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Diastereo- and Enantioselective Ruthenium-Catalyzed C-C Coupling of 1-Arylpropynes and Alcohols: Alkynes as Chiral Allylmetal Precursors in Carbonyl *anti*-(α-Aryl)allylation

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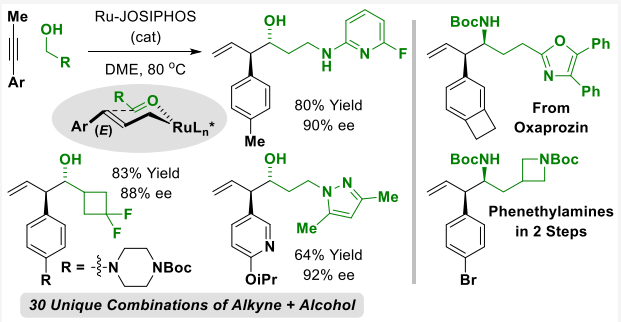
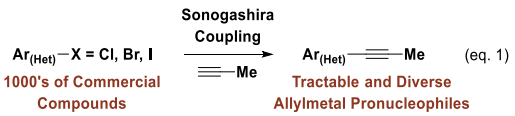
ABSTRACT: Highly tractable 1-aryl-1-propynes, which are readily accessible via Sonogashira coupling, serve as chiral allylmetal pronucleophiles in ruthenium-JOSIPHOS-catalyzed *anti*-diastereo- and enantioselective aldehyde (α-aryl)allylations with primary aliphatic or benzylic alcohol proelectrophiles. This method enables convergent construction of homoallylic *sec*-phenethyl alcohols bearing tertiary benzylic stereocenters. Both steric and electronic features of aryl sulfonic acid additives were shown to contribute to the efficiency with which a more selective and productive iodide-bound ruthenium catalyst is formed. As corroborated by isotopic labeling studies, a dual catalytic process is operative in which alkyne-to-allene isomerization is followed by allene-carbonyl reductive coupling via hydrogen auto-transfer. Crossover of ruthenium hydrides emanating from these two discrete catalytic events is observed. The utility of this method is illustrated by conversion of selected reaction products to the corresponding phenethylamines and the first total syntheses of the neolignan natural products (−)-crataegusanoids A–D.



INTRODUCTION

Carbonyl addition is the Proteus of metal-mediated C-C couplings.[1] Recent analysis of >9 million patents from the pharmaceutical industry shows that carbonyl addition (alongside the Suzuki coupling) persists as one of the most widely utilized methods for C–C bond formation in process R&D.[2] Despite its importance, the majority of methods for carbonyl addition require preformed carbanions, which can be hazardous and are often generated using multiple sacrificial reagents, for example, through halogenation-metalation-transmetalation sequences. Metal-catalyzed carbonyl reductive coupling of unsaturated pronucleophiles has emerged as an alternative to stoichiometric carbanions, but many reductants used in such processes are not ideal for chemical manufacture on scale (e.g., Mn, Zn, Et_3B, Et_2Zn, SiR_3).[3,4] We have advanced a broad, new family of metal-catalyzed carbonyl reductive couplings that exploit feedstock pronucleophiles in combination with feedstock reductants (H_2, 2-PrOH, HCO_2H), as well as related hydrogen auto-transfer processes wherein alcohols serve dually as reductants and carbonyl proelectrophiles.[4] These efforts include processes that exploit alkynes as allylmetal pronucleophiles.[5−7]

Given the tractability of 1-aryl-1-propynes and their wide availability via Sonogashira coupling (eq 1), we sought to develop catalytic enantioselective carbonyl (α-aryl)allylations via transfer hydrogenative couplings of 1-aryl-1-propynes with primary alcohols (Figure 1). Despite decades of work on



asymmetric carbonyl allylation,[7] enantioselective carbonyl (α-aryl)allylations are largely limited to isolated examples that embody moderate levels of asymmetric induction and deliver simple aryl fragments. These methods fall into two categories: (a) those involving chiral auxiliaries[8] and (b) catalytic enantioselective protocols.[9,10] In the former category, one systematic study involving allylbenzene pronucleophiles was reported by Gong,[8g] but this method is restricted to aryl aldehydes (Figure 1). In the latter category, systematic studies are limited to activated aldehydes (glyoxamides,[9e] formaldehyde,[10a] fluoral and difluoroacetaldehyde[10b]) and a Nozaki–Hiyama–Kishi (α-aryl)allylation to form quaternary benzylic stereocenters.[9i] *Catalytic enantioselective carbonyl (α-aryl)allylations applicable to both aliphatic and aromatic aldehydes are unknown*, and would enable convergent

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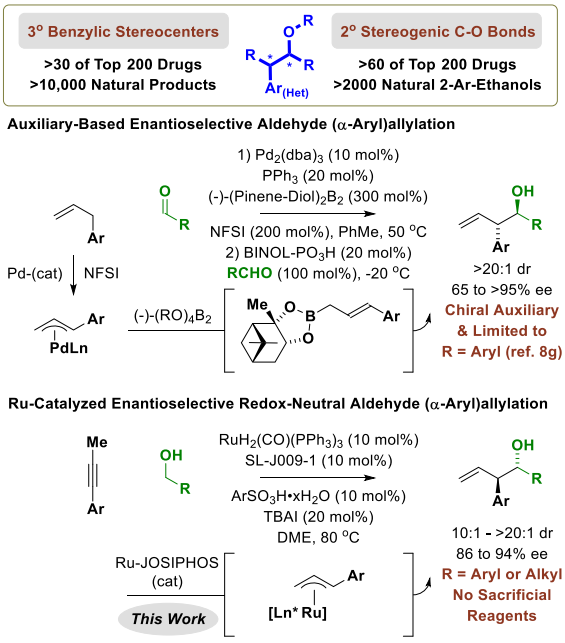


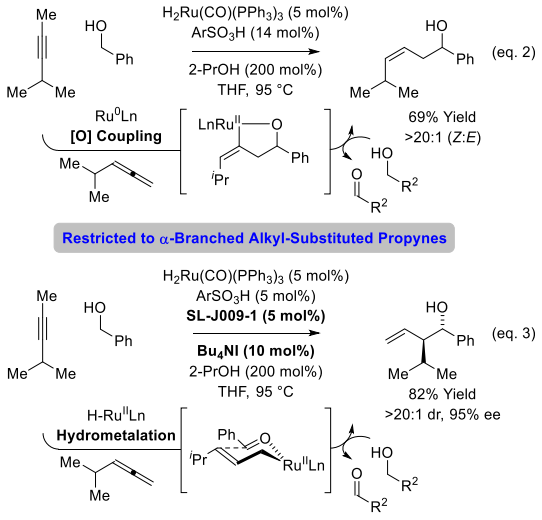
Figure 1. Convergent construction of *sec*-phenethyl alcohols bearing tertiary benzylic stereocenters via enantioselective carbonyl *anti*-(α-aryl)allylation of unactivated aldehydes.

construction of tertiary benzylic stereocenters and stereogenic C−O bonds, which are ubiquitous among natural products and FDA approved drugs. Here, using a ruthenium catalyst modified by the JOSIPHOS ligand SL-J009-1, we report that diverse 1-aryl-1-propynes engage in C-C coupling with primary aliphatic or benzylic alcohols to furnish products of (α-aryl)allylation bearing relatively complex aryl moieties in good yield with complete *anti*-diastereoselectivity and high levels of enantioselectivity.

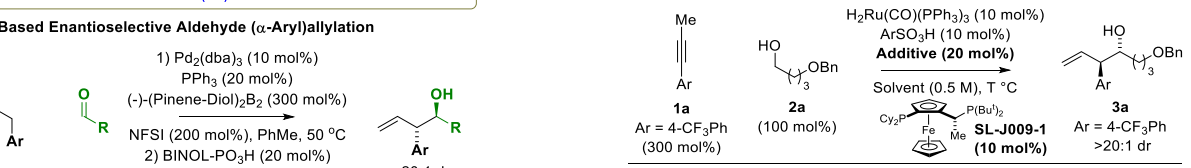
RESULTS AND DISCUSSION

In prior work from our laboratory,[6c] it was found that protonation of $H_2Ru(CO)(PPh_3)_3$ by the aryl sulfonic acid 2,4,6-(^{i}Pr)$_3$PhSO$_3$H delivers a cationic ruthenium(II) complex

Scheme 1. Alkynes as Latent Allenes in Alcohol-Mediated Hydrohydroxyalkylation to Form Linear or Branched Homoallylic Alcohols (Ar = 2,4,6-Triisopropylphenyl)



Scheme 2. Influence of Arylsulfonic Acid in the Reaction of 1-(4-CF$_3$-phenyl)-1-propyne 1a and Alcohol 2a to Form the Product of Carbonyl (α-Aryl)allylation 3a[a]



Entry	Additive	ArSO$_3$H	Solvent	T °C	**3a** (Yield, ee)
1	Bu_4NI	2,4,6-(^{i}Pr)$_3$-PhSO$_3$H	THF	95 °C	17%, 75%[b]
2	Bu_4NI	2,4,6-(^{i}Pr)$_3$-PhSO$_3$H	THF	95 °C	30%, 75%
3	Bu_4NI	4-MePhSO$_3$H•H$_2$O	THF	95 °C	59%, 82%
4	Bu_4NI	4-NO$_2$PhSO$_3$H•xH$_2$O	THF	95 °C	75%, 82%
5	Bu_4NI	2,4,6-(^{i}Pr)$_3$-PhSO$_3$H	DME	95 °C	25%, 78%
6	Bu_4NI	2,4,6-(^{i}Pr)$_3$-PhSO$_3$H	DME	80 °C	< 5%, ---
7	Bu_4NI	4-NO$_2$PhSO$_3$H•xH$_2$O	THF	80 °C	80%, 87%
➡ 8	**Bu_4NI**	**4-NO$_2$PhSO$_3$H•xH$_2$O**	**DME**	**80 °C**	**85%, 88%**
9	---	4-NO$_2$PhSO$_3$H•xH$_2$O	DME	80 °C	15%, 13%
10	Bu_4NCl	4-NO$_2$PhSO$_3$H•xH$_2$O	DME	80 °C	20%, 67%
11	Bu_4NBr	4-NO$_2$PhSO$_3$H•xH$_2$O	DME	80 °C	28%, 81%
12	Bu_4NI	(+)-Camphor-SO$_3$H	DME	80 °C	60%, 0%[c]

[a]Yields of material isolated by silica gel chromatography. Enantioselectivities were determined by chiral stationary phase HPLC analysis. Diastereoselectivities were determined via ^{1}H NMR analysis of crude reaction mixtures. [b]Conditions described in Scheme 1, eq 3, were applied using $H_2Ru(CO)(PPh_3)_3$ (5 mol %), SL-J009-1 (5 mol %), Bu_4NI (10 mol %). [c]DIPPF (10 mol %) was used as ligand.

that exists in equilibrium with a ruthenium(0) complex. This ruthenium(0) species promotes two discrete catalytic events: (a) alkyne-to-allene isomerization and (b) transfer hydrogenative allene-carbonyl reductive coupling by way of a transient oxaruthenacycle. This process converts alkyl-substituted alkynes and primary alcohols to linear secondary (*Z*)-homoallylic alcohols (Scheme 1, eq 2).[6c] Remarkably, in the presence of iodide and a chelating phosphine ligand, an alternate dual catalytic process becomes operative in which alkyne-to-allene isomerization is followed by hydrometalation of the transient allene to form an allylruthenium(II) species. This process converts alkyl-substituted alkynes and primary alcohols to branched secondary homoallylic alcohols with excellent control of regio-, diastereo-, and enantioselectivity (Scheme 1, eq 3).[6e] As corroborated by deuterium labeling studies, both processes involve alkyne-to-allene isomerization. The fate of the resulting allene largely depends on the intervention of cationic vs neutral ruthenium complexes, which partition entry into catalytic cycles involving either allene-carbonyl oxidative coupling or allene hydrometalation, respectively.[6c,e,11]

Both catalytic processes are largely restricted to α-branched alkyl-substituted propynes, such as 4-methyl-2-pentyne. We speculate that α-branched alkyl groups at the acetylenic position may facilitate alkyne-to-allene isomerization by favorably influencing the regioselectivity of alkyne hydrometalation. Initial attempts to exploit 1-aryl-1-propynes as pronucleophiles for asymmetric carbonyl (α-aryl)allylation were inefficient, and especially low isolated yields were observed for 1-aryl-1-propynes bearing electron deficient aromatic rings. To overcome this limitation, efforts to optimize the carbonyl (α-aryl)allylation of 1-(4-CF$_3$-phenyl)-1-propyne **1a** and primary aliphatic alcohol **2a** were undertaken (Scheme 2). Under conditions effective for couplings of 4-methyl-2-pentyne (but without 2-PrOH, which is used to reduce uncoupled aldehyde so it can reenter the catalytic cycle),[6d] the product of carbonyl (α-aryl)allylation **3a** was obtained in 17%

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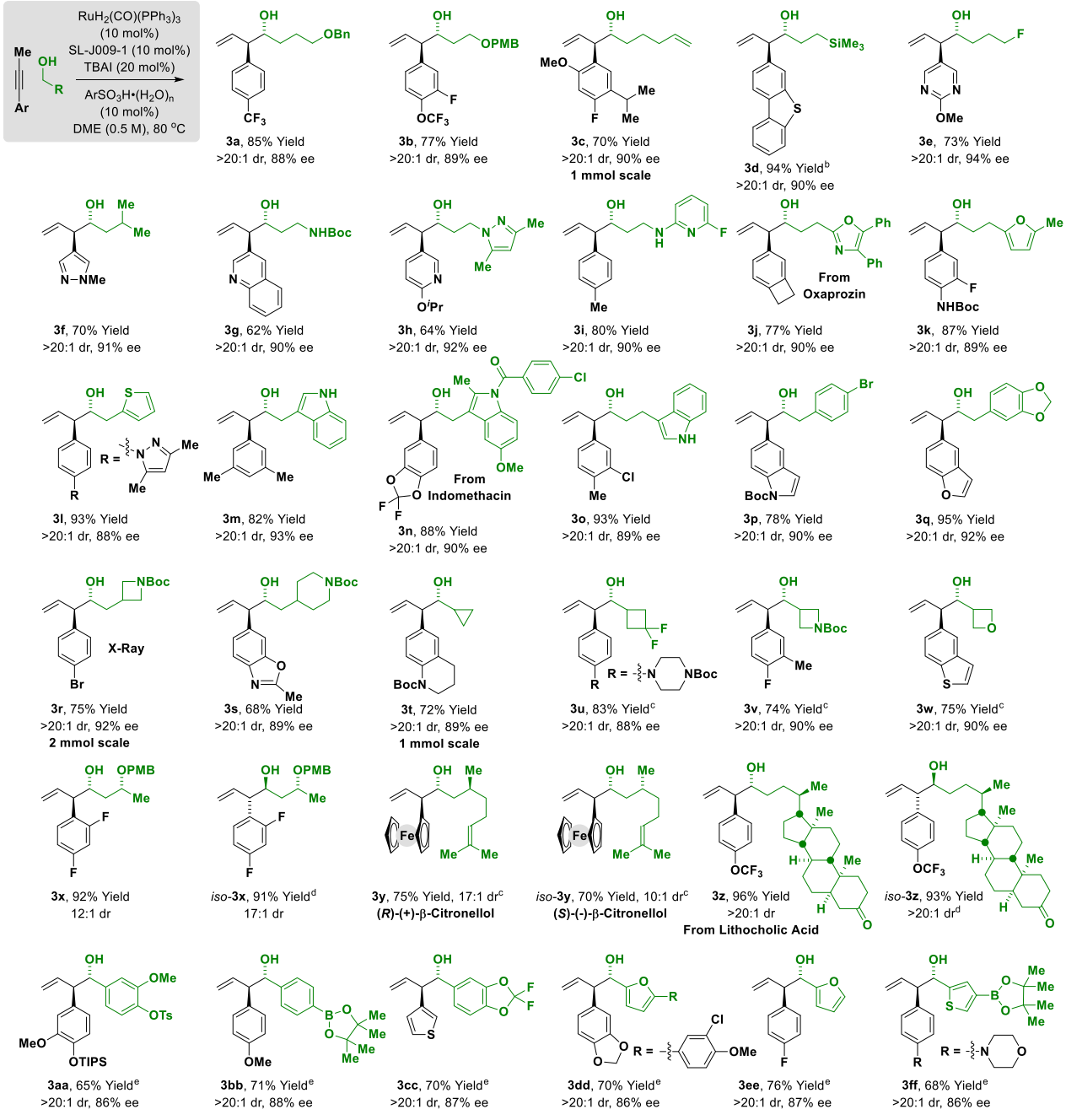
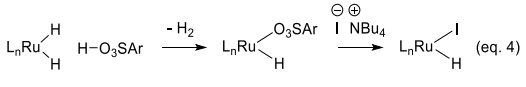
J. Am. Chem. Soc. 2021, 143, 2838−2845

Table 1. Ruthenium-Catalyzed Coupling of 1-Aryl-1-propynes 1a−1ff with Primary Alcohols 2a−2ff to Form Enantiomerically Enriched Phenethyl Alcohols 3a−3ff[a]



[a]Yields of material isolated by silica gel chromatography. Enantioselectivities were determined by chiral stationary phase HPLC analysis. Diastereoselectivities were determined via ^{1}H NMR analysis of crude reaction mixtures. For standard conditions, see Scheme 2, entry 7, 0.2 mmol scale, 48 h. See the Supporting Information for further experimental details. [b]75 °C. [c]90 °C. [d]SL-J009-2. [e]65 °C.

yield with only modest levels of enantiomeric enrichment (Scheme 2, entry 1). When the catalyst loading was doubled, a proportionate increase in the yield of **3a** was observed (Scheme 2, entry 2). Replacing 2,4,6-(^{i}Pr)$_3$PhSO$_3$H with 4-MePhSO$_3$H and 4-NO$_2$PhSO$_3$H led to successive improvements (Scheme 2, entries 3 and 4, respectively). These data are significant, as they reveal both steric and electronic features of the catalyst impact efficiency and enantioselectivity. Using 2,4,6-(^{i}Pr)$_3$PhSO$_3$H in DME, slightly higher enantioselectivity was observed (Scheme 2, entries 2 vs 5), but lower temperatures limited conversion (Scheme 2, entry 6). The iodide-bound catalyst is generated through the acid-base reaction of the ruthenium dihydride with the arylsulfonic acid, followed by substitution by iodide (eq 4).[12] Notably, the



more acidic, less hindered arylsulfonic acid 4-NO$_2$PhSO$_3$H appears to enhance the efficiency of this process, allowing temperature to be reduced, augmenting enantioselectivity without diminishing conversion (Scheme 2, entry 7). Under

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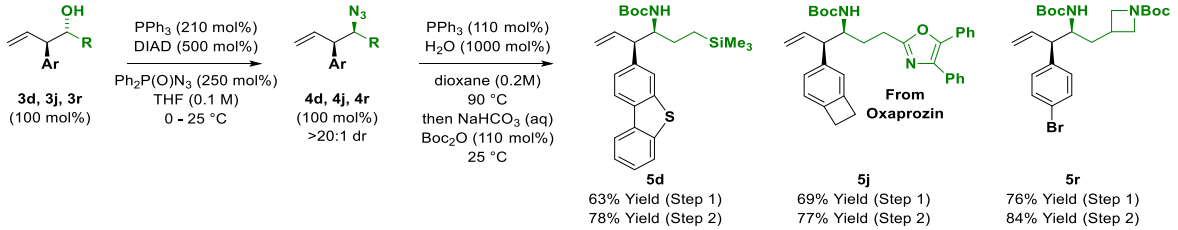
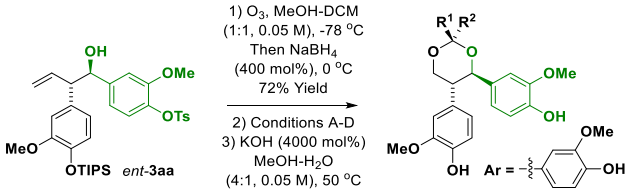
J. Am. Chem. Soc. 2021, 143, 2838−2845

Scheme 3. Conversion of Phenethyl Alcohols 3d, 3j, and 3r to Phenethylamines 5d, 5j, and 5r[a]



[a]Yields of material isolated by silica gel chromatography. See the Supporting Information for further experimental details.

Scheme 4. Total Syntheses of Neolignan Natural Products (−)-Crataegusanoids A−D[a]

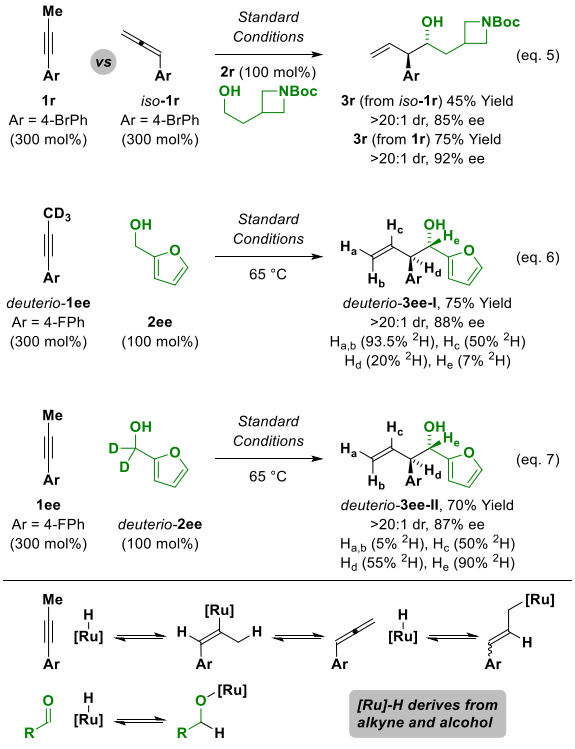


(-)-Crataegusanoid A, R^1 = Ar, R^2 = H, 70% Yield (Step 1), 92% Yield, >20:1 dr (Step 2)
(-)-Crataegusanoid B, R^1 = CH=CHAr, R^2 = H, 48% Yield (Step 1), 72% Yield, >20:1 dr (Step 2)
(-)-Crataegusanoid C, R^1 = R^2 = Me, 76% Yield (Step 1), 74% Yield (Step 2)
(-)-Crataegusanoid D, R^1 = R^2 = H, 55% Yield (Step 1), 82% Yield (Step 2)

Condition A: ArCHO (200 mol%), CSA (20 mol%), $MgSO_4$ (500 mol%), DCM (0.05 M), 25 °C
Condition B: ArCH=CHCHO (200 mol%), CSA (20 mol%), Na_2SO_4 (500 mol%), $CHCl_3$ (0.05 M), 25 °C
Condition C: $Me_2C(OMe)_2$ (500 mol%), CSA (20 mol%), DCM (0.05 M), 25 °C
Condition D: $H_2C(OMe)_2$ (500 mol%), BF_3OEt_2 (200 mol%), DCM (0.05 M), 25 °C

[a]Yields of material isolated by silica gel chromatography. See the Supporting Information for further experimental details.

Scheme 5. Experiments Corroborating Intervention of Allenes as Reactive Intermediates[a]



[a]Yields of material isolated by silica gel chromatography. See the Supporting Information for further experimental details.

these conditions, moving from THF to DME solvent, **3a** could be obtained in 85% yield with >20:1 *anti*-diastereoselectivity and high enantioselectivity (88% ee) (Scheme 2, entry 8). Omission of Bu_4NI led to a significant decrease in yield and selectivity that could not be fully restored through use of Bu_4NCl or Bu_4NBr (Scheme 2, entries 9−11). Racemic product was obtained using the achiral ligand DIPPF in combination with (+)-camphor sulfonic acid (Scheme 2, entry 12). The collective data suggest both conversion and enantioselectivity depend on the efficiency with which the iodide-bound catalyst is formed.[13]

Under these conditions, the ruthenium-catalyzed coupling of diverse 1-aryl-1-propynes **1a−1ff** with primary alcohols **2a−2ff** to form enantiomerically enriched phenethyl alcohols **3a−3ff** was explored (Table 1). As illustrated by the formation of phenethyl alcohols **3c**, **3x**, and *iso*-**3x**, *ortho*-substituted aryl propynes are competent partners for C-C coupling. Heteroaryl-substituted propynes are converted to adducts **3d−3h**, **3p**, and **3s**, establishing compatibility with Lewis basic sulfur (**3d**) and nitrogen (**3e−3h**, **3p**, **3s**) functional groups. Additionally, as demonstrated by the formation of adducts **3g−3o**, primary alcohols bearing a tethered *N*-Boc amine (**3g**) or pyrazole (**3h**), 2-aminopyridine (**3i**), oxazole (**3j**), furan (**3k**), thiophene (**3l**), and indole (**3m−3o**) moieties are competent partners for arylpropyne-mediated asymmetric (*α*-aryl)-allylation. Notably, adducts **3j** and **3n** derive from the FDA approved therapeutic agents oxaprozin and indomethacin, respectively, highlighting the potential applicability of this method to drug discovery. Adducts derived from primary alcohols that incorporate strained saturated ring systems, including cyclopropanes (**3t**), difluorocyclobutanes (**3u**), azetidines (**3r**, **3v**), and oxetanes (**3w**), were well tolerated. Whereas low conversion was associated with the use of acyclic *α*-stereogenic primary alcohols, the corresponding *β*-stereogenic primary alcohols were converted to products of (*α*-aryl)allylation (**3x**, *iso*-**3x**, **3y**, *iso*-**3y**) with high levels of catalyst-directed diastereoselectivity. Finally, primary benzylic alcohols undergo (*α*-aryl)allylation as shown by the formation of adducts **3aa−3ff**. Here, compatibility of pinacolboronate functional groups, as demonstrated by formation of **3bb** and **3ff**, is significant. In certain cases, minor decreases or increases in reaction temperature were made to improve enantioselectivity or increase conversion, respectively. The assignment of absolute stereochemistry for adducts **3a−3ff** is made in analogy to that determined for compound **3r** by single crystal X-ray diffraction analysis. Attempted coupling of the more highly substituted aryl alkyne, 1-phenyl-1-butyne, results in internal redox-isomerization to form the terminal *π*-allyl, delivering products of carbonyl *anti*-(*α*-benzyl)allylation in low yield.

Phenethylamines represent a broad class of psychoactive substances.[14] To further illustrate the potential utility of this

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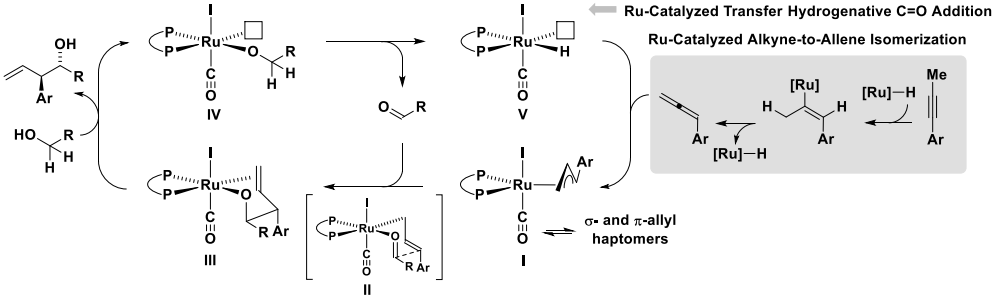
Scheme 6. Proposed Catalytic Cycle for Ruthenium-Catalyzed C-C Coupling of 1-Arylpropynes with Primary Alcohols to Form Products of Carbonyl (α-Aryl)allylation



method to discovery efforts in pharmaceutical research, representative adducts **3d**, **3j**, and **3r** were transformed to the corresponding *N*-Boc-protected phenethylamines (Scheme 3). The phenethyl alcohols **3d**, **3j**, and **3r** were exposed to diphenylphosphoryl azide in the presence of diisopropyl azodicarboxylate and triphenylphosphine to furnish the azides **4d**, **4j**, and **4r** with complete inversion of stereochemistry and only trace quantities of competing elimination to form the conjugated dienes.[15] One-pot Staudinger reduction[16] of **4d**, **4j**, and **4r**, followed by treatment with di-*tert*-butyl dicarbonate, provided phenethylamines **5d**, **5j**, and **5r**, respectively, in good yield.

(−)-Crataegusanoids A−D[17] were recently isolated from the fruit of the Chinese mountain hawthorn tree, *Crataegus pinnatifida*, which are used to make "haw flakes," a traditional candy from northern China. In an *in vitro* evaluation against two human hepatocellular carcinoma cell lines, HepG2 and Hep3B, (−)-crataegusanoids A and B displayed moderate cytotoxicity. To further illustrate the utility of the present method for asymmetric alkyne-mediated carbonyl (α-aryl)-allylation, total syntheses of neolignan natural products (−)-crataegusanoids A−D were undertaken (Scheme 4). To this end, phenethyl alcohol *ent*-**3aa** was subjected to ozonolysis, followed by treatment with $NaBH_4$, to provide a 1,3-diol. Acetal or ketal formation, followed by concomitant cleavage of the TIPS silyl ether and phenolic tosylate moieties, delivered (−)-crataegusanoids A−D.

A series of experiments were performed to probe the reaction mechanism (Scheme 5). Under standard reaction conditions, allene *iso*-**1r** is converted to the product of carbonyl (α-aryl)allylation **3r** in 45% yield (eq 5). This experiment demonstrates that allenes are competent partners for carbonyl (α-aryl)allylation, corroborating their role as reactive intermediates. Notably, the yield of **3r** obtained from allene *iso*-**1r** is significantly lower than the yield of **3r** obtained from the corresponding 1-aryl-1-propyne **1r** (eq 5). These data highlight the value of utilizing tractable 1-aryl-1-propynes as reservoirs for less stable and less abundant aryl-substituted allenes. Exposure of *deuterio*-**1ee** to furfuryl alcohol **2ee** under standard conditions delivers *deuterio*-**3ee-I** (eq 6). Deuterium is transferred to the internal vinylic position (50% ^2H at H_c) and allylic positions (20% ^2H at H_d). These data corroborate alkyne isomerization through successive, reversible alkyne hydrometalation-β-hydride elimination, and that *the ruthenium hydrides initiating hydrometalation and arising via β-hydride elimination can emanate from either the alkyne or the alcohol.* Additionally, a small, but significant, loss of deuterium is observed at the olefinic terminus (93.5% ^2H at $H_{a,b}$), indicating allene hydrometalation occurs reversibly with incomplete regioselectivity. In alignment with this interpretation, the reaction of alkyne **1ee** with the deuterated furfuryl alcohol *deuterio*-**2ee** (eq 7) also results in transfer of deuterium to the internal vinylic position (50% ^2H at H_c), and hydrogen-deuterium exchange occurs at the carbinol position of the primary alcohol in both reactions (7% ^2H at H_e, eq 6; 90% ^2H at H_e, eq 7) likely via reversible alcohol dehydrogenation.[18] In eq 6, deuterium content is not completely conserved, which may be due to exchange with adventitious water.

The collective data are consistent with the indicated catalytic cycle (Scheme 6). Ruthenium-catalyzed alkyne-to-allene isomerization is followed by allene hydrometalation to form fluxional σ-allyl- and π-allylruthenium complexes **I**.[19] Aldehyde coordination, followed by stereospecific carbonyl addition by way of the (*E*)-σ-allyliridium through the chairlike transition structure **II**, delivers a homoallylic ruthenium alkoxide **III**, which, upon exchange with the primary alcohol, releases the product of carbonyl (α-aryl)allylation and forms the ruthenium alkoxide **IV**. β-Hydride elimination from ruthenium alkoxide **IV** delivers the ruthenium hydride **V** along with aldehyde to close the catalytic cycle. The π-bound alkene in **III** prevents β-hydride elimination at this stage by occupying the adjacent coordination site. Notably, two discrete catalytic events are operative: (a) alkyne-to-allene isomerization and (b) transfer hydrogenative carbonyl addition. Yet, as demonstrated by deuterium labeling studies (eqs 5 and 6), crossover of ruthenium hydrides that arise in these two catalytic processes is observed.

■ CONCLUSIONS

In summary, we report that abundant, tractable 1-aryl-1-propynes serve as chiral allylmetal pronucleophiles in reactions with primary alcohol proelectrophiles to form products of carbonyl (α-aryl)allylation. These hydrogen auto-transfer processes enable access to homoallylic phenethyl alcohols with excellent control of diastereo- and enantioselectivity. This method was successfully applied to the synthesis of psychoactive phenethylamines, as well as the neolignan natural products (−)-crataegusanoids A−D. Both steric and electronic features of the aryl sulfonic acid additive were shown to contribute to the efficiency with which a more productive and selective iodide-bound ruthenium catalyst is formed. As established by deuterium labeling studies, the present processes contribute to a growing class of enantioselective metal-catalyzed C-C and C-X coupling reactions in which alkynes serve as reservoirs for less abundant and less stable allenes.[5,6] Future work will focus on the development of related catalytic C-C couplings of π-unsaturated feedstocks that occur in the absence of stoichiometric organometallic reagents.[4,20,21]

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■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.0c12242.

Experimental procedures and spectroscopic data for all new compounds (^{1}H NMR, ^{13}C NMR, IR, HRMS), including images of NMR spectra and HPLC traces for racemic and enantiomerically enriched compounds. Single crystal X-ray diffraction data for compound **3r** (PDF)

Accession Codes

CCDC 2021653 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Author Contributions

M.X. and A.G. contributed equally to this work.

Notes

The authors declare no competing financial interest.

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(21) A referee of the present paper brought to our attention an "archived preprint" (not yet peer-reviewed) on enantioselective cobalt-BPE-catalyzed carbonyl (α-aryl)allylation employing allylbenzenes as allylmetal pronucleophiles. Sacrificial $AlMe_3$ (150 mol%) is

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J. Am. Chem. Soc. 2021, 143, 2838−2845

required to mediate π-allyl formation. Relatively modest yields and stereoselectivities are observed (typically 50−60% yield, 90:10 dr, 80% ee): Zhang, H.; Huang, J.; Meng, F. Cobalt-Catalyzed Diastereo- and Enantioselective Allyl Addition to Aldehydes and α-Ketoesters through Allylic C−H Functionalization. DOI: 10.21203/rs.3.rs-58188/v1.

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