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

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Supporting Information

**ABSTRACT:** We report an enantioselective coupling between $\alpha$-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.

Although common in Nature, using two catalysts to activate synergistically 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 co-workers achieved stereodivergence in their $\alpha$-alkylation of aldehydes with allylic alcohols,[2a−c] where any stereoisomer could be favored based on the Ir and amine combination chosen. Although 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 $\alpha$-allylation of $\alpha$-hydroxyketones.[2d]

Herein, we communicate a complementary method to access $\gamma,\delta$-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.

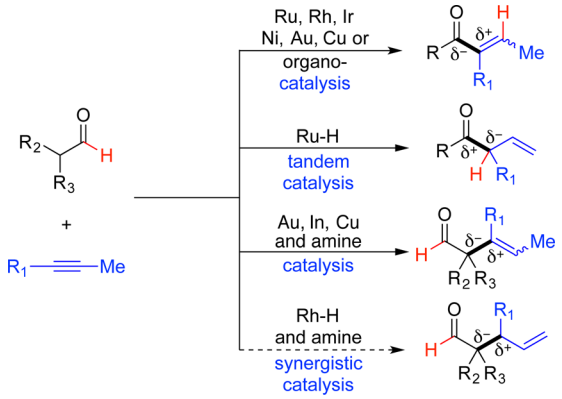


**Figure 1.** Divergence in aldehyde−alkyne coupling enabled by different modes of catalysis.

Functional groups have inherent polarities that can be activated or inverted by catalysis. Discovered over 25 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 $\alpha,\beta$-unsaturated isomer under a wide-range of protocols.[6] By using tandem Ru-hydride catalysis, we and others switched the conventional regioselectivity to generate $\beta,\gamma$-unsaturated isomers via a nucleophilic $\pi$-allyl species.[7] We envisioned that a Rh-hydride and amine catalyst duo[8] could enable unprecedented access to the $\gamma,\delta$-unsaturated aldehyde via an electrophilic $\pi$-allyl complex.[9] This synergistic pairing produces $\alpha$-allylated aldehydes, in contrast to previous metal-organocatalyst studies (where intramolecular alkyne coupling gave $\alpha$-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-$\pi$-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-$\pi$-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 $\alpha$-branched aldehydes would help avoid aldol-dimerization pathways via enamine catalysis.[2b,13] Moreover, successful transformation of $\alpha$-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-$\pi$-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-

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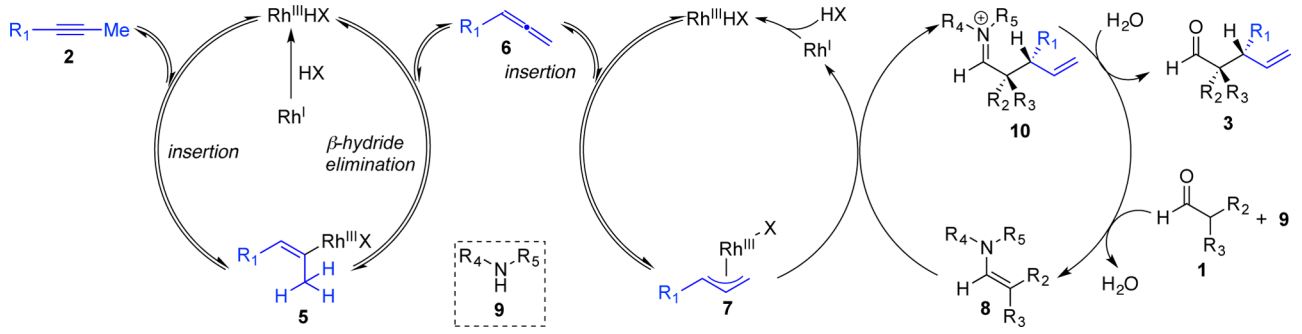
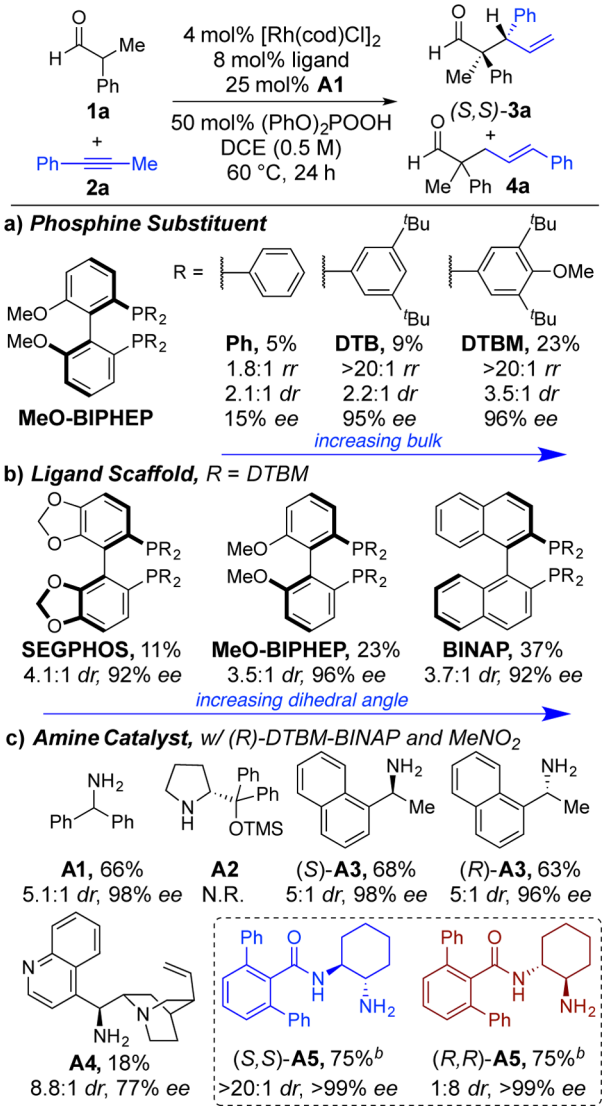


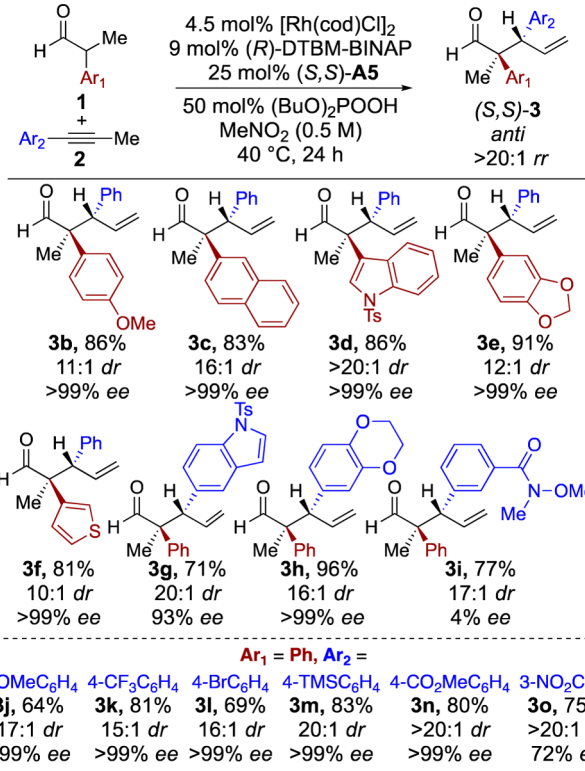

**Figure 2.** Proposed dual-catalytic aldehyde-alkyne coupling via a triple cascade.

**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.

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, whereas (*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 toward 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


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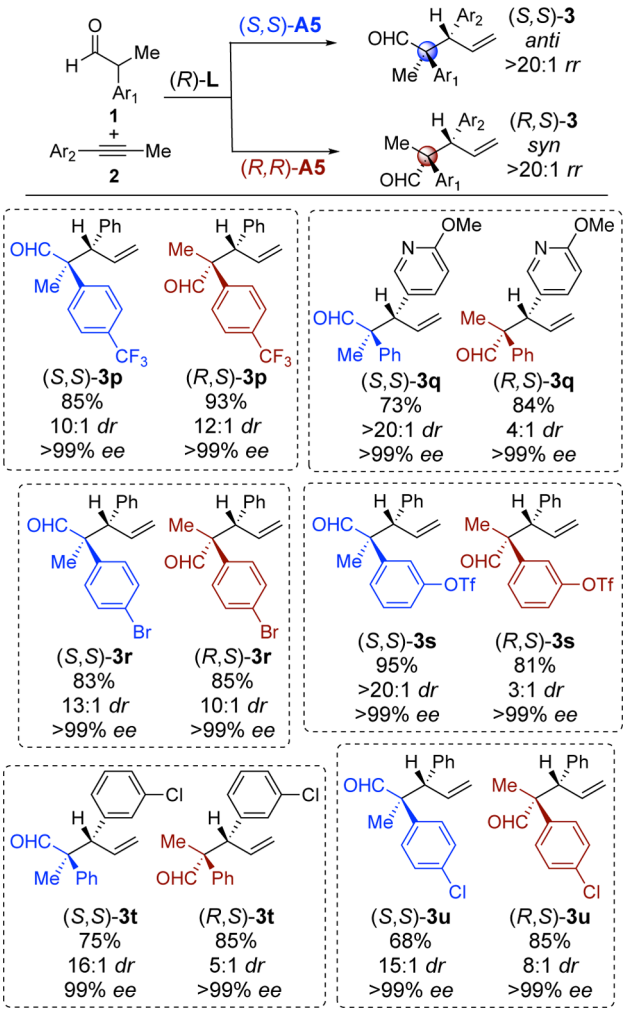
**Table 2. Stereodivergent Aldehyde−Alkyne Coupling**[a]




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

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 $\alpha$-hydroxylation and $\alpha$-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-naphthlalene, *N*-tosyl-3-indole, benzodioxole, and 3-thiophene also undergo efficient and selective coupling (**3c**−**3f**). Electron-rich, electron-deficient, and bromine-containing alkynes (**3j**−**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*-chloro 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 $\gamma,\delta$-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.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.6b10680.

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

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### Notes

The authors declare no competing financial interest.

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(16) See SI for safety regarding $MeNO_2$.

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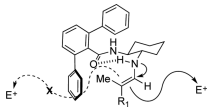


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