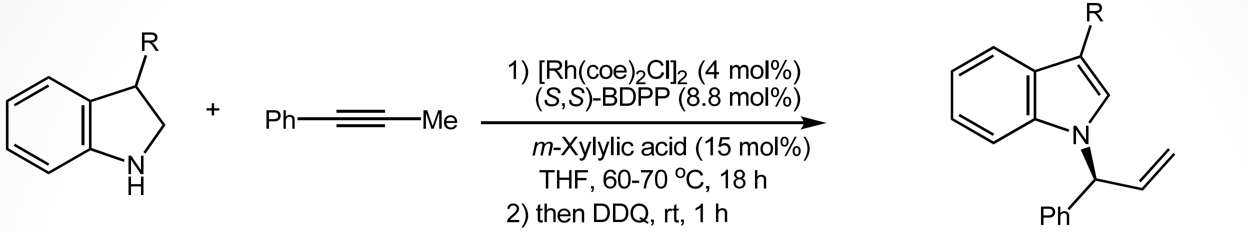
Rh-Catalyzed Hydroamination of Alkynes



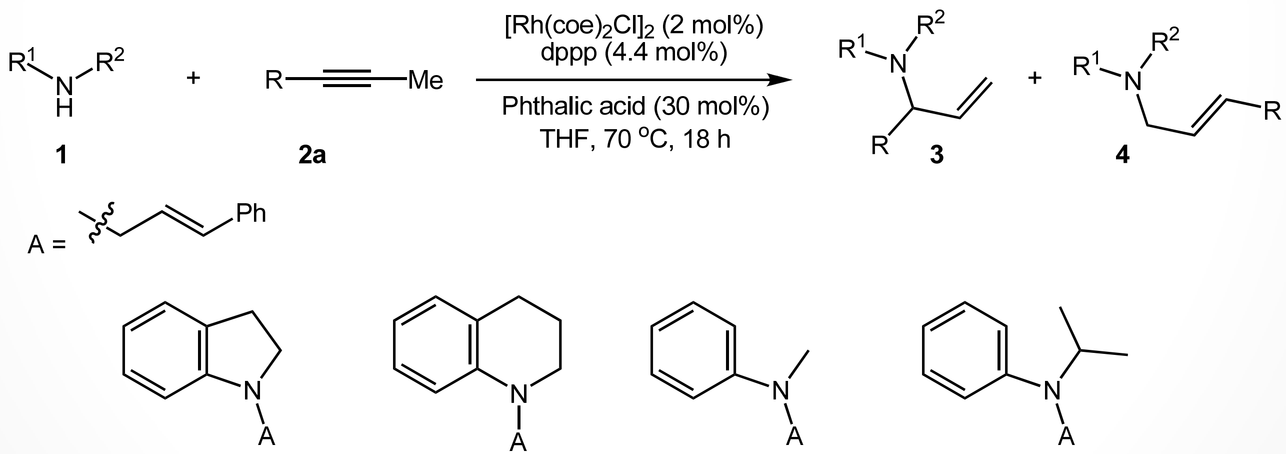
Entry[a]	**R^1/R^2 in 2**	**3/4**	Yield (%)[b]	Ee (%)[b]
1	4-MeC_6H_4/Me (**2b**)	>20:1	73	91 (**3ab**)
2[c]	4-$MeOC_6H_4$/Me (**2c**)	>20:1	70	82 (**3ac**)
3	4-FC_6H_4/Me (**2d**)	20:1	87	90 (**3ad**)
4	4-ClC_6H_4/Me (**2e**)	11:1	83	92 (**3ae**)
5	4-BrC_6H_4/Me (**2f**)	5:1	69	86 (**3af**)
6	4-$CF_3C_6H_4$/Me (**2g**)	3:1	70	91 (**3ag**)
7	3-MeC_6H_4/Me (**2h**)	>20:1	79	90 (**3ah**)
8	3-FC_6H_4/Me (**2i**)	11:1	82	94 (**3ai**)
9	3-ClC_6H_4/Me (**2j**)	8:1	81	93 (**3aj**)
10	3-Thienyl/Me (**2k**)	7:1	80	65 (**3ak**)
11[c]	Cy/Me (**2l**)	2:1	15	27 (**3al**)
12[c]	Bn/H (**2m**)	19:1	37	89 (**3am**)
13[c]	*n*-C_6H_{13}/H (**2n**)	7:1	29	7 (**3an**)

[a] **1a** (0.20 mmol), **2** (0.30 mmol), $[Rh(cod)_2Cl]_2$ (4.0 mol %), (*S*,*S*)-BDPP (8.8 mol %), *m*-xylylic acid (15 mol %), THF (0.25 mL), 60 °C. The ratio of **3/4** was determined by ^{1}H NMR analysis of reaction mixture. [b] Isolated yield and ee of **3**. [c] At 70 °C.

Rh-Catalyzed Hydroamination of Alkynes

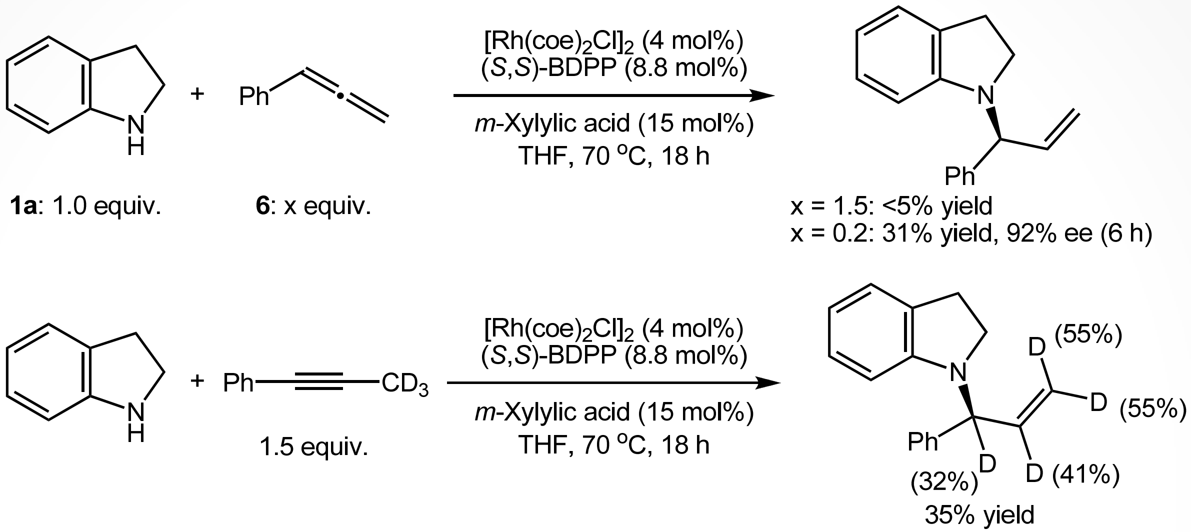


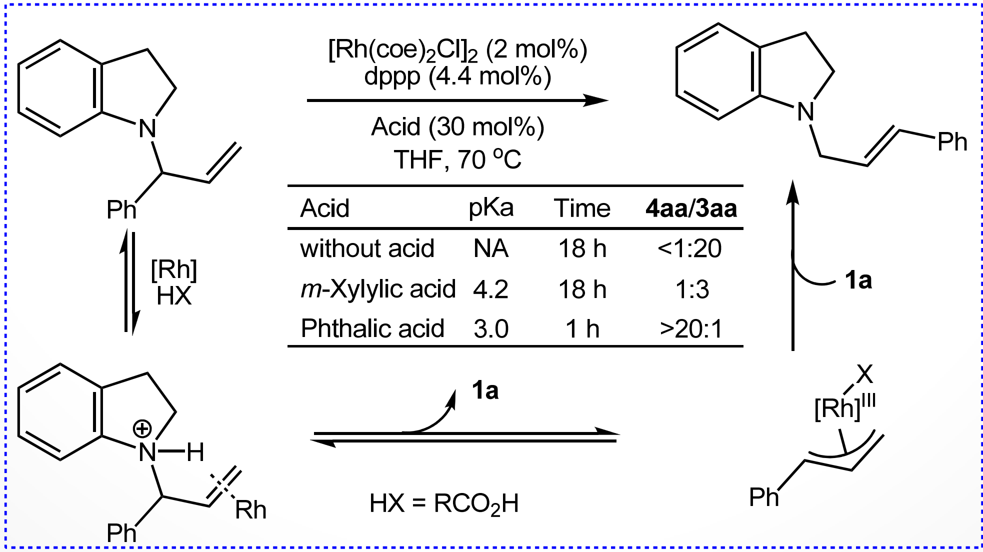
5aa: R = H 77% yield, 90%ee
5ba: R = Me 72% yield, 85% ee



4aa: >20:1, 91% yield
4la: 99% yield
4ma: 95% yield
4na: 85% yield

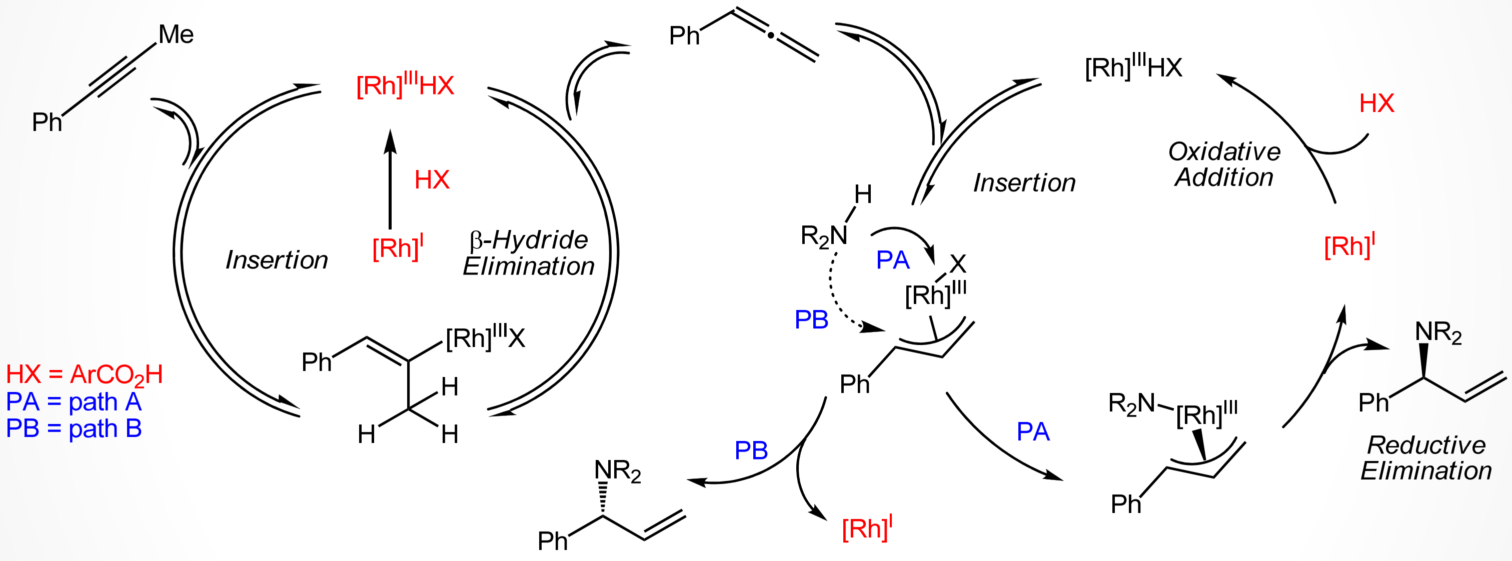
Rh-Catalyzed Hydroamination of Alkynes



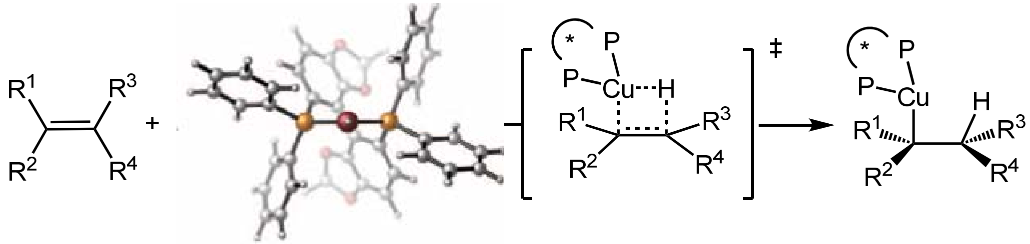


Acid	pKa	Time	**4aa/3aa**
without acid	NA	18 h	<1:20
m-Xylylic acid	4.2	18 h	1:3
Phthalic acid	3.0	1 h	>20:1

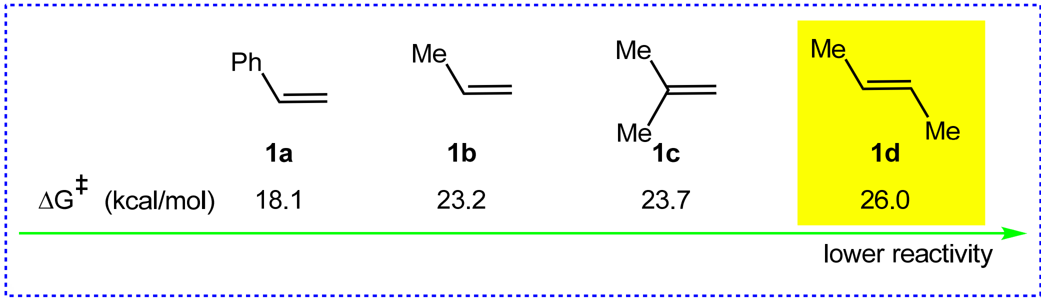
Rh-Catalyzed Hydroamination of Alkynes



Cu-Catalyzed Hydroamination

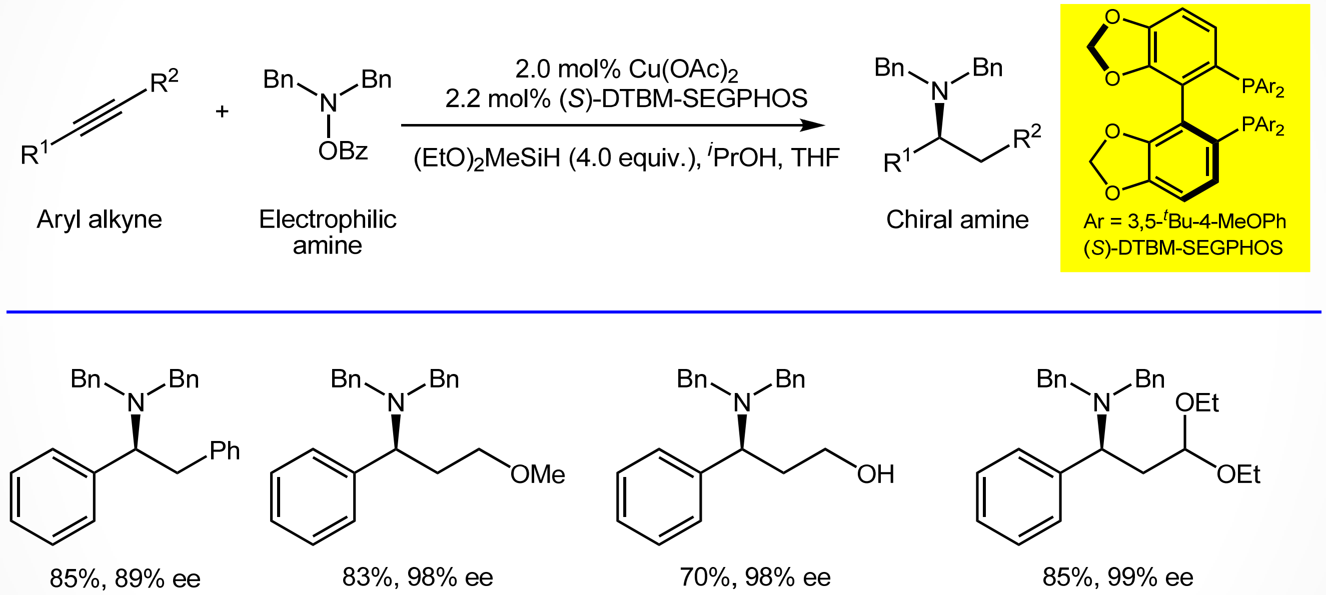


L*CuH
L* = SEGPHOS



Buchwald, S. L. *et al. J. Am. Chem. Soc.* **2013**, *135*, 15746−15749.
Buchwald, S. L. *et al. J. Am. Chem. Soc.* **2014**, *136*, 15913−15916.
Buchwald, S. L. *et al. Angew. Chem. Int. Ed.* **2015**, *54*, 1638−1641.

Cu-Catalyzed Hydroamination of Alkynes



Buchwald, S. L. *et al. Nat. Chem.* **2015**, *7*, 38−44.

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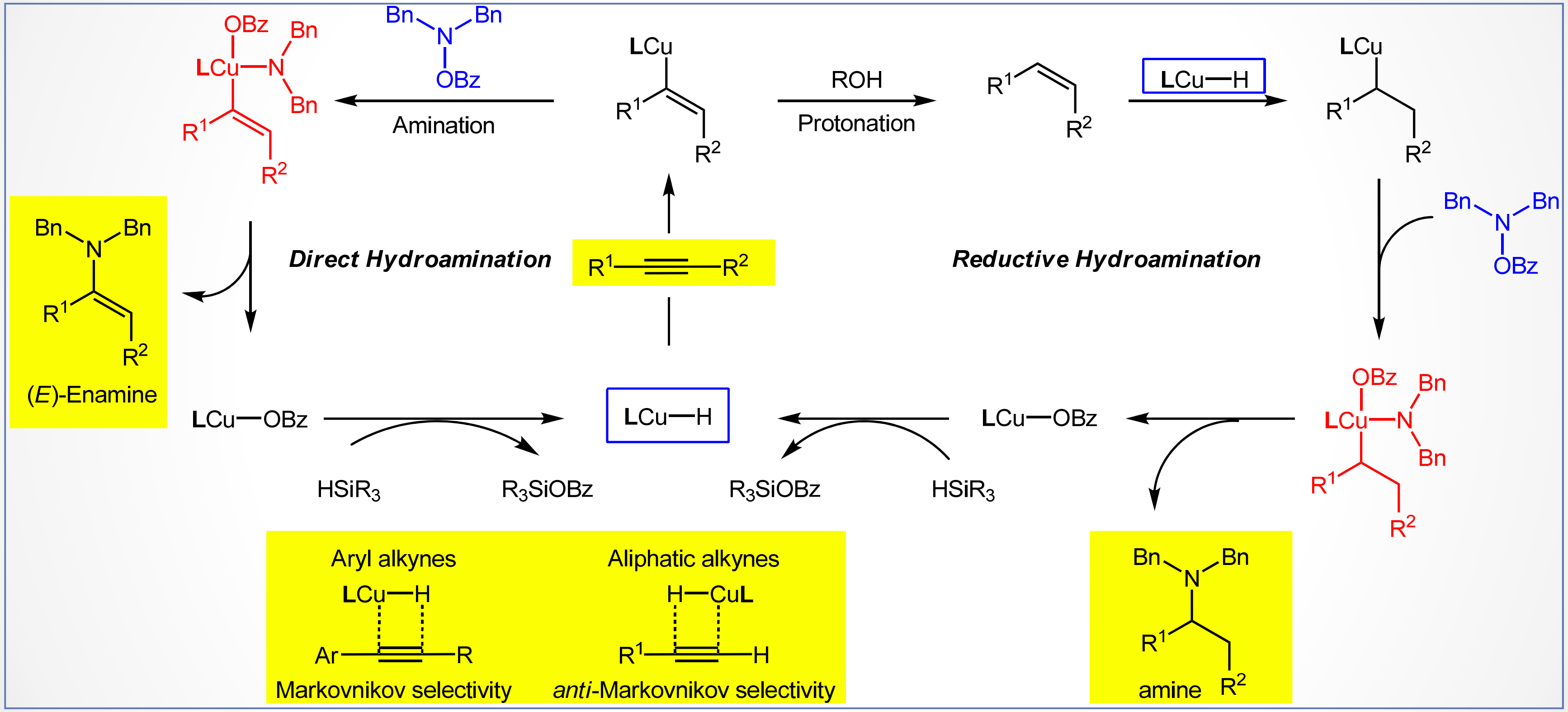
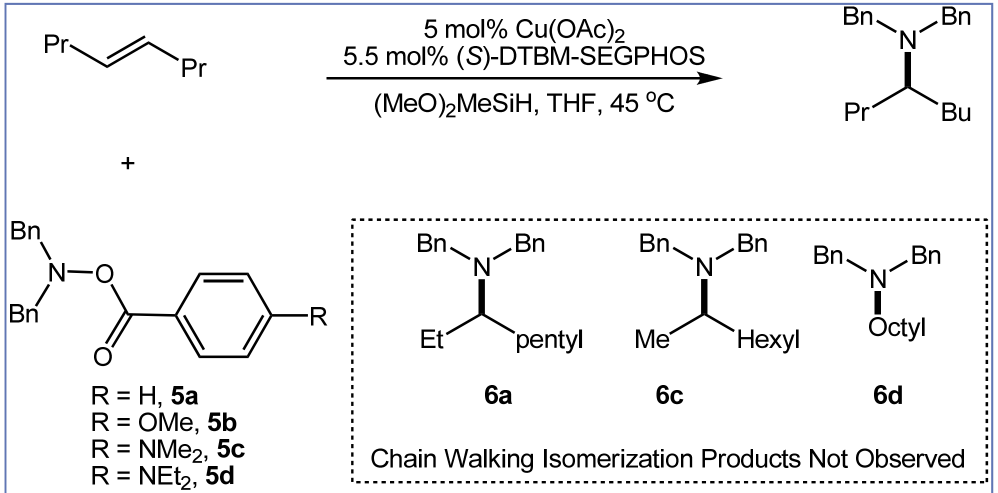
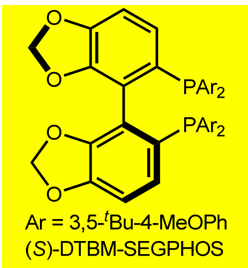


Cu-Catalyzed Hydroamination of Alkenes



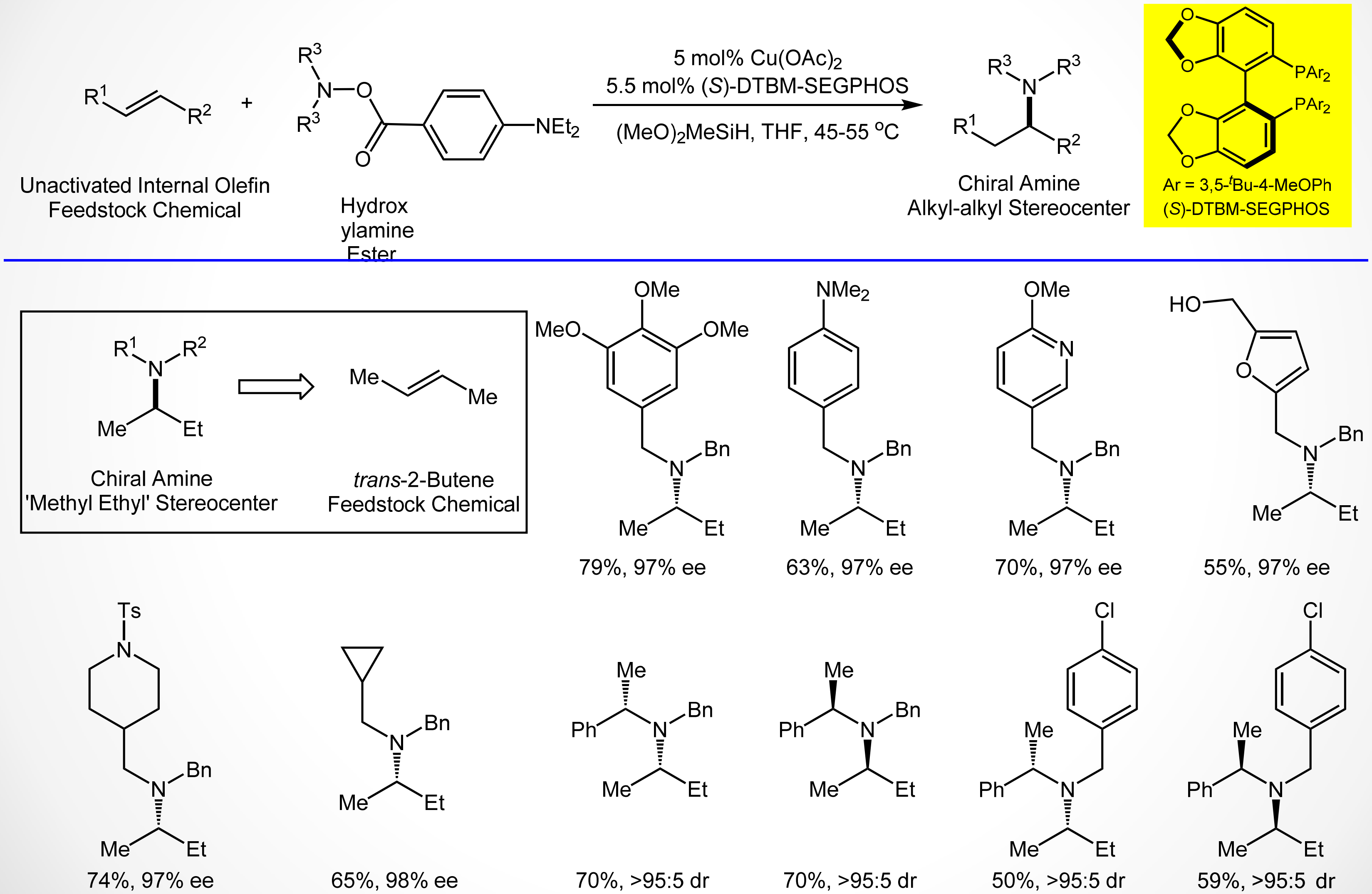


5	R	yield of **6a**	ee of **6a**
5a*	H	<1%	--
5a	H	34%	98%
5b	OMe	47%	98%
5c	NMe$_2$	65%	98%
5d	NEt$_2$	75% (84%)$^+$	98% (98%)$^+$

*(*S*)-SEGPHOS was used in place of (*S*)-DTBM-SEGPHOS
$^+$6 mol% PPh$_3$ was added

Buchwald, S. L. *et al. Science* **2015**, *349*, 62−66.

Cu-Catalyzed Hydroamination of Alkenes



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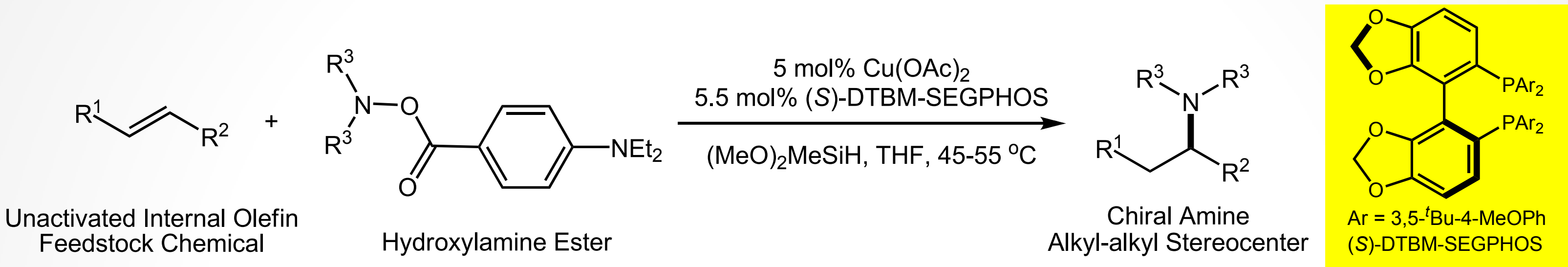

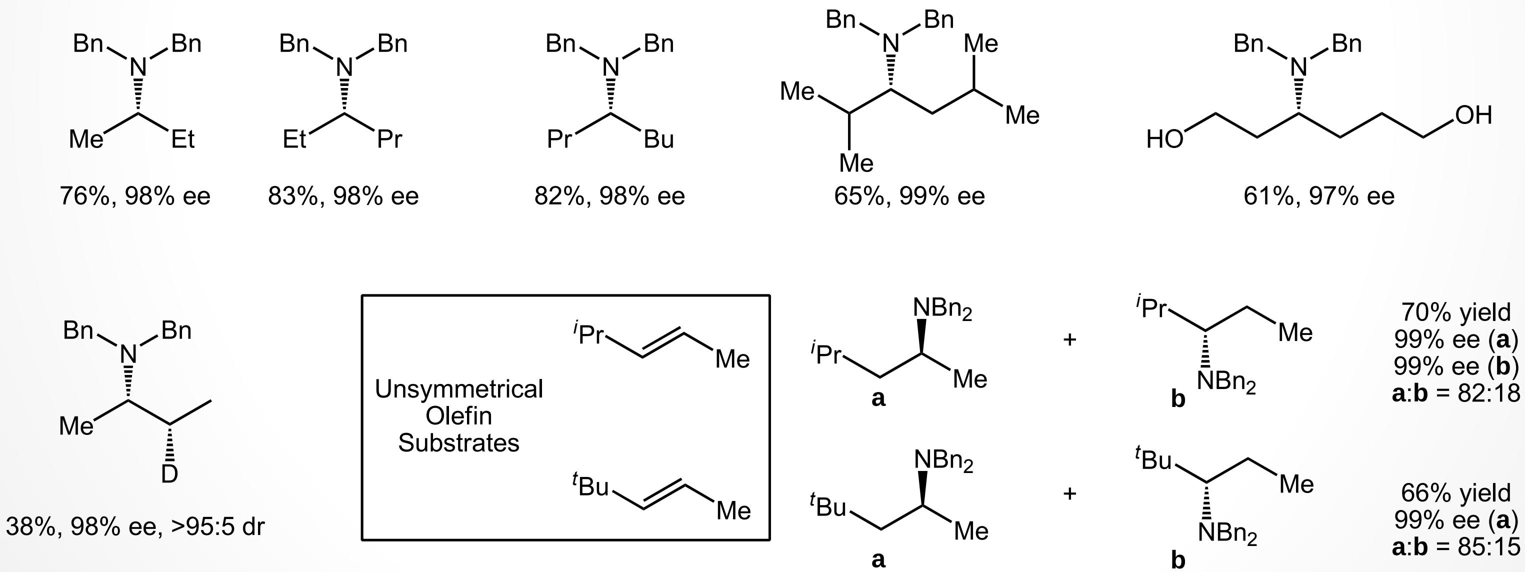

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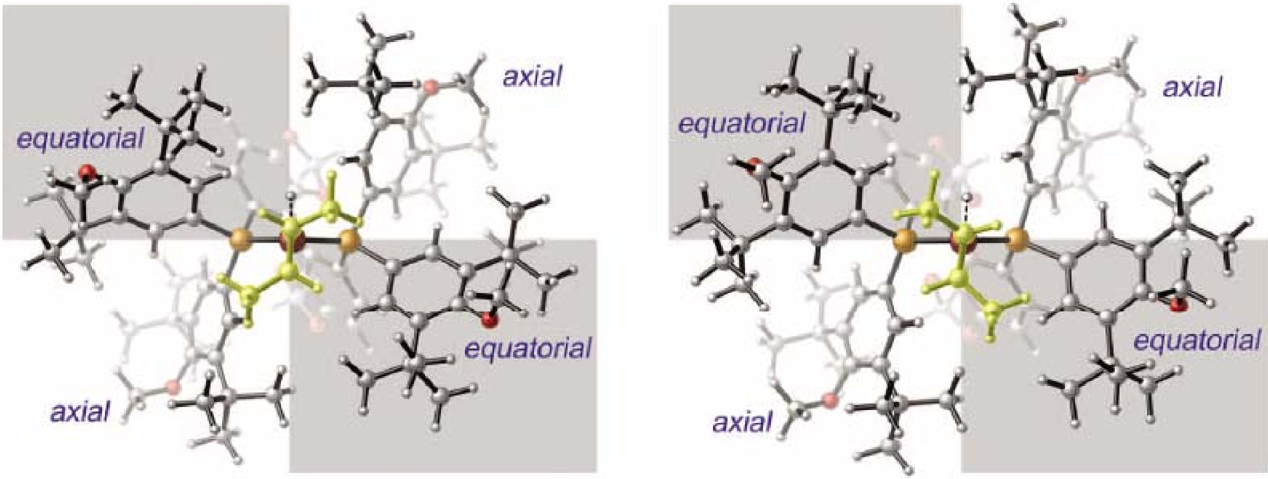
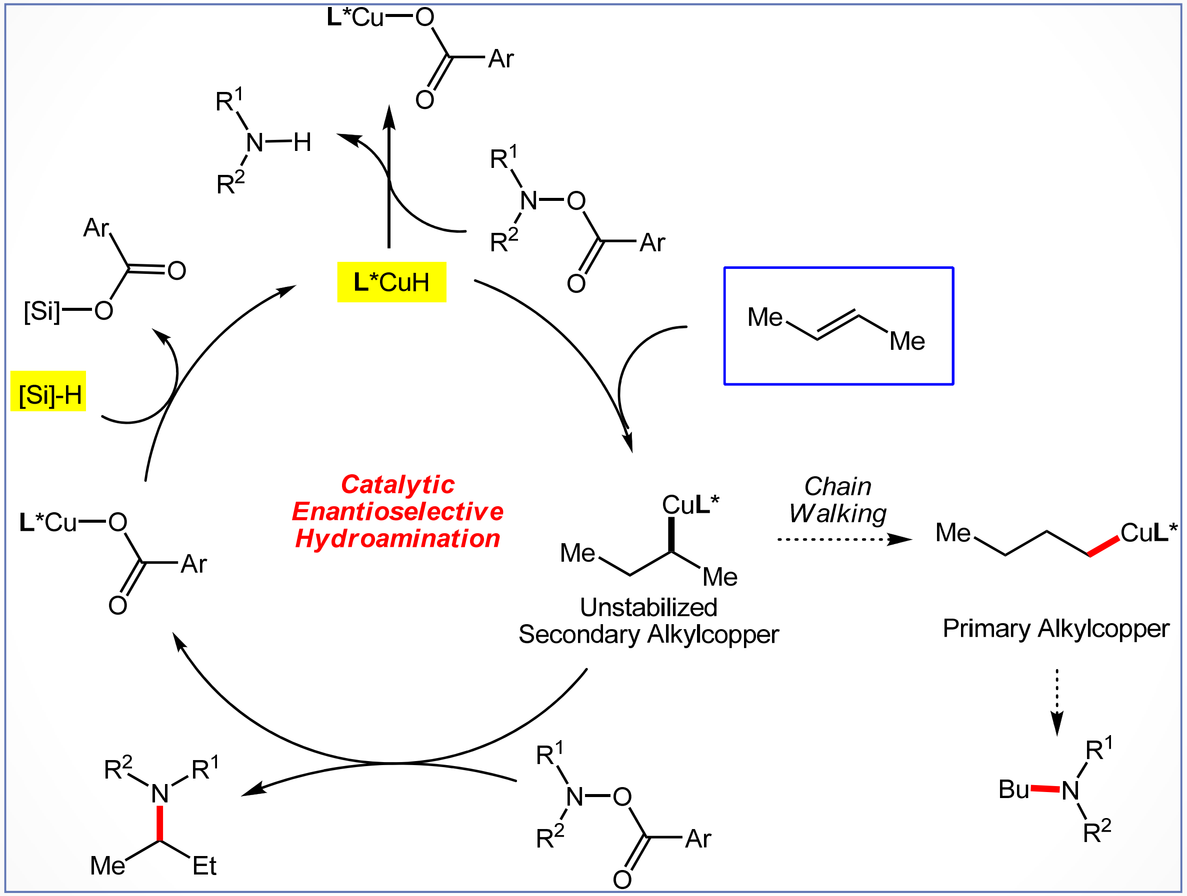


TS2a-favored
(*Re*)-face attack
$\Delta G^{\ddagger}$ = 23.3 kcal/mol
$\Delta H^{\ddagger}$ = 8.6 kcal/mol

TS2b-disfavored
(*Si*)-face attack
$\Delta G^{\ddagger}$ = 26.6 kcal/mol
$\Delta H^{\ddagger}$ = 10.9 kcal/mol

Cu-Catalyzed Hydroamination of Alkenes



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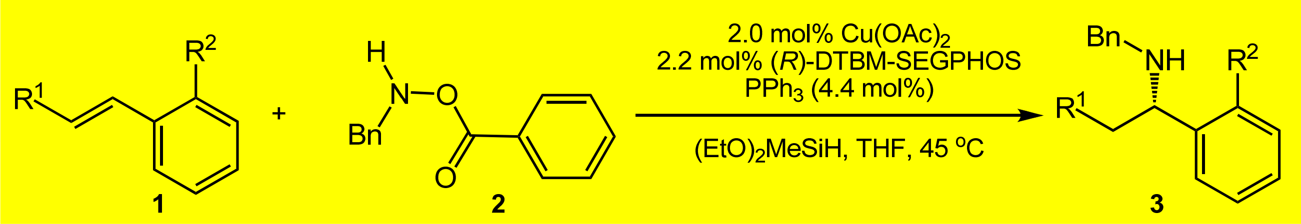

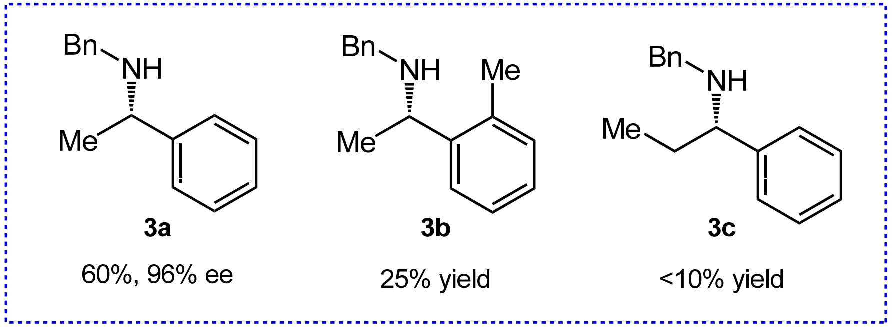

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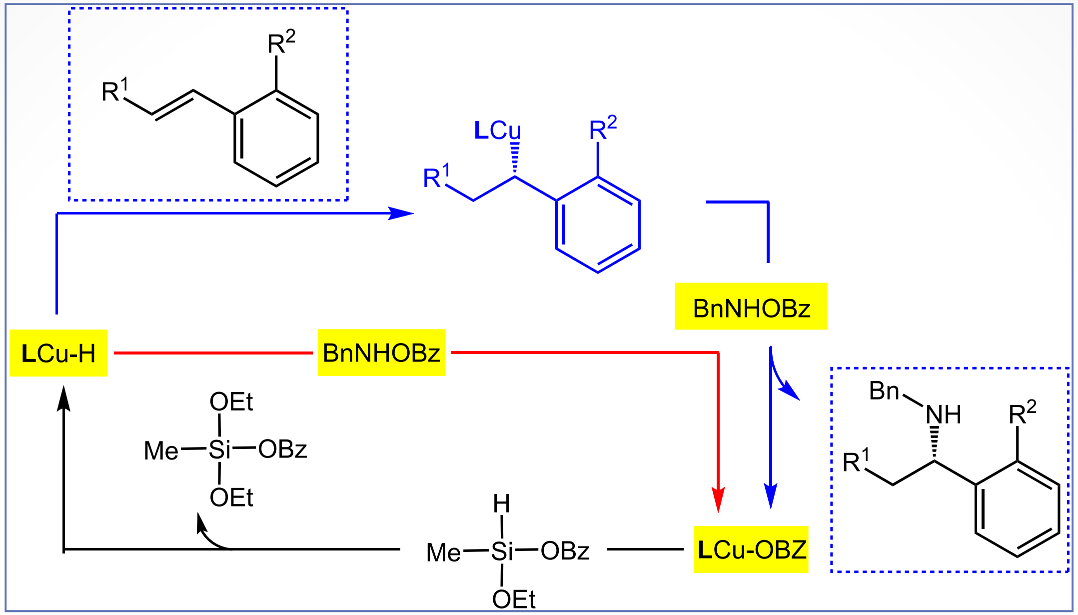
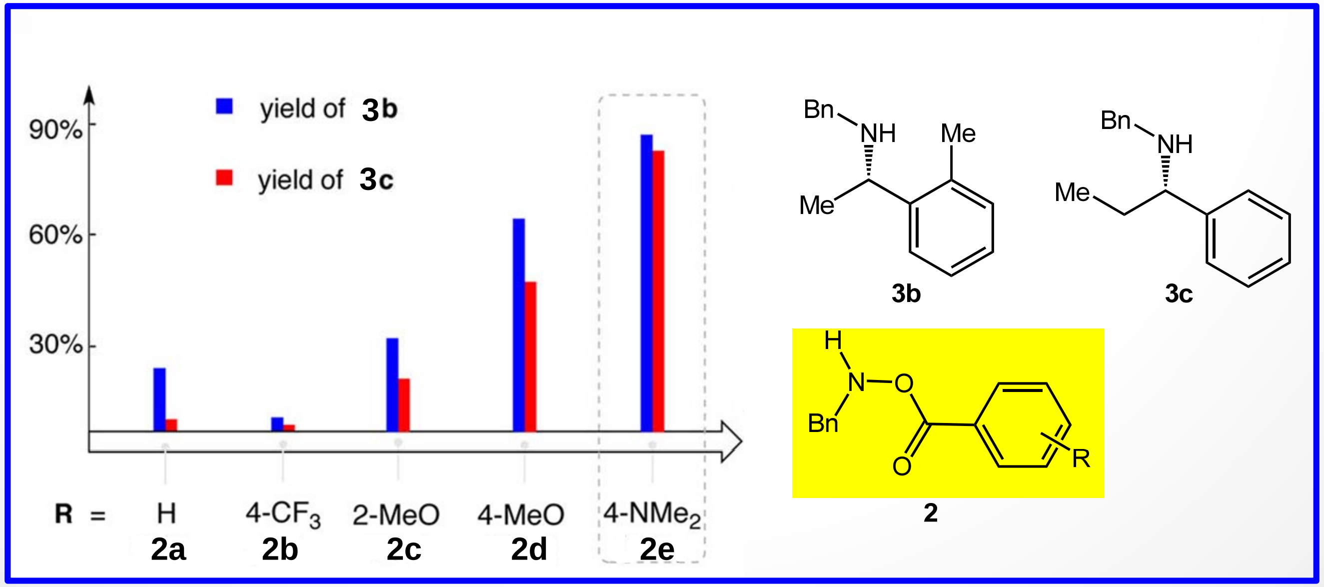
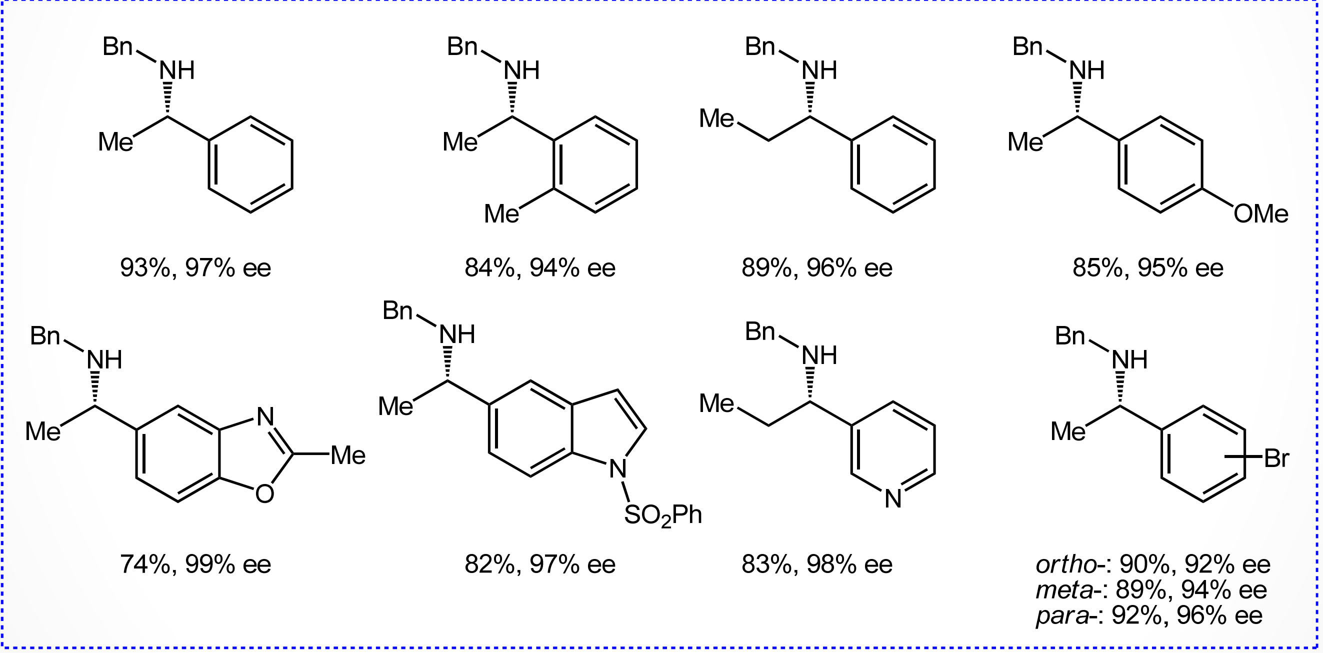
Cu-Catalyzed Hydroamination of Alkenes





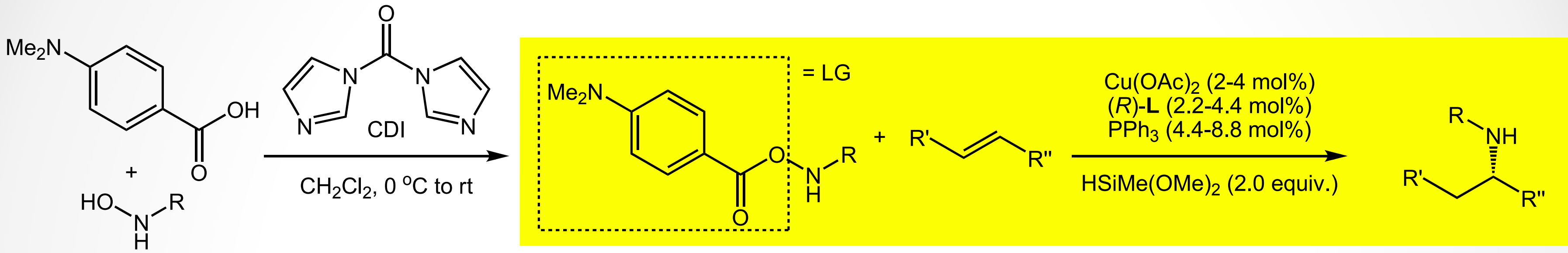
Cu-Catalyzed Hydroamination of Alkenes

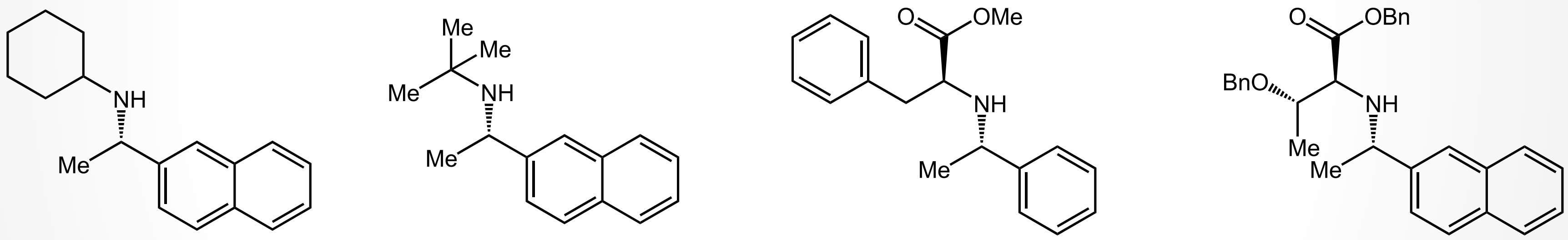
Scope of Different Styrenes in Hydroamination Reactions



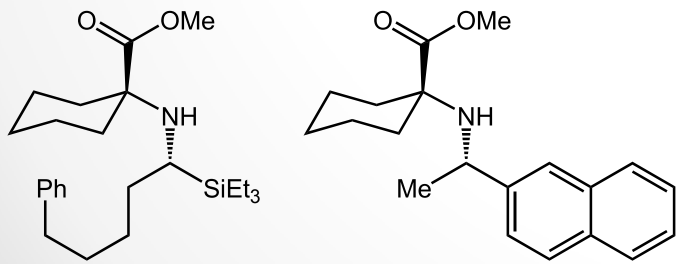
Cu-Catalyzed Hydroamination of Alkenes

Scope of Amine Transfer Reagents in Hydroamination Reactions

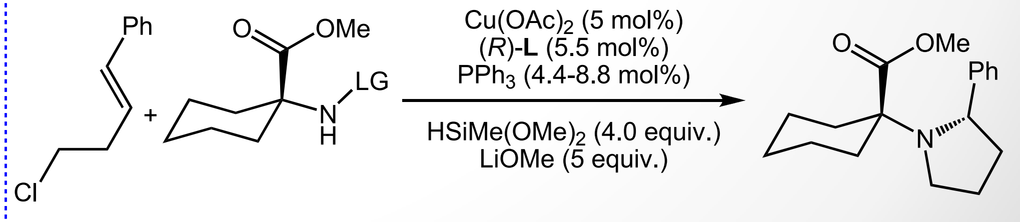




91%, 96% ee | 91%, 93% ee | 66%, >20:1 dr | 64%, >20:1 dr



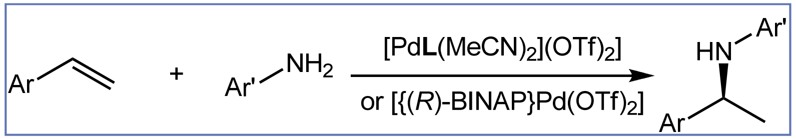
79%, 99% ee | 92%, 95% ee



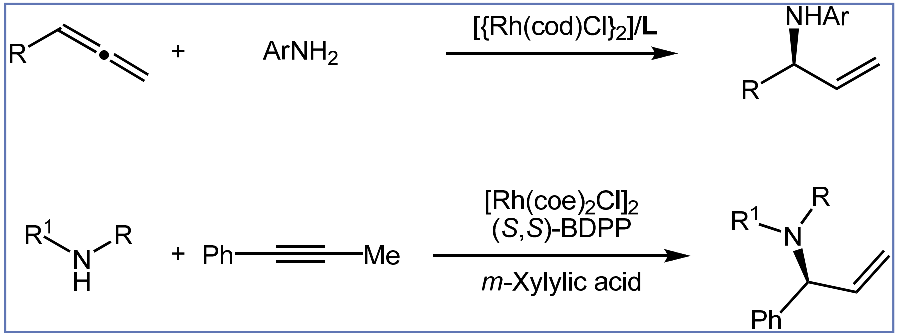
55%, 97% ee

Summary

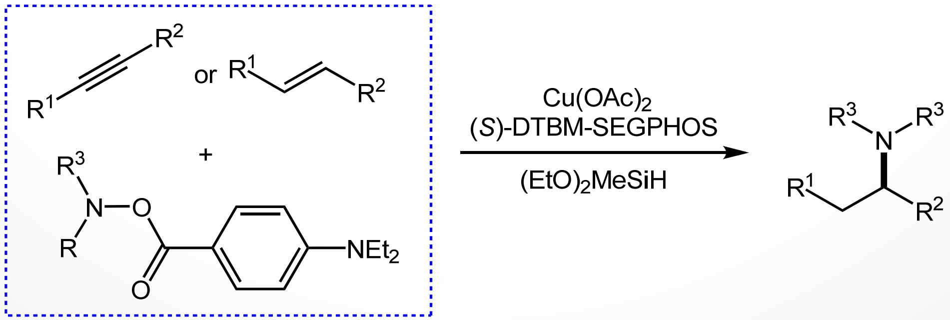
Pd-Catalyzed Hydroamination Ractions



Rh-Catalyzed Hydroamination Ractions



Cu-Catalyzed Hydroamination Ractions



Constructing C−N bonds with high regio- and enantiocontrol represents an important challenge given the occurrence of amines in agrochemicals, fine chemicals, and pharmaceuticals. Transition-metal catalysis has enabled the coupling of amines with allylic electrophiles to provide either the branched or linear isomers. The hydroamination of alkynes has emerged as an attractive approach for C−N bond formation because of its high atom economy. The majority of metal catalysts investigated provide enamine or imine products. In contrast, Yamamoto demonstrated a Pd catalyzed hydroamination of internal alkynes to yield allylic amines, with preference for the linear isomers. While a promising approach, no intermolecular variants have been shown to access the corresponding branched isomers. Herein, we demonstrate a Rh-catalyzed alkyne hydroamination that allows access to either the branched or linear isomers, with high regiocontrol by the choice of carboxylic acid additive used. This communication showcases the first enantioselective intermolecular hydroamination of alkynes.

Our Rh-catalyzed hydroamination provides an atom economical synthesis of allylic amines that complements traditional allylic aminations, which require the use of leaving groups. Mechanistic studies support the in situ formation of an allene which undergoes hydroamination to provide allylic amines, rather than the typically observed products of alkyne hydroamination (e.g., imines and enamines). Phthalic acid promotes isomerization of the kinetically favored isomers to yield the more stable linear isomers. Future studies will focus on catalyst design to extend substrate scope and develop other variants.