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Journal

Journal of the American Chemical Society, 139(3)

ISSN

0002-7863

Authors

Cruz, Faben A
Dong, Vy M

Publication Date

2017-01-25

DOI

10.1021/jacs.6b10680

Published in final edited form as:
J Am Chem Soc. 2017 January 25; 139(3): 1029–1032. doi:10.1021/jacs.6b10680.

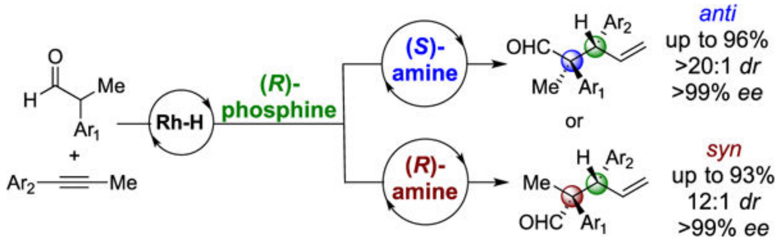
Stereodivergent Coupling of Aldehydes and Alkynes via Synergistic Catalysis using Rh and Jacobsen's Amine

Faben A. Cruz, **Vy M. Dong***
Department of Chemistry, University of California, Irvine, California, 92697, United States

Abstract

We report an enantioselective coupling between α-branched aldehydes and alkynes to generate vicinal quaternary and tertiary carbon stereocenters. The choice of Rh and organocatalyst combination allows for access to all possible stereoisomers with high enantio-, diastereo-, and regioselectivity. Our study highlights the power of catalysis to activate two common functional groups and provide access to divergent stereoisomers and constitutional structures.

Graphical Abstract



While common in Nature, using two catalysts to synergistically activate two substrates has emerged as a powerful strategy for chemical synthesis.[1] In comparison to enzymes, the relative configuration in a pair of chiral synthetic catalysts is readily altered. Seizing this advantage, Carreira and coworkers achieved stereodivergence in their α−alkylation of aldehydes with allylic alcohols,[2a-c] where any stereoisomer could be favored based on the Ir and amine combination chosen. While efficient and modular, stereodivergent dual catalysis remains rare and warrants further study.[3] Recently, Zhang has used dual Ir and Zn catalysis to achieve a stereodivergent α-allylation of α-hydroxyketones.[2d]

Herein, we communicate a complementary method to access γ,δ-unsaturated aldehydes by coupling aldehydes and alkynes (Figure 1). While expanding stereodivergent hydrofunctionalization, our study also highlights how different modes of catalysis can provide access to different constitutional isomers.

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*Corresponding Author dongv@uci.edu.

ASSOCIATED CONTENT

Supporting Information.

The Supporting Information is available free of charge on the ACS Publications website.

Experimental procedures and spectral data for all new compounds (PDF)

The authors declare no competing financial interest.

Functional groups have inherent polarities that can be activated or inverted by catalysis. Discovered over twenty-five years ago,[4] the hydroacylation of alkynes represents a classic *umpolung* transformation where the aldehyde's natural electrophilic polarity has been inverted to generate a nucleophilic acyl-metal-hydride species.[5] The hydroacylation of alkynes typically generates the α,β-unsaturated isomer under a wide-range of protocols.[6] By using tandem Ru-hydride catalysis, we and others switched the conventional regioselectivity to generate β,γ-unsaturated isomers *via* a *nucleophilic* π-allyl species.[7] We envisioned that a Rh-hydride and amine catalyst duo[8] could enable unprecedented access to the γ,δ-unsaturated aldehyde *via* an *electrophilic* π-allyl complex.[9] This synergistic pairing produces α-allylated aldehydes, in contrast to previous metal-organocatalyst studies (where intramolecular alkyne coupling gave α-vinylated aldehydes).[10]

We designed this atom-economic transformation on the basis of the triple cascade mechanism depicted in Figure 2.[11] Breit first demonstrated that Rh-hydride catalysts can promote the isomerization of alkynes (**2**) to generate allenes (**6**).[12a] Such allenes (**6**) undergo Rh-hydride insertion to generate electrophilic Rh-π-allyl species (**7**), which have been intercepted by various heteroatom-based nucleophiles.[12b-e] However, use of this strategy to achieve enantioselective C–C bond formation has been elusive.[12f-h] To address this challenge, we proposed that an enamine (**8**), generated *in situ* from an aldehyde (**1**) and amine (**9**), would trap Rh-π-allyl **7** and generate **3**. In light of Carreira's study,[2a] we recognized the challenge of identifying the appropriate Rh and amine combination for both reactivity and selectivity.

To test our hypothesis, we chose to study the coupling of 2-phenylpropanal (**1a**) and 1-phenyl-1-propyne (**2a**). Using α-branched aldehydes would help avoid aldol-dimerization pathways *via* enamine catalysis.[2b, 13] Moreover, successful transformation of α-branched aldehydes would result in formation of either products **3a** or **4a**, both bearing a quaternary carbon stereocenter.[14] The regioselectivity reflects where C–C bond formation occurs on Rh-π-allyl **7** (*i.e.*, at the more or less substituted carbon). The phosphoric acid allows for generation of the requisite Rh–H catalyst, and aids with enamine formation. With this model system, we discovered that biaryl atropisomeric bisphosphine ligands were most promising for our aldehyde-alkyne coupling. Examination of various MeO-BIPHEP derivatives revealed that phosphine substitution influenced regio- and enantioselectivity (Chart 1a). A phenyl-substituted MeO-BIPHEP afforded (*S,S*)-**3a** in 5% yield with modest selectivities (1.8:1 *rr*, 2.1:1 *dr*, 15% *ee*). Increasing the steric bulk of the phosphine substituents gave improved regio- and enantioselectivity (>20:1 *rr*, 96% *ee*) albeit in 23% yield and 3.5:1 *dr*.

Dihedral angles of biaryl ligands can be tuned by changing the backbone of the ligand and this angle is known to impact the efficiency in enantioselective hydrogenation.[15a] Thus, we next investigated a series of DTBM-variants with varying dihedral angles and observed improved yields with larger dihedral angles (Chart 1b).[15b] (*R*)-DTBM-SEGPHOS afforded (*S,S*)-**3a** in 11% yield, while (*R*)-DTBM-MeO-BIPHEP gave (*S,S*)-**3a** in 23% yield. Increasing the ligand dihedral angle further, *via* (*R*)-DTBM-BINAP, resulted in an improved 37% yield. Changing solvent from DCE to $MeNO_2$ gave (*S,S*)-**3a** in 66% yield (Chart 1c).[16]

While aiming to maintain high levels of regio- and enantioselectivity, we turned our attention towards improving diastereoselectivity. A variety of amine catalysts (*e.g.*, diaryl prolinol, diamines, amino alcohols and cinchona alkaloids) were examined, but these scaffolds did not provide high reactivity and selectivity (Chart 1c). Amine (*S*)-**A3** gave similar results to **A1**. However, switching the enantiomer of **A3** had no effect on diastereoselectivity. Next, we investigated Jacobsen's recently reported primary amine catalyst **A5**,[17a] which was used for enantioselective aldehyde α-hydroxlyation and α-fluorination. This catalyst features an amide that imparts facial bias *via* hydrogen-bonding.[17b] In our study, Jacobsen's amine (*S,S*)-**A5** provided excellent diastereoselectivity and reactivity (75%, >20:1 *dr*, >99% *ee*).[18] Diastereoselectivity can be switched by using (*R,R*)-**A5** instead of (*S,S*)-**A5** in combination with a Rh-(*R*)-DTBM-BINAP catalyst, to enable access to the *syn*-diastereomer (*R*,*S*)-**3a** (75%, 8:1 *dr*, >99% *ee*).

With this catalyst-combination in hand, we investigated the *anti*-selective coupling of various aldehydes **1** and alkynes **2** (Table 1). Aldehydes with electron-rich phenyl rings underwent stereoselective coupling in 86% yield (**3b**). Aldehydes with aromatic and heteroaromatic rings, like 2-naphthylene, *N*-tosyl-3-indole, benzodioxole, and 3-thiophene also undergo efficient and selective coupling (**3c**–**3f**). Electron-rich, electron-deficient, and bromine-containing alkynes (**3k**–**3l**) can be used. Alkynes with silyl (**3m**) and nitro groups (**3o**) are also suitable coupling partners, however the nitro-containing alkyne gave diminished *ee*'s (72% *ee*). Alkynes with heterocycles, such as indoles and benzodioxanes can also be used (**3g**–**3h**, 71–96%, >20:1 *rr*, 16:1– >20:1 *dr*, 93–>99% *ee*). Chemoselective aldehyde-alkyne coupling occurs with alkynes bearing electrophilic functionality like Weinreb amides (**3i**) or methyl esters (**3n**), but low *ee* (4% *ee*) with high *dr* (17:1 *dr*) is observed with with amide **3i**.

Finally, we compared the efficiency for *syn*- versus *anti*-selective coupling using a second set of model substrates (Table 2). By simply altering the relative chirality of the catalyst combination, we could access either diastereomer. Notably, the *syn*- (*R*,*S*) and *anti*-motifs (*S*,*S*) can be accessed with comparably high selectivities when using aldehydes containing trifluoromethyl groups (**3p**) or bromine (**3r**). However, relatively lower diastereoselectivities were observed for the *syn*-diastereomers when using aldehydes with chlorine (**3u**, 8:1 vs. 15:1 *dr*) or triflates (**3s**, 3:1 vs. >20:1 *dr*), or alkynes with *meta*-chloride substitution (**3t**, 5:1 vs. 16:1 *dr*) or pyridine (**3q**, 4:1 vs. >20:1 *dr*); these results suggest partial matching between the enamine and Rh-allyl species.[19]

Our dual-catalyst protocol provides an atom-economic route to γ,δ-unsaturated aldehydes *via* alkyne hydrofunctionalization. The use of a Rh-catalyst and Jacobsen's amine allows for enantio-, diastereo-, and regioselective access to all possible stereoisomers, by simply changing the handedness of each catalyst. In addition, this synergistic system demonstrates how different modes of catalysis can enable divergent coupling of aldehydes and alkynes to generate different constitutional isomers. Insights from this study will guide future enantioselective alkyne hydrofunctionalizations *via* C–C bond formation.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGMENT

Funding provided by UC Irvine and the National Institutes of Health (GM105938). We are grateful to Eli Lilly for a Grantee Award. F. A. C. is grateful for an NSF Graduate Research Fellowship. We thank Mr. Zhiwei Chen for checking the experimental procedures for (*R*,*S*)-**3a** and (*R*,*S*)-**3r**.

REFERENCES

(1). For a definition and review of synergistic catalysis, see: (a) Allen AE; MacMillan DW C. Chem. Sci 2012, 3, 633;For an early example, see: (b) Jellerichs BG; Kong J-R; Krische MJ J. Am. Chem. Soc 2003, 125, 7758. [PubMed: 12822967]

(2). For dual catalysis to achieve stereodivergence, see: (a) Krautwald S; Sarlah D; Schafroth MA; Carreira EM Science 2013, 340, 1065. [PubMed: 23723229] (b) Krautwald S; Schafroth MA; Sarlah D; Carreira EM J. Am. Chem. Soc 2014, 136, 3020. [PubMed: 24506196] (c) Sandmeier T; Krautwald S; Zipfel HF; Carreira EM Angew. Chem., Int. Ed 2015, 54, 14363;(d) Huo X; He R; Zhang X; Zhang WJ Am. Chem. Soc 2016, 138, 11093;(e) Jiang X; Beiger JJ; Hartwig JF J. Am. Chem. Soc 2016, DOI: 10.1021/jacs.6b11692.

(3). For perspectives on stereodivergent dual catalysis, see: (a) Schindler CS; Jacobsen EN Science 2013, 340, 1052. [PubMed: 23723222] (b) Oliveira MT; Luparia M; Audisio D; Maulide N Angew. Chem., Int. Ed 2013, 52, 13149.For an example of cascade dual organocatalysis, see: (d) Huang Y; Walji AM; Larsen CH; MacMillan DWCJ Am. Chem. Soc 2005, 127, 15051.For early examples of stereodivergent catalysis, see: (e) Lee EC; Hodous BL; Bergin E; Shih C; Fu GC J. Am. Chem. Soc 2005, 127, 11586; [PubMed: 16104719] (f) Wang B; Wu F; Want Y Liu X; Deng L J. Am. Chem. Soc 2007, 129, 768; [PubMed: 17243806] For an example of combined catalyst control and stereospecificity, see: (g) Shi S-L; Wong ZL; Buchwald SL Nature 2016, 532, 353 [PubMed: 27018656]

(4). Tsuda T; Kiyoi T; Saegusa T J. Org. Chem 1990, 55, 2554.

(5). Seebach D Angew. Chem., Int. Ed 1979, 18, 239.

(6). For select reviews, see: (a) Jun C-H; Jo E-A; Park J-W Eur. J. Org. Chem 2007, 1869.(b) Willis M Chem. Rev 2010, 110, 725. [PubMed: 19873977] (c) Leung J; Krische M Chem. Sci 2012, 3, 2202.For select examples not involving C–H oxidative addition, see: (d) Williams VM; Leung JC; Patman RL; Krische MJ Tetrahedron 2009, 65, 5024; [PubMed: 20613891] (e) Patman RL; Chaulagain MR; Williams VM; Krische MJ J. Am. Chem. Soc 2009, 131, 2066; [PubMed: 19173651] (f) Miura K; Yamamoto K; Yamanobe A; Ito K; Kinoshita H; Ichikawa J; Hosomi A Chem. Lett, 2010, 39, 766.(g) Biju AT; Wurz NE; Glorius FJ Am. Chem. Soc 2010, 132, 5970;

(7). (a) Obora Y; Hatanaka S; Ishii Y Org. Lett 2009, 11, 3510. [PubMed: 19719194] (b) Park BY; Nguyen KD; Chaulagain MR; Komanduri V; Krische MJ J. Am. Chem. Soc 2014, 136, 11902. [PubMed: 25075434] (c) Chen Q-A; Cruz FA; Dong VM J. Am. Chem. Soc 2015, 137, 3157. [PubMed: 25608143] (d) Liang T; Nguyen KD; Zhang WD; Krische MJ J. Am. Chem. Soc 2015, 137, 3161; [PubMed: 25734220] (e) Liang T; Zhang W; Chen T-Y; Nguyen KD; Krische MJ J. Am. Chem. Soc 2015, 137, 13066; [PubMed: 26418572] (f) Liang T; Zhang W; Krische MJ J. Am. Chem. Soc 2015, 137, 16024. [PubMed: 26671223]

(8). For reviews on combining amino and metal catalysis, see: (a) Deng YM; Kumar S; Wang H Chem. Commun 2014, 50, 4272.(b) Afewerki S; Cordova A Chem. Rev 2016, 116, 13512; [PubMed: 27723291] For select examples of linear selective dual catalytic aldehyde allylation, see: (c) Mo X; Hall DG J. Am. Chem. Soc 2016, 138, 10762. [PubMed: 27518200] (d) Usui I; Schmidt S; Breit B Org. Lett 2009, 11, 1453. [PubMed: 19243116] (e) Jiang G; List B Angew. Chem., Int. Ed 2011, 50, 9471.(f) Huo X; Yang G; Liu D; Liu Y; Gridnev ID; Zhang W Angew. Chem., Int. Ed 2014, 53, 6776.(g) Wang P-S; Lin H-C; Zhai Y-J; Han Z-Y; Gong L-Z Angew. Chem., Int. Ed 2014, 53, 12218.

(9). For select reviews on transition metal catalyzed allylic substitution, see: (a) Trost BM; Van Vranken DL Chem. Rev 1996, 96, 395. [PubMed: 11848758] (b) Liu Y; Han S-J; Liu W-B; Stoltz BM Acc. Chem. Res 2015, 48, 740. [PubMed: 25715056] (c) Zhuo C-X; Zheng C; You S-L Acc. Chem. Res 2014, 47, 2558. [PubMed: 24940612] (d) Hartwig JF; Stanley LM Acc. Chem. Res 2010, 43, 1461. [PubMed: 20873839]

(10). (a) Binder JT; Crone B; Haug TT; Menz H; Kirsch SF Org. Lett 2008, 10, 1025. [PubMed: 18232707] (b) Montaignac B; Praveen C; Vitale MR; Michelet V; Ratovelomanana-Vidal V Chem. Commun 2012, 48, 6559.

(11). Trost BM Science 1991, 254, 1471. [PubMed: 1962206]

(12). For a review, see: (a) Koschker P; Breit B Acc. Chem. Res 2016, 49, 1524. [PubMed: 27455048] For a seminal report using Ir, see: (b) Kim IS; Krische MJ Org. Lett 2008, 10, 513; [PubMed: 18181640] For an example of C–N bond formation, see: (c) Chen Q-A; Chen Z; Dong VM J. Am. Chem. Soc 2015, 137, 8392. [PubMed: 26107923] For an example of C–O bond formation, see: (d) Lumbroso A; Koschker P; Vautravers NR; Breit BJ Am. Chem. Soc 2011, 133, 2386.For an example of C–S bond formation, see: (e) Xu K; Khakyzadeh V; Bury T; Breit BJ Am. Chem. Soc 2014, 136, 16124.Previous studies with 1,3-diketone and β-keto acid nucleophiles failed to provide high enatiocontrol: (f) Beck TM; Breit B Org. Lett 2016, 18, 124. [PubMed: 26683497] (g) Cruz FA; Chen Z; Kurtoic SI; Dong VM Chem. Commun 2016, 52, 5836.(h) Li C; Grugel C; Breit B Chem. Commun 2016, 52, 5840.For select examples using Pd, see: (i) Kadota I; Shibuya A; Gyoung YS; Yamamoto YJ Am. Chem. Soc 1998, 120, 10262.(j) Yang C; Zhang K; Wu Z; Yao H; Lin A Org. Lett 2016, 18, 5332. [PubMed: 27684319]

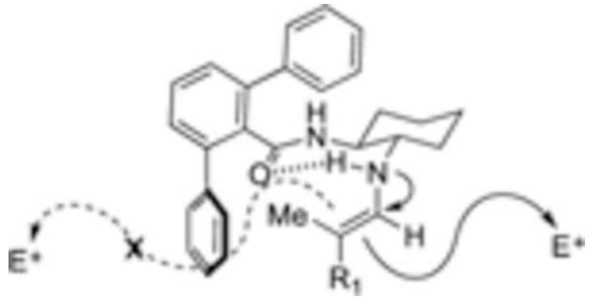
(13). Mukherjee S; Yang JW; Hoffmann S; List B Chem. Rev 2007, 107, 5471. [PubMed: 18072803]

(14). For select reviews on enantioselective quaternary stereocenter formation, see: (a) Quasdorf KW; Overman LE Nature 2014, 516, 181. [PubMed: 25503231] (b) Marek I; Minko Y; Pasco M; Mejuch T; Gilboa N; Chechik H; Das JP J. Am. Chem. Soc 2014, 136, 2682. [PubMed: 24512113]

(15). (a) Shimizu H; Nagasaki I; Matsumura K; Sayo N; Saito T Acc. Chem. Res 2007, 40, 1385. [PubMed: 17685581] (b) We expect the DTBM-variants in our study to show a similar trend in dihedral angle to the phenyl-substituted ligands (SEGPHOS = 65.0°, MeO-BIPHEP = 68.6°, and BINAP = 73.5°) whose dihedral angles have been determined via molecular mechanics

(16). See SI for safety regarding MeNO2

(17). (a) Witten MR; Jacobsen EN Org. Lett 2015, 17, 2772. [PubMed: 25952578] (b) The hydrogen-bonding rigidifies the enamine structure so that the terphenyl group blocks one enamine face from electrophile approach



(18). 3a’s absolute and relative configuration was determined by comparison of optical rotation and 1H NMR to literature, see ref. 2a

(19). Evans DA; Dart MJ; Duffy JL; Rieger DL J. Am. Chem. Soc 1995, 117, 9073.

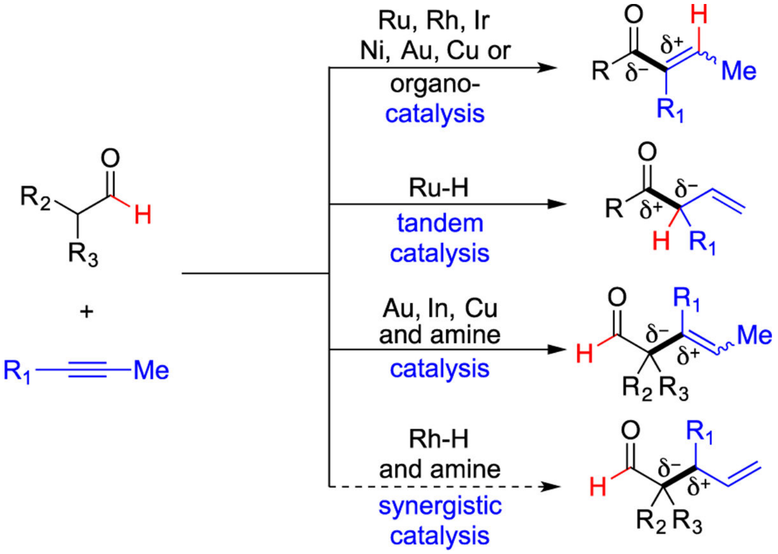


Figure 1.

Divergence in Aldehyde-Alkyne Coupling Enabled by Different Modes of Catalysis.

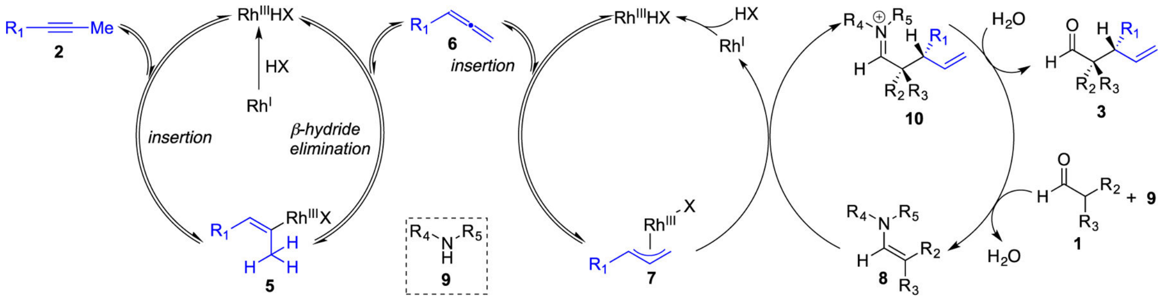


Figure 2.

Proposed Dual-Catalytic Aldehyde-Alkyne Coupling *via* a Triple Cascade.

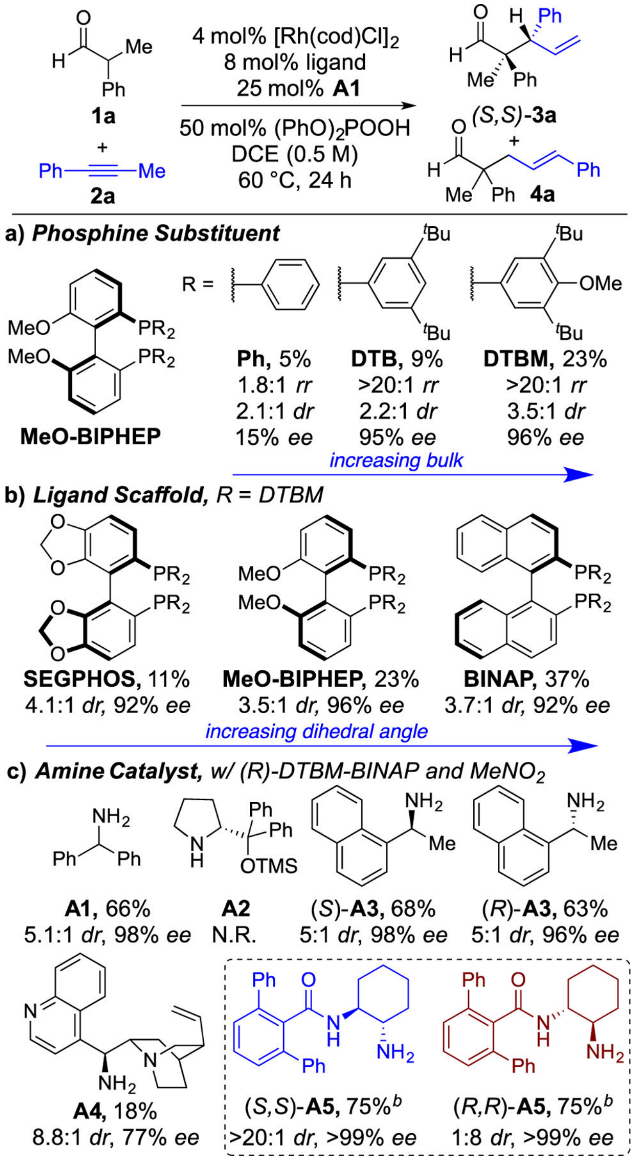


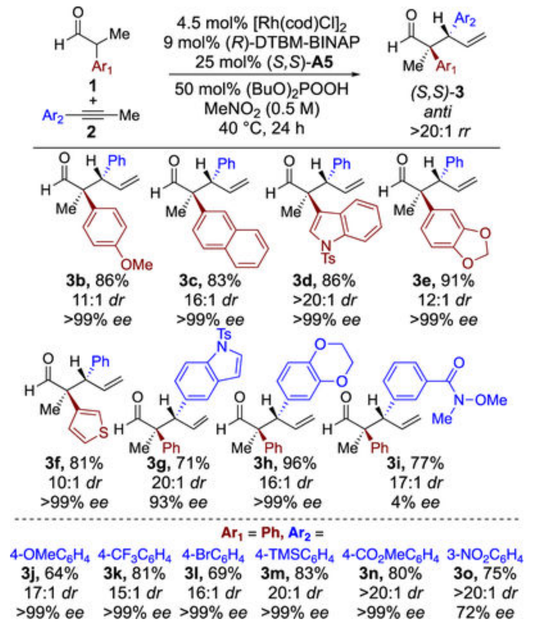
Chart 1.

Ligand and Amine Effects on Aldehyde-Alkyne Coupling[a]

[a] See SI for reaction conditions. Yields determined by ^{1}H NMR using an internal standard. *rr*'s and *dr*'s determined by ^{1}H NMR analysis of the crude reaction mixture. *ee*'s determined by SFC analysis. [b] 4.5 mol% $[Rh(cod)Cl]_2$, 50 mol% $(BuO)_2POOH$ instead, run at 40 °C.

Table 1.

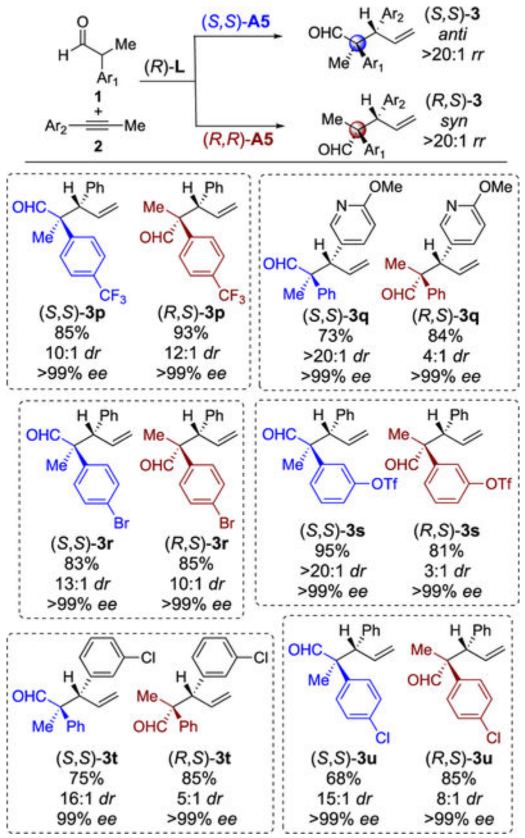
Anti-selective Aldehyde-Alkyne Coupling [a]



[a] Isolated yields. See SI for reaction conditions.

Table 2.

Stereodivergent Aldehyde-Alkyne Coupling[a]



[a] Isolated yields. See SI for reaction conditions.