

Rhodium-Catalyzed Enantioselective Hydroamination of Alkynes with Indolines

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S Supporting Information

ABSTRACT: The hydroamination of internal alkynes via tandem rhodium catalysis gives branched *N*-allylic indolines with high regio- and enantioselectivity. An acid switch provides access to the linear isomer in preference to the branched isomer by an isomerization mechanism. Mechanistic studies suggest formation of an allene intermediate, which undergoes hydroamination to generate allylic amines instead of the enamine or imine products typically observed in alkyne hydroaminations.

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 (Figure 1a).¹ The hydroamination of alkynes has emerged as an attractive approach for C–N bond formation because of its high atom economy.² The majority of metal catalysts investigated provide enamine or imine products (Figure 1b). In contrast, Yamamoto demonstrated a Pd-catalyzed hydroamination of internal alkynes to yield allylic

amines, with preference for the linear isomers (Figure 1c).³ While a promising approach, no intermolecular variants have been shown to access the corresponding branched isomers. Herein, we demonstrate a Rh-catalyzed alkyne hydroamination⁴ that allows access to either the branched or linear isomers, with high regiocontrol by the choice of carboxylic acid additive used (Figure 1d). This communication showcases the first enantioselective intermolecular hydroamination of alkynes.

Late transition-metal hydrides (e.g., Ru, Rh, Ir, Pd) are known to convert alkynes to π -allyl metal intermediates. Since Yamamoto's report,³ Ishii,⁵ Krische,⁶ and our group⁷ have used metal-hydride catalysis to couple internal alkynes with alcohols or aldehydes to generate C–C bonds. The Breit group pioneered the use of terminal alkynes to form allylrhodium intermediates that undergo C–O and C–S bond formations.⁸ Encouraged by this emerging concept, we focused on the functionalization of alkynes to generate C–N bonds with both regio- and enantiocontrol.

To test our hypothesis, we chose the coupling of indoline **1a** and 1-phenyl-1-propyne **2a** as model substrates (Table 1). Commercially available metal hydride complexes (e.g., RuHCl(CO)(PPh₃)₃, RhH(CO)(PPh₃)₃, or IrH(CO)(PPh₃)₃) did not promote hydroamination. In contrast, a mix of [Rh(COE)₂Cl]₂/L1 and benzoic acid⁸ afforded the desired branched indoline **3aa** in trace amounts (4% yield, entry 1).⁹ More electron-rich and bulky ligands L2 and L3 improved the reactivity and gave high regioselectivities (**3aa/4aa**) and moderate enantioselectivities (47–55% ee, entries 2–3). Among the bidentate phosphines bearing point chirality that we studied, (S,S)-BDPP L6 gave the most promising regio- and enantioselectivity (87% ee, entry 6). We assume this ligand shows enhanced reactivity and selectivity due to its ability to promote isomerization and hydroamination in parallel. In the absence of acid, no hydroamination was observed. By investigating other acid additives, we found higher enantioselectivity using *m*-xylylic acid (90% ee, entry 7).

With this protocol in hand, we explored the hydroamination of alkyne **2a** with various amines **1** (Table 2). Good yields (72% and 81%) and high enantioselectivities (90% ee) were obtained using indolines with varying substituents at the 4-position (**3ba** and **3ca**). Substrates bearing fluoro, chloro, and bromo at the 5-position were transformed into allylic amines with similar efficiency (**3da**–**3fa**). A slight decrease in enantioselectivity was observed with indolines containing electron-donating substituents at the 5- or 6-position (**3ga** vs **3ha**, **3ia**). In contrast, an aliphatic amine, such as morpholine, showed poor reactivity

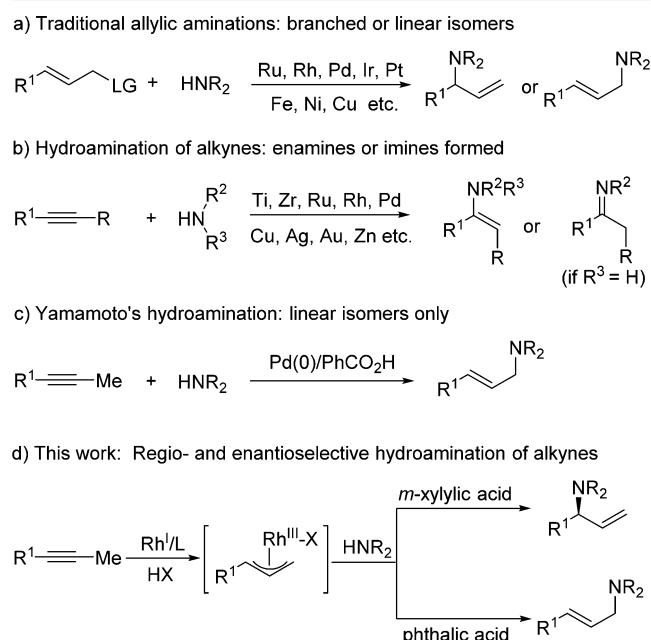
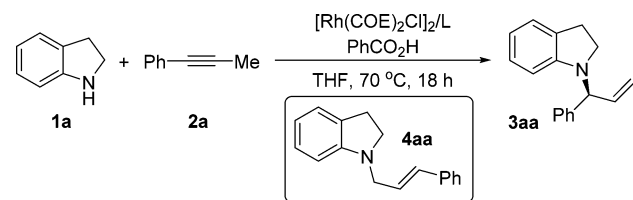


Figure 1. Allylic aminations versus alkyne hydroaminations.

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Table 1. Ligand Effects on Hydroamination of Alkyne^a

entry	ligand	3aa/4aa ^b	yield of 3aa (%) ^b	ee (%) ^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

L1 (R)-BINAP

L2 (R)-MeO-BIPHEP

L3 (R)-DTBM-MeO-BIPHEP
Ar = 3,5-^tBu₂-4-MeOC₆H₂

L4 (S,S)-ChiraPhos

L5 (R,R)-DIOP

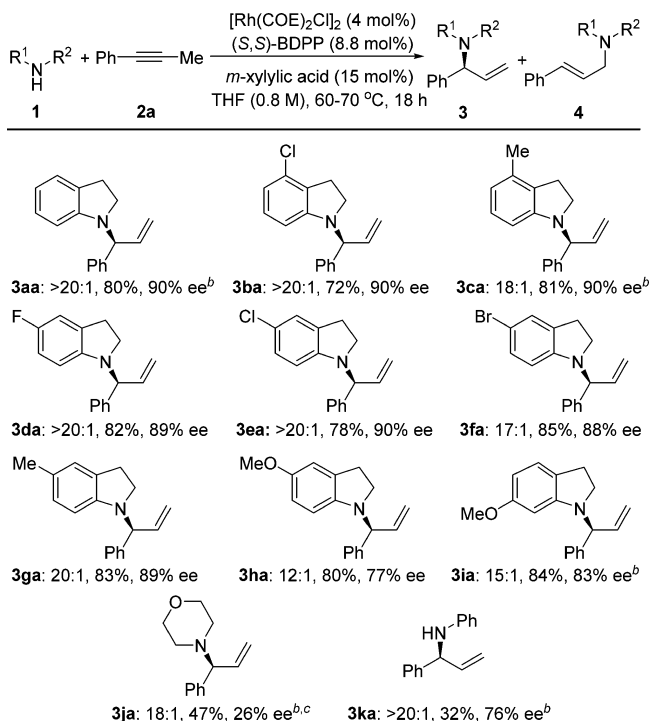
L6 (S,S)-BDPP

^a1a (0.10 mmol), 2a (0.12 mmol), [Rh(COE)₂Cl]₂ (2 mol %), Ligand (4.4 mol %), PhCO₂H (30 mol %), THF (0.25 mL), 70 °C, 18 h. ^bDetermined by ¹H NMR or GC-FID with 1,3,5-trimethoxybenzene as the internal standard; ND = not determined. ^cDetermined by chiral SFC. ^d1a (0.20 mmol), 2a (0.30 mmol), [Rh(COE)₂Cl]₂ (4 mol %), (S,S)-BDPP (8.8 mol %), *m*-xylylic acid (15 mol %). ^eIsolated yield.

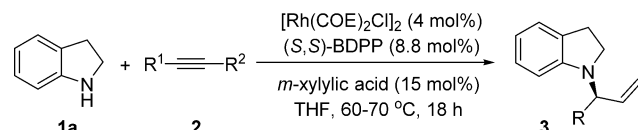
under this protocol (8% yield, 3ja). An improved yield (47%, 3ja) could be obtained by using more *m*-xylylic acid (50 mol %). Aniline 1k was coupled with alkyne 2a in good selectivity (>20:1 b/l, 76% ee, 3ka) without bisallylation. In all cases, we observed excellent regioselectivity for the branched isomers in preference to the linear isomers.

Next, we examined the scope of alkynes (Table 3). The use of electron-rich 1-aryl-1-propynes 2b–c gave branched allylic amines in >20:1 regioselectivities, 70–73% yields, and 82–91% ee (entries 1–2). Although a decrease in regioselectivity (from 20:1 to 3:1) was observed with electron-deficient alkynes 2d–g, high enantioselectivities (86–92%) were still achieved (entries 3–6). The coupling of indoline with *meta*-substituted 1-phenyl-1-propynes 2h–j gave a slight increase in enantioselectivity (90–94%, entries 7–9). This protocol tolerated a heterocycle-substituted alkyne 2k (80% yield, entry 10). However, low reactivity (15% yield) and selectivity (27% ee) were obtained using the internal alkyne 2l bearing an aliphatic group (entry 11). The hydroamination of terminal alkyne 2m gave the same product as that of 2a, with similar regio- and enantioselectivity but lower reactivity (entry 12). Poor enantioselectivity (7%) was observed in the hydroamination of 1-octyne 2n (entry 13).¹⁰ These results suggest that an aromatic substituent on alkyne 2 is critical for high yield and selectivity.

A one-pot protocol was developed, using Rh-catalyzed asymmetric hydroamination and subsequent oxidative dehy-

Table 2. Branched-Selective Hydroamination with Various Amines^a

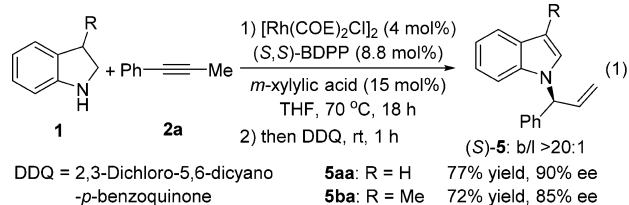
^a1 (0.20 mmol), 2a (0.30 mmol), [Rh(COE)₂Cl]₂ (4.0 mol %), (S,S)-BDPP (8.8 mol %), *m*-xylylic acid (15 mol %), 60 °C. The ratio of (3/4) was determined by ¹H NMR analysis of reaction mixture. ^bAt 70 °C. ^c*m*-Xylylic acid (50 mol %).

Table 3. Branched-Selective Hydroamination of Various Alkynes^a

entry	R ¹ /R ² in 2	3/4	yield (%) ^b	ee (%) ^b
1	4-MeC ₆ H ₄ /Me (2b)	>20:1	73	91 (3ab)
2 ^c	4-MeOC ₆ H ₄ /Me (2c)	>20:1	70	82 (3ac)
3	4-FC ₆ H ₄ /Me (2d)	20:1	87	90 (3ad)
4	4-ClC ₆ H ₄ /Me (2e)	11:1	83	92 (3ae)
5	4-BrC ₆ H ₄ /Me (2f)	5:1	69	86 (3af)
6	4-CF ₃ C ₆ H ₄ /Me (2g)	3:1	70	91 (3ag)
7	3-MeC ₆ H ₄ /Me (2h)	>20:1	79	90 (3ah)
8	3-FC ₆ H ₄ /Me (2i)	11:1	82	94 (3ai)
9	3-ClC ₆ H 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 (3aa)
13 ^c	<i>n</i> -C ₆ H ₁₃ /H (2n)	7:1	29	7 (3an)

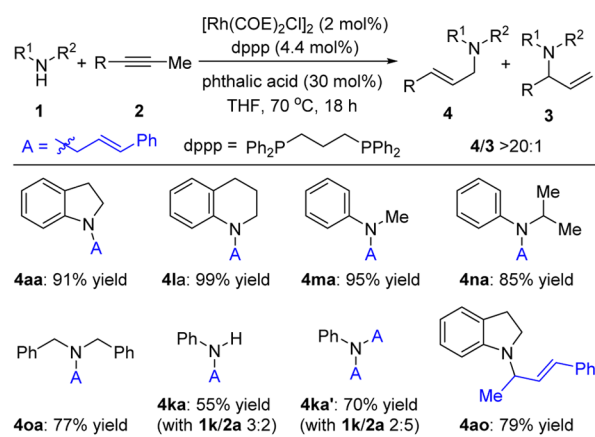
^a1a (0.20 mmol), 2 (0.30 mmol), [Rh(COE)₂Cl]₂ (4.0 mol %), (S,S)-BDPP (8.8 mol %), *m*-xylylic acid (15 mol %), THF (0.25 mL), 60 °C. The ratio of 3/4 was determined by ¹H NMR analysis of reaction mixture. ^bIsolated yield and ee of 3. ^cAt 70 °C.

droaromatization of indolines 3, to provide facile access to *N*-allylic indoles¹¹ 5aa (90% ee) and 5ba (85% ee) (eq 1). The absolute configuration of 5aa was determined to be (S) by comparison of its optical rotation with literature data.^{11c,d,12}



During our optimization studies, we found that using phthalic acid (benzene-1,2-dicarboxylic acid)¹³ instead of *m*-xylylic acid gave linear allylic amines with high regioselectivity (>20:1). A number of amines are suitable coupling partners (4aa–4la, 4a–4oa, Table 4). By tuning the stoichiometry of aniline 1k (PhNH₂) and

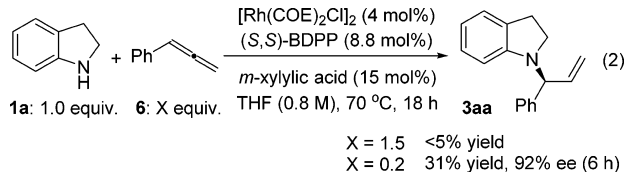
Table 4. Linear-Selective Hydroamination of Alkynes



alkyne 2a, either monoallylated product 4ka or bisallylated product 4ka' could be formed exclusively. This protocol can be applied to 1-phenyl-1-butyne 2n, which bears an ethyl group, to generate allylic amine 4ao.

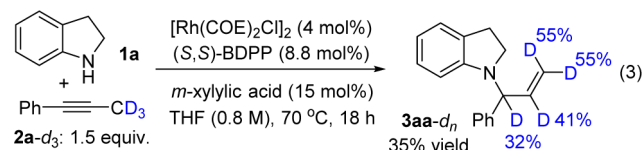
On the basis of literature^{1,8} and our observations, we propose a pathway involving tandem Rh-catalysis (Figure 2). The oxidative addition of carboxylic acid with a Rh(I) precursor generates a rhodium(III)-hydride species. The insertion of alkyne 2a into the Rh(III)–H gives Rh-vinyl intermediate A, which subsequently undergoes β -hydride elimination to form intermediate allene 6 and regenerate the Rh(III)–H species. Reinsertion of the terminal allene 6 into Rh(III)–H yields chiral π -allyl rhodium complex B. Two competing pathways can be considered for formation of product 3.¹⁴ For path A, a ligand exchange of amine 1 with the benzoate (X) on complex B will give π -allyl rhodium species C, which can undergo reductive elimination to yield allylic amine 3. In path B, amine 1 undergoes nucleophilic attack at the carbon center to deliver allylic amine 3.

To support the proposed allene intermediate, phenylallene 6 was prepared and then subjected to coupling with indoline 1a under otherwise standard conditions (eq 2).¹⁵ Only a trace



amount of the expected allylic amine was generated using a high concentration (~1.20 M) of allene 6. However, the allene was transformed into the expected allylic amine when using a lower concentration (~0.16 M). Our results support the feasibility of allene 6 as the intermediate and suggest that high concentrations of allene inhibit catalysis. Using alkynes as allene surrogates can enable transformations that would be sluggish with allene precursors.^{6a,7}

When the hydroamination was performed with deuterated alkyne 2a-d₃, the deuterium label was scrambled into the α -, β -, and γ -positions of amine 3aa-d_n (eq 3). The observed incorporation of hydrogen at the γ -position of amine 3aa-d_n indicates the reversibility of β -hydride elimination during allene formation.



To better understand the regioselective switch (Table 2 vs 4), we isolated and subjected racemic 3aa to various conditions (Figure 3). No isomerization was observed in the absence of

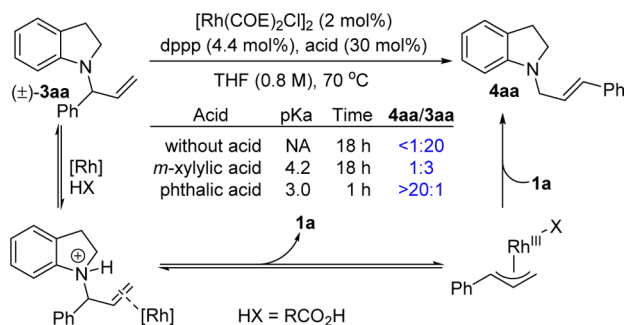


Figure 3. Acid-promoted isomerization study.

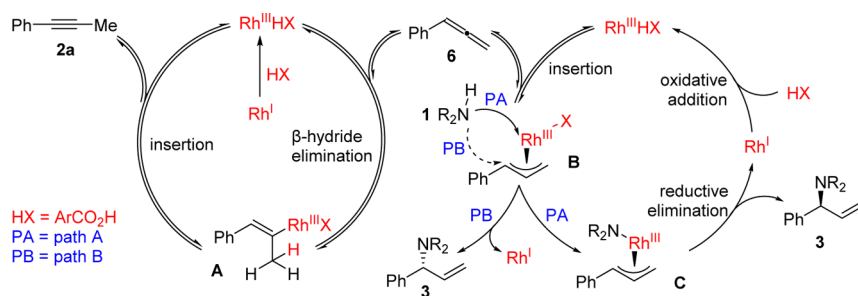


Figure 2. Tandem Rh-catalysis: proposed mechanism for hydroamination of alkynes.

either Rh or acid. However, the branched isomer **3aa** underwent isomerization to the linear product **4aa** faster in the presence of a more acidic additive (e.g., *m*-xylylic vs phthalic acid). Thus, the branched isomer is the kinetic product, which can be generated in high yield using *m*-xylylic acid. In contrast, our phthalic acid protocol generates linear products by a thermodynamically controlled isomerization. Indeed, when we monitored the reaction profile for our linear-selective hydroamination, we observed formation of the branched isomer at early time points followed by its conversion to the linear. Yudin observed a related isomerization of allylic amines under Pd-catalysis, whereby the kinetic (branched) product was favored by addition of DBU.¹⁶

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.

■ ASSOCIATED CONTENT

● Supporting Information

Experimental procedures and spectral data for all new compounds. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.5b05200.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

- (1) For selected reviews on allylic substitutions, see: (a) Tsuji, J.; Minami, I. *Acc. Chem. Res.* **1987**, *20*, 140. (b) Trost, B. M.; Van Vranken, D. L. *Chem. Rev.* **1996**, *96*, 395. (c) Johannsen, M.; Jørgensen, K. A. *Chem. Rev.* **1998**, *98*, 1689. (d) Trost, B. M.; Crawley, M. L. *Chem. Rev.* **2003**, *103*, 2921. (e) Helmchen, G.; Dahnz, A.; Dübon, P.; Schelwies, M.; Weihofen, R. *Chem. Commun.* **2007**, 675. (f) Falciola, C. A.; Alexakis, A. *Eur. J. Org. Chem.* **2008**, 3765. (g) Lu, Z.; Ma, S. *Angew. Chem., Int. Ed.* **2008**, *47*, 258. (h) Trost, B. M.; Zhang, T.; Sieber, J. D. *Chem. Sci.* **2010**, *1*, 427. (i) Hartwig, J. F.; Stanley, L. M. *Acc. Chem. Res.* **2010**, *43*, 1461. (j) Poli, G.; Prestat, G.; Liron, F.; Kammerer-Pentier, C. *Top. Organomet. Chem.* **2012**, *38*, 1. (k) Milhau, L.; Guiry, P. J. *Top. Organomet. Chem.* **2012**, *38*, 95. (l) Liu, W.-B.; Xia, J.-B.; You, S.-L. *Top. Organomet. Chem.* **2012**, *38*, 155. (m) Begouin, J.-M.; Klein, J. E. M. N.; Weickmann, D.; Plietker, B. *Top. Organomet. Chem.* **2012**, *38*, 269.
- (2) For selected reviews on hydroaminations, see: (a) Müller, T. E.; Beller, M. *Chem. Rev.* **1998**, *98*, 675. (b) Nobis, M.; Drießen-Hölscher, B. *Angew. Chem., Int. Ed.* **2001**, *40*, 3983. (c) Pohlki, F.; Doye, S. *Chem. Soc. Rev.* **2003**, *32*, 104. (d) Alonso, F.; Beletskaya, I. P.; Yus, M. *Chem. Rev.* **2004**, *104*, 3079. (e) Odom, A. L. *Dalton Trans.* **2005**, 225. (f) Severin, R.; Doye, S. *Chem. Soc. Rev.* **2007**, *36*, 1407. (g) Müller, T. E.; Hultzs, K. C.; Yus, M.; Foubelo, F.; Tada, M. *Chem. Rev.* **2008**, *108*, 3795. (h) Hannedouche, J.; Schulz, E. *Chem.—Eur. J.* **2013**, *19*, 4972. (i) Reznichenko, A. L.; Nawara-Hultzs, A. J.; Hultzs, K. C. *Top. Curr. Chem.* **2014**, *343*, 191. (j) Huang, L.; Arndt, M.; Goößen, K.; Heydt, H.; Goößen, L. J. *Chem. Rev.* **2015**, *115*, 2596.
- (3) (a) Kadota, I.; Shibuya, A.; Lutete, L. M.; Yamamoto, Y. *J. Org. Chem.* **1999**, *64*, 4570. (b) Lutete, L. M.; Kadota, I.; Yamamoto, Y. *J. Am. Chem. Soc.* **2004**, *126*, 1622. (c) Patil, N. T.; Lutete, L. M.; Wu, H.; Pahadi, N. K.; Gridnev, I. D.; Yamamoto, Y. *J. Org. Chem.* **2006**, *71*, 4270. (d) Patil, N. T.; Wu, H.; Yamamoto, Y. *J. Org. Chem.* **2007**, *72*, 6577. (e) Narsireddy, M.; Yamamoto, Y. *J. Org. Chem.* **2008**, *73*, 9698.
- (4) For the synthesis of enamines or imines by Rh-catalyzed alkyne hydroaminations, see: (a) Hartung, C. G.; Tillack, A.; Trauthwein, H.; Beller, M. *J. Org. Chem.* **2001**, *66*, 6339. (b) Fukumoto, Y.; Asai, H.; Shimizu, M.; Chatani, N. *J. Am. Chem. Soc.* **2007**, *129*, 13792. (c) Alonso-Moreno, C.; Carrillo-Hermosilla, F.; Romero-Fernández, J.; Rodríguez, A. M.; Otero, A.; Antiñolo, A. *Adv. Synth. Catal.* **2009**, *351*, 881. (d) Sakai, K.; Kochi, T.; Kakiuchi, F. *Org. Lett.* **2011**, *13*, 3928. (e) Kumaran, E.; Leong, W. K. *Organometallics* **2012**, *31*, 1068.
- (5) (a) Obora, Y.; Hatanaka, S.; Ishii, Y. *Org. Lett.* **2009**, *11*, 3510. (b) Hatanaka, S.; Obora, Y.; Ishii, Y. *Chem.—Eur. J.* **2010**, *16*, 1883.
- (6) (a) Park, B. Y.; Nguyen, K. D.; Chaulagain, M. R.; Komanduri, V.; Krische, M. J. *J. Am. Chem. Soc.* **2014**, *136*, 11902. (b) Liang, T.; Nguyen, K. D.; Zhang, W.; Krische, M. J. *J. Am. Chem. Soc.* **2015**, *137*, 3161.
- (7) Chen, Q.-A.; Cruz, F. A.; Dong, V. M. *J. Am. Chem. Soc.* **2015**, *137*, 3157.
- (8) (a) Lumbroso, A.; Koschker, P.; Vautravers, N. R.; Breit, B. *J. Am. Chem. Soc.* **2011**, *133*, 2386. (b) Lumbroso, A.; Abermil, N.; Breit, B. *Chem. Sci.* **2012**, *3*, 789. (c) Gellrich, U.; Meißner, A.; Steffani, A.; Kähny, M.; Drexler, H.-J.; Heller, D.; Plattner, D. A.; Breit, B. *J. Am. Chem. Soc.* **2014**, *136*, 1097. (d) Xu, K.; Khakyzadeh, V.; Bury, T.; Breit, B. *J. Am. Chem. Soc.* **2014**, *136*, 16124. (e) Koschker, P.; Kähny, M.; Breit, B. *J. Am. Chem. Soc.* **2015**, *137*, 3131.
- (9) For the synthesis of **3aa** by Ir-catalyzed allylic amination, see: Shu, C. T.; Leitner, A.; Hartwig, J. F. *Angew. Chem., Int. Ed.* **2004**, *43*, 4797.
- (10) For alkyne **2l**, no decomposition of starting materials was observed after 18 h. For alkyne **2m**, competitive alkyne decomposition (dimerization and trimerization) was observed by GC/MS. The use of other internal alkynes (e.g., 1-phenyl-1-butyne) gave trace amounts of product.
- (11) For the asymmetric synthesis of *N*-allylic indoles, see: (a) Stanley, L. M.; Hartwig, J. F. *Angew. Chem., Int. Ed.* **2009**, *48*, 7841. (b) Cui, H.-L.; Feng, X.; Peng, J.; Lei, J.; Jiang, K.; Chen, Y.-C. *Angew. Chem., Int. Ed.* **2009**, *48*, 5737. (c) Liu, W.-B.; Zhang, X.; Dai, L.-X.; You, S.-L. *Angew. Chem., Int. Ed.* **2012**, *51*, 5183. (d) Ye, K.-Y.; Dai, L.-X.; You, S.-L. *Chem.—Eur. J.* **2014**, *20*, 3040. (e) Chen, L.-Y.; Yu, X.-Y.; Chen, J.-R.; Feng, B.; Zhang, H.; Qi, Y.-H.; Xiao, W.-J. *Org. Lett.* **2015**, *17*, 1381.
- (12) The absolute configurations of all other amines **3** were assigned by analogy.
- (13) Other acids (TFA, tartaric acid, malonic acid) which have pK_a's from −0.3 to 3 promote the linear selective hydroamination. Phthalic is the optimal acid with respect to substrate generality.
- (14) For Rh-catalyzed enantiospecific or enantioselective allylic aminations, see: (a) Evans, P. A.; Robinson, J. E.; Nelson, J. D. *J. Am. Chem. Soc.* **1999**, *121*, 6761. (b) Evans, P. A.; Clizbe, E. A. *J. Am. Chem. Soc.* **2009**, *131*, 8722. (c) Vrieze, D. C.; Hoge, G. S.; Hoerter, P. Z.; Van Haitsma, J. T.; Samas, B. M. *Org. Lett.* **2009**, *11*, 3140. (d) Arnold, J. S.; Nguyen, H. M. *J. Am. Chem. Soc.* **2012**, *134*, 8380. (e) Arnold, J. S.; Mwenda, E. T.; Nguyen, H. M. *Angew. Chem., Int. Ed.* **2014**, *53*, 3688.
- (15) For Rh-catalyzed hydroamination of allenes, see: (a) Cooke, M. L.; Xu, K.; Breit, B. *Angew. Chem., Int. Ed.* **2012**, *51*, 10876. (b) Li, C.; Kähny, M.; Breit, B. *Angew. Chem., Int. Ed.* **2014**, *53*, 13780. (c) Xu, K.; Thieme, N.; Breit, B. *Angew. Chem., Int. Ed.* **2014**, *53*, 2162. (d) Xu, K.; Thieme, N.; Breit, B. *Angew. Chem., Int. Ed.* **2014**, *53*, 7268.
- (16) (a) Watson, I. D. G.; Yudin, A. K. *J. Am. Chem. Soc.* **2005**, *127*, 17516. (b) Dubovyk, I.; Watson, I. D. G.; Yudin, A. K. *J. Org. Chem.* **2013**, *78*, 1559.