HHS Public Access

Author manuscript

Chem Commun (Camb). Author manuscript; available in PMC 2017 April 30.

Published in final edited form as:

Chem Commun (Camb). 2016 April 30; 52(34): 5836–5839. doi:10.1039/c6cc02522f.

Tandem Rh-Catalysis: Decarboxylative β-Keto Acid and Alkyne Cross-Coupling

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Abstract

Herein, we describe a regioselective Rh-catalyzed decarboxylative cross-coupling of β–keto acids and alkynes to access branched γ,δ–unsaturated ketones. Rh-hydride catalysis enables the isomerization of an alkyne to generate a metal-allyl species that can undergo carbon-carbon bond formation. Ketones are generated under mild conditions, without the need for base or activated electrophiles.

A range of natural processes are driven by the loss of carbon dioxide, from polyketide synthesis to γ-aminobutyric acid (GABA) production.[1] Various synthetic strategies have emerged using the formation of CO_2 gas as the driving force. Tsuji and Saegusa independently reported decarboxylative allylation of β-keto allyl esters.[2,3] Shair developed a decarboxylative aldol using malonic acid half thioesters,[4] while Gooßen pioneered decarboxylative biaryl cross-couplings.[5] More recently, MacMillan and Doyle have used CO_2 gas extrusion and photoredox catalysis to generate a wide range of cross-couplings, including those that generate Csp^2–Csp^3 bonds.[6] Most relevant to our study, Breit has developed a bioinspired coupling of β-keto acids with allenes under Rh-hydride catalysis.[7,8] It occurred to us that by using tandem Rh-catalysis, we could achieve a complementary cross-coupling of β-keto acids with alkynes. We chose alkynes as allyl electrophiles because they are a common and readily accessible functional group. Our approach would enable unique access to ketones under mild conditions, without the need for generating enolates or the use of activated allylating agents.[9–13]

On the basis of previous studies from Yamamoto,[14] Breit,[15] and our laboratory,[16] we proposed a pathway involving tandem Rh-catalysis to enable decarboxylative coupling between β-keto acids **1** and alkynes **2** (Scheme 1).[17] First, β-keto acid **1** and a Rh(I) species combine to generate a Rh(III)-hydride intermediate.[18] Insertion of alkyne **2** into the Rh(III)–H bond gives Rh-vinyl species **5**. Subsequent β-hydride elimination generates allene **6** and regenerates the Rh(III)-hydride species. Insertion of allene **6** into the Rh(III)-H bond then forms Rh(III)-allyl species **7** that can be trapped with a carbon-based nucleophile.[19] Indeed,

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Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/x0xx00000x

Breit recently reported the coupling of 1,3-diketones with terminal alkynes.[20] In the presence of β-keto acid **1**, C–C bond formation yields allylated β-keto acid **8**.[21] Finally, decarboxylation affords the desired ketone **3**.

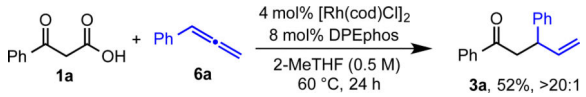
To test our mechanistic proposal, we investigated the cross-coupling of benzoylacetic acid (**1a**) and 1-phenyl-1-propyne (**2a**). In the presence of 5 mol% of $[Rh(cod)Cl]_2$ and 10 mol% 1,3-bis(diphenylphosphino)propane (dppp), the desired branched γ, δ–unsaturated ketone **3a** was observed in 5% yield with >20:1 branched to linear regioselectivity (Figure 1). Notably, no allyl ester formation was observed despite the precedence for C–O bond formation between carboxylic acids and alkynes.[22] The major by-product observed was acetophenone arising from decarboxylation of benzoylacetic acid (**1a**). From further evaluation of bidentate phosphine ligands, we observed a relationship between ligand bite angle and reactivity. Bisphosphine ligands with larger bite angles than dppp, such as 1,4-bis(diphenylphosphino)butane (dppb) and 1, 1'-bis(diphenylphosphino)ferrocene (dppf), resulted in increased reactivity. Further increasing the bite angle by use of Xantphos as a ligand resulted in a dramatic decrease in reactivity. Using DPEphos provided an optimal bite angle of approximately 101° for promoting the desired transformation.[23] By switching from THF to 2-MeTHF and increasing the equivalents of benzoylacetic acid (**1a**), the catalyst loading can be decreased while increasing the yield to 97%.

With this protocol in hand, we explored the coupling of various β–keto acids **1** with 1-phenyl-1-propyne (**2a**). Aliphatic β–keto acids, bearing multiple acidic α-hydrogens, were alkylated with >20:1 regioselectivity (Figure 2). Primary (**3b, 3e**, and **3f**), secondary (**3c**), and tertiary (**3d**) substitution are all tolerated (61–92%). Notably, β–keto acids with electron-withdrawing groups (phenyl and phenylsulfonyl) can be used to give ketones formally derived from the methyl-ketone dianions (highlighted in blue, **3e** and **3f**). β–keto acids bearing aromatic rings with a variety of substituents underwent alkylation with high branched to linear regioselectivity. Halogenated aromatic rings are well tolerated (**3g**–**3i**, 70–91%). Regioselective coupling still occurs when the aromatic ring has an *ortho*-methyl group (**3j**). In addition, electron-deficient *para*-trifluoromethyl and electron-rich *para*-methoxy substituted rings are tolerated (**3k** and **3l**, 63% and 61%, respectively). Finally, β–keto acids with heterocycles (*e.g.*, furan and thiophene) can be used as carbon pronucleophiles to yield **3m** and **3n** (90% and 89%, respectively).

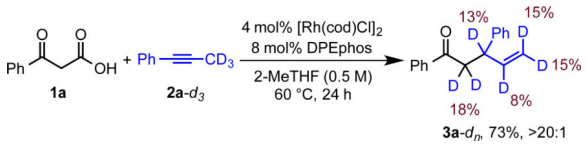
Next, we examined the coupling benzoylacetic acid (**1a**) with various alkynes **2** (Figure 3). Halogenated 1-aryl-1-propynes were used to alkylate benzoylacetic acid (**1a**) with >20:1 regioselectivity (**3o**–**3q**, 57–75%). In addition, alkynes with electron-deficient *para*-trifluoromethyl and electron-rich *para*-methoxy phenyl rings are amenable to alkylating **1a** to afford ketones **3r** and **3s** (81% and 55%, respectively). Benzoylacetic acid (**1a**) can be alkylated using alkynes with aliphatic substitution in place of aromatic. Aliphatic alkynes present a challenge as a result of having more than one possible site for β-hydride elimination for allene formation. Given this challenge, we were pleased to find that using alkynes bearing aliphatic substituents gave the branched ketone product bearing a terminal olefin. Both free and protected alcohols are tolerated. A sensitive functional group handle (*e.g.*, the tosyl group) remains intact under these alkylating conditions (**3t**, 85%). Silylated,

benzoylated, and benzylated alcohols are all also well-tolerated (**3u**, **3w**, and **3x**, 51–90%). Phthalimide protected amines, as well as Boc and Ts protected amines can be installed on the alkyne coupling partner (**3y** and **3z**, 52% and 59%, respectively). Acidic N-H bonds are tolerated as shown by the formation of ketone **3aa** in 82% yield. Notably, using alkynes with free alcohols or amines, as in **3v** and **3aa**, does not result in intramolecular cyclization to form the corresponding tetrahydrofuran or pyrrolidine. These results highlight the high chemoselectivity of this protocol. Finally, electrophilic functionalities can be tolerated as evidenced by the formation of ketones **3ab**–**3ae** bearing an alkyl bromide, Weinreb amide, ketone, and aldehyde, respectively (46–79%).

To provide evidence for the proposed allene intermediate, we used allene **6a** as a substitute for alkyne **2a** under standard reaction conditions. Ketone **3a** was obtained in 52% yield with >20:1 regioselectivity (eq 1). This result suggests the feasibility of an allene intermediate in the catalytic cycle. To better understand the proposed β-hydride elimination, we performed an experiment with deuterated 1-phenyl-1-propyne **2a**-d_3 (eq 2). Ketone **3a**-d_n was obtained in 73% yield with high-branched regioselectivity. We observed deuterium scrambling which suggests reversible β-hydride elimination during allene formation. Initial studies with chiral ligands resulted in moderate enantioselectivities (up to 54% *ee*) using a MeOBIPHEP-based ligand.[24] These results support the proposed role of the Rh-phosphine complex in the key C-C bond formation, however, developing highly enantioselective variants warrants further efforts.



(1)



(2)

Conclusions

This Rh-catalyzed decarboxylative coupling between β-keto acids and alkynes provides a complementary approach to generate ketones, without need for enolate generation and activated allylic electrophiles. In addition, alkylation at specific sites can be performed in the presence of multiple reactive sites due to the directing effect of the carboxylic acid. Our study contributes to the emerging use of alkynes in various cross-couplings to generate C–O,[25] C–N,[26] C–S,[27] and C–C bonds.[28] Further studies are underway to expand the scope of carbon pronucleophiles and identify more enantioselective variants for tandem Rh-catalysis.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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.

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See ESI.

25.
For select examples of C–O bond formation from alkynes, see: references 14c, 15b and 15d.

26.
For select examples of C–N bond formation from alkynes, see: references 14a, 14b, 14c, 14d, 14e, 14f, 14h, 14i and 16.

27.
For a select example of C–S bond formation from alkynes, see: reference 15c.

28.
For select examples of C–C bond formation from alkynes, see: references 14c, 14f, 14g, 14j, 14k and 19.

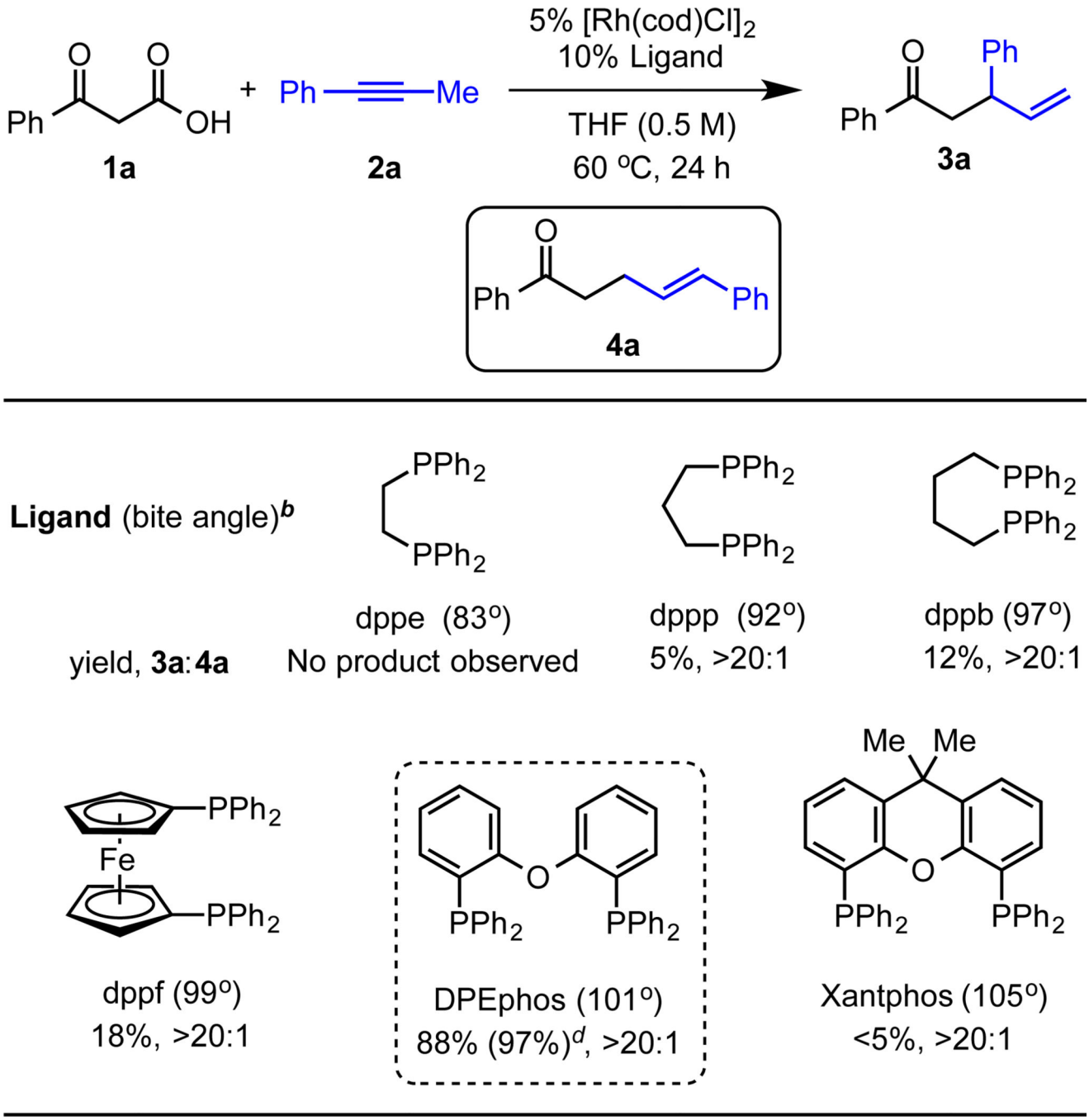


Figure 1.

Ligand Effects on Decarboxylative β-keto Acid and Alkyne Coupling.[a]

[a]Reaction conditions: 0.1 mmol **1a**, 0.1 mmol **2a**, 5 mol% $[Rh(cod)Cl]_2$, 10 mol% ligand, 0.2 mL THF (0.5 M), 60 °C, 24 hours. [b]See ref 23. [c]Determined by GC-FID analysis using mesitylene as internal standard. [d]Using 0.2 mmol **1a**, 4 mol% $[Rh(cod)Cl]_2$, 8 mol% DPEphos, and 2-MeTHF instead.

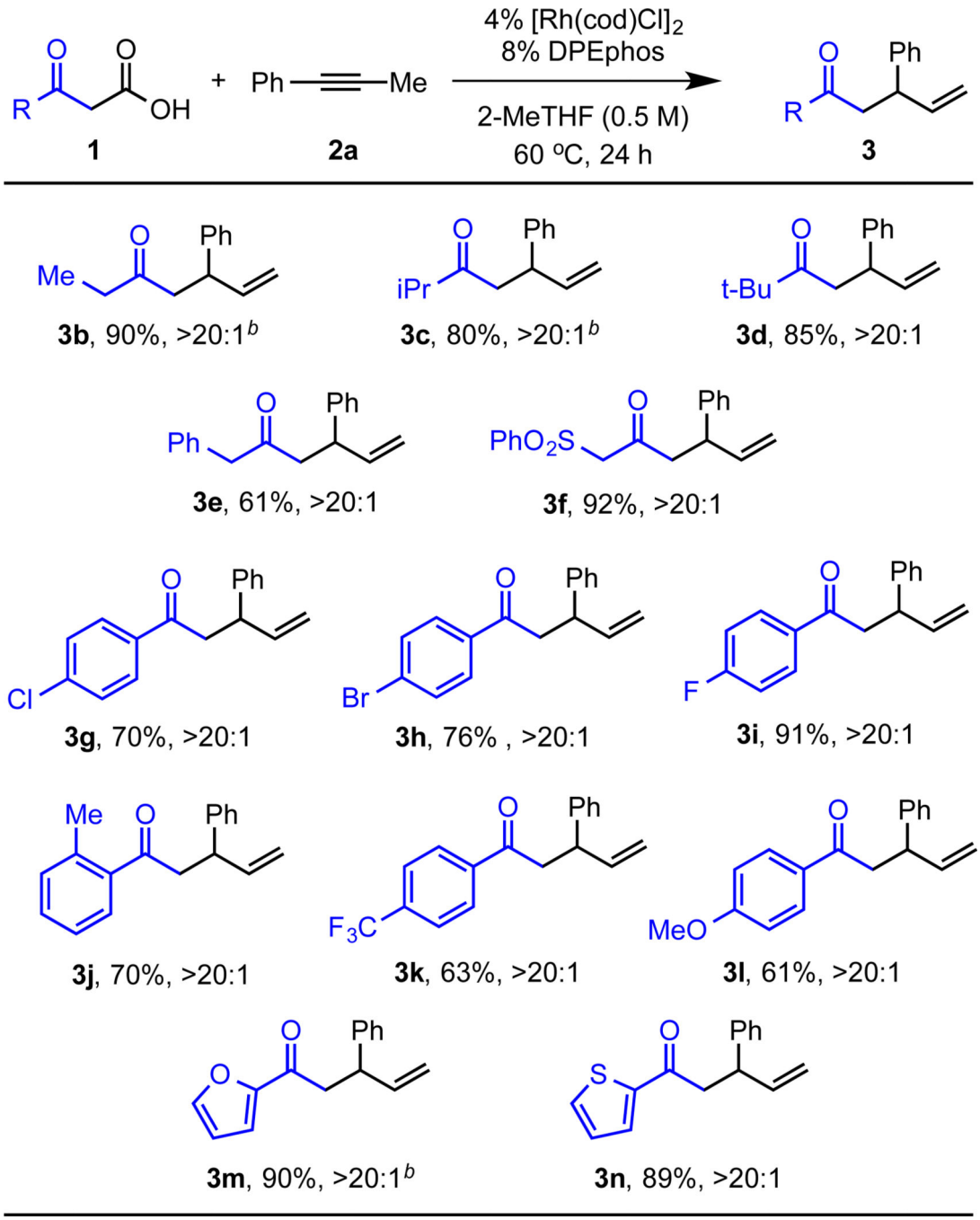


Figure 2.

Branched Selective Decarboxylative Coupling of Alkyne **2a** with Various β –keto Acids.[a]

[a]Reaction conditions: 0.4 mmol **1**, 0.2 mmol **2a**, 4 mol% $[Rh(cod)Cl]_2$, 8 mol% DPEphos, 0.4 mL 2-MeTHF, 60 °C, 24 hours. >20:1 denotes the ratio of **3**:**4**. [b]Reaction ran with 50 mol% benzoic acid.

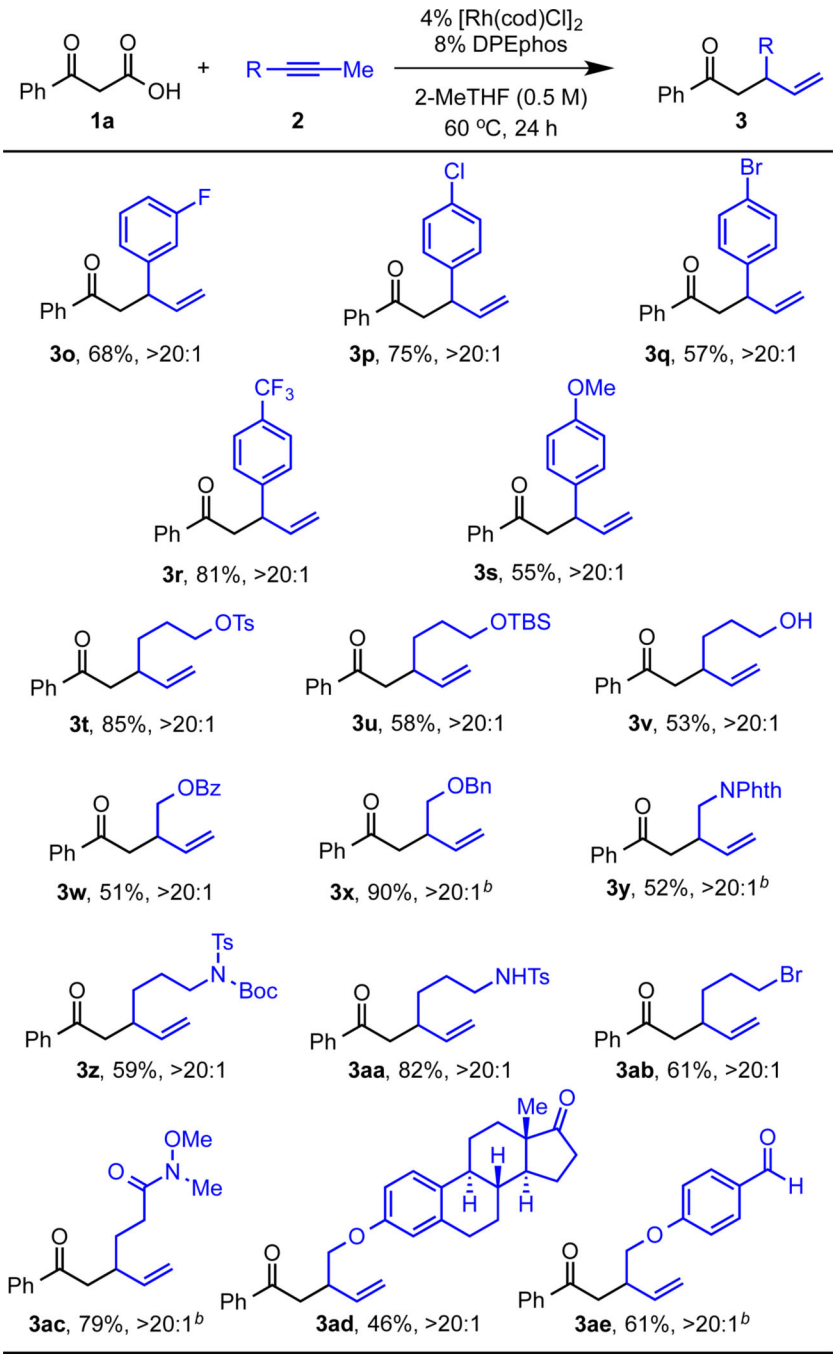
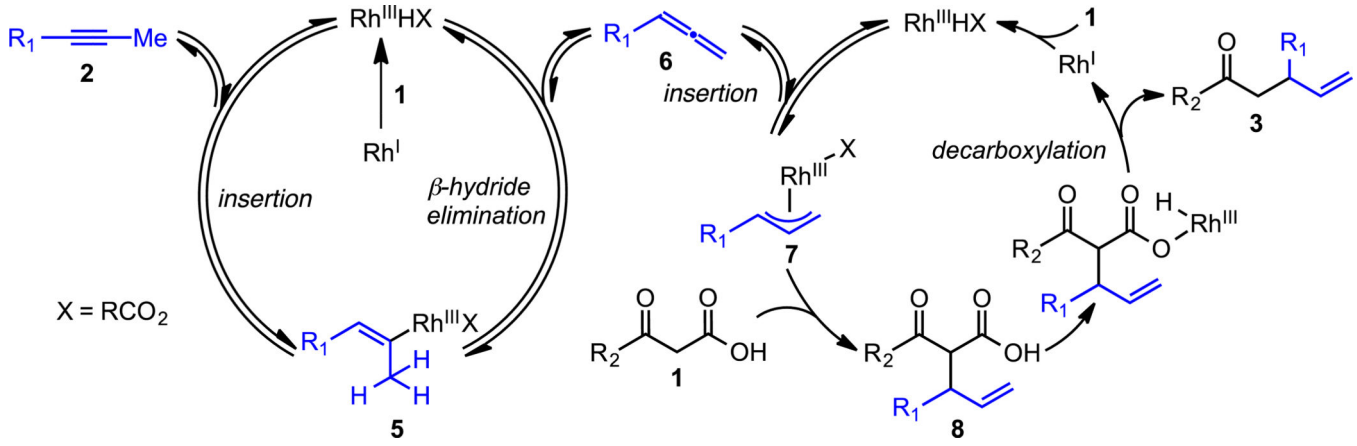


Figure 3.

Branched Selective Decarboxylative Coupling of β–keto acids **1a** with Various Alkynes.[a]

[a]Reaction conditions: 0.4 mmol **1a**, 0.2 mmol **2**, 4 mol% $[Rh(cod)Cl]_1$, 8 mol% DPEphos, 0.4 mL 2-MeTHF, 60 °C, 24 hours. >20:1 denotes the ratio of **3**:**4**. [b]Reaction ran with 50 mol% benzoic acid.



Scheme 1.

Proposed decarboxylative β-keto acid and alkyne coupling via tandem Rh-Catalysis.