Organic LETTERS

Letter

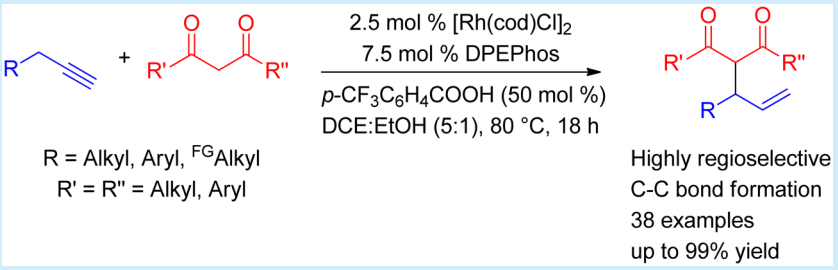
pubs.acs.org/OrgLett

# Regioselective Rhodium-Catalyzed Addition of 1,3-Dicarbonyl Compounds to Terminal Alkynes

Thorsten M. Beck and Bernhard Breit*

Institut für Organische Chemie, Albert-Ludwigs-Universität Freiburg, Albertstr. 21, 79104 Freiburg im Breisgau, Germany

Supporting Information




**ABSTRACT:** A new method for the rhodium-catalyzed regioselective C−C bond formation using terminal alkynes and 1,3-dicarbonyl compounds to achieve valuable branched $\alpha$-allylated 1,3-dicarbonyl products is reported. With a Rh(I)/DPEphos/$p$-$CF_3$-benzoic acid as the catalyst system, the desired products can be obtained in good to excellent yields and with perfect regioselectivity. A broad range of functional groups were tolerated, and first experimental insights of a plausible reaction mechanism were obtained.

Recently, we reported on a series of rhodium-catalyzed addition of different pronucleophiles to allenes[1] and terminal alkynes,[2] which can be regarded as an atom economic alternative to the transition metal-catalyzed allylic substitution[3−7] and the palladium-catalyzed allylic oxidation.[8,9] Although terminal allenes[10] displayed in many cases higher reactivity, the isomeric terminal alkynes[11] are much easier accessible substrates and thus synthetically more appealing starting materials.

Unfortunately, the reactivity of terminal alkynes is so far restricted to the additions of carboxylic acids furnishing allylic esters (C−O bond formation)[2a,c] as well as to the addition of sulfonylhydrazides furnishing allylic sulfones (C−S bond formation).[2b]

However, the addition of carbon nucleophiles would be synthetically very attractive since this allows for further carbon skeleton extension. Mechanistic investigations indicated that the reaction of terminal alkynes and carboxylic acids proceed via a $\sigma$-allyl rhodium complex as the resting state.[12] We speculated that a suitable carbon nucleophile such as a 1,3-dicarbonyl species could serve to trap this $\sigma$-allyl complex by a C−C bond formation.

We herein report on the successful realization of this concept achieving a regioselective rhodium-catalyzed addition of 1,3-dicarbonyl compounds to terminal alkynes as an efficient method for the formation of valuable branched $\alpha$-allylated 1,3-dicarbonyl compounds (Scheme 1).

Our studies emanated by employing 1-dodecyne (**1**, 2.0 equiv) and acetylacetone (**2**, 1.0 equiv) as model system (Table 1).[13] After first reactivity assays[14] we were pleased to find that applying $[Rh(COD)Cl]_2$ (2.5 mol %) and DPEphos (**3**, 7.5 mol %) as catalyst and benzoic acid (100 mol %) as an additive in DCE at 80 °C led to the desired branched product **4** in 64% yield (Table 1, entry 1). In the absence of benzoic acid, only traces of product could be observed (entry 2) demonstrating its importance for the title reaction. Studying different *para* substituted benzoic acid

**Scheme 1. Proposed Pathway for Carbon−Carbon Bond Formation from Terminal Alkynes**

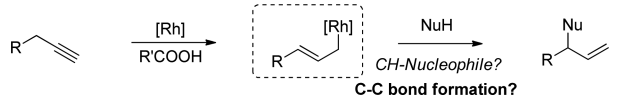
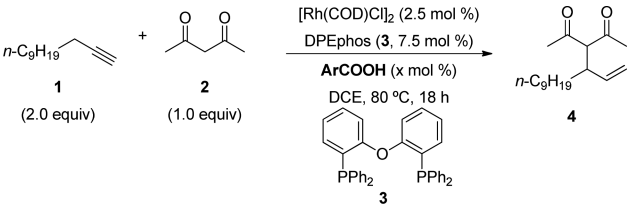



**Table 1. Ligand Screening and Optimizations**




| entry | Ar | $x$ (mol %) | yield[a] (%) |
|---|---|---|---|
| 1 | Ph | 100 | 64 |
| 2 | Ph | 0 | traces |
| 3 | $p$-$CF_3C_6H_4$ | 100 | 93 |
| **4**[b] | **$p$-$CF_3C_6H_4$** | **50** | **97** |

[a]Isolated yield of the branched product **4**. [b]Reaction performed in DCE/EtOH (5:1).

**Received:** November 26, 2015

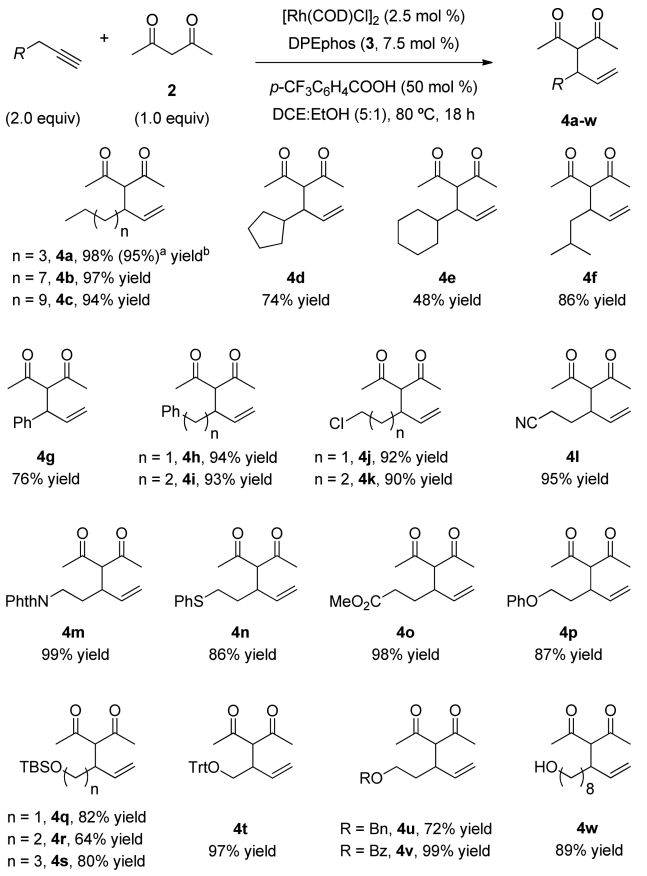



DOI: 10.1021/acs.orglett.5b03391
*Org. Lett.* XXXX, XXX, XXX−XXX

derivatives revealed that $p$-$CF_3C_6H_4CO_2H$ was most effective, leading to 93% yield of **4** (entry 3). Also the solvent plays an important role in this reaction. An optimized solvent mixture of DCE and ethanol (5:1) allowed to reduce the amount of $p$-$CF_3C_6H_4CO_2H$ to 50 mol %, still providing the highest yield (entry 4). In all cases the branched allylic addition product was the only regioisomer that could be observed.

With these optimized conditions in hand we next explored the scope of alkynes. A large number of commercially available or easily accessible terminal alkynes were suitable substrates for the reaction and afforded exclusively branched products in good to excellent yields (Scheme 2). Additionally, linear alkyl-, aliphatic

**Scheme 2. Scope of Alkynes with Acetylacetone (2)**

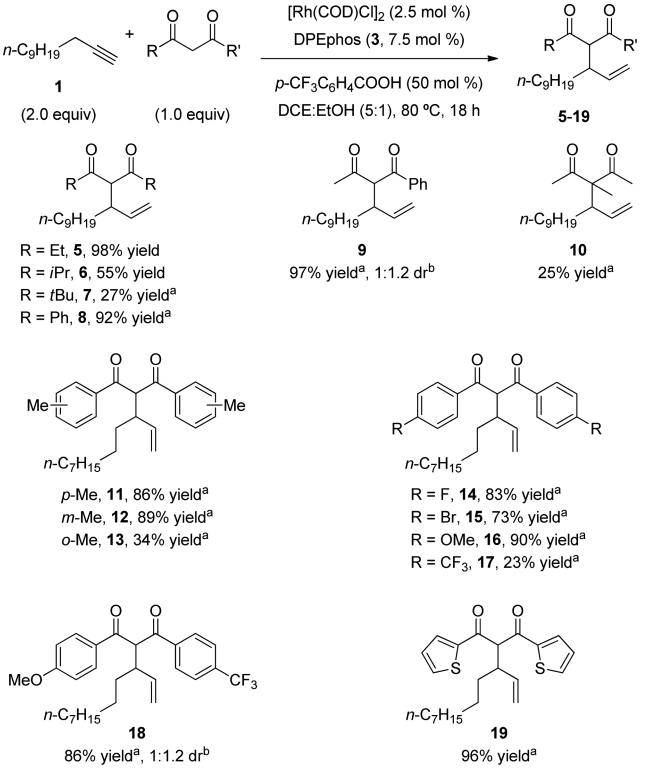



[a]This reaction was additionally performed in a 5 mmol scale and gave **4a** in 95% isolated yield. [b]All yields are isolated yields.

cyclic-, phenyl-, and linear $\omega$-substituted alkynes were applicable. To our delight even prehalogenated alkynes were tolerated well (**4j**, **4k**), and additionally, several other functional groups such as a cyano substituent (**4l**), a phthalimidoyl function (**4m**), and a thioether function(**4n**) were compatible. Also substrates with protecting groups for hydroxy functions, including silyl ether (**4q**−**4s**), trityl ether (**4t**), benzyl ether (**4u**), and benzoate functions (**4v**) behaved well. Even the presence of a hydroxy group was well tolerated (**4w**).

Next, the reaction could be applied to a variety of 1,3-diketones (Scheme 3). The reaction of heptane-3,5-dione with 1-dodecyne (**1**) led to the branched product **5** with an excellent yield of 98% (Scheme 3), albeit yields dropped for sterically more congested derivatives. The addition of the symmetric bisbenzoyl

**Scheme 3. Scope of 1,3-Dicarbonyl Compounds with 1-Dodecyne (1)**




[a]Reaction was carried out over 66 h. [b]The diastereomeric ratio (dr) was determined by $^1$H NMR analysis.

methane led to **8** in 92% yield. Also, with benzoyl acetone, high yields of **9** (97%, 1:1.2 dr) were obtained.

Varying the pattern of functional groups on the aryl moiety of bisbenzoyl methane was possible and furnished the desired addition products in mostly good yields. Furthermore, the heterocyclic bisthiophenoyl propane-1,3-dione could be applied to yield **19** in 96% yield.

The resulting $\alpha$-allylated 1,3-dicarbonyl compounds are useful starting materials for heterocycle synthesis of medicinal interest.[15,16] Hence, reaction of **4a** with hydroxylamine led to the oxazole **20**. Correspondingly, reaction with hydrazine and phenylhydrazine furnished the pyrazoles **21** and **22**, respectively, in good to excellent yields (Scheme 4). Pyrazoles are suitable substrates for a further functionalization by rhodium-catalyzed N-allylation with allenes developed in our laboratories.[1j] Subjection of the $\alpha$-allylated 1,3-dicarbonyl compounds to ethanolic potassium hydroxide solution initiated a deacetylation resulting in the formation of $\gamma,\delta$-unsaturated ketones in quantitative yield (Scheme 4). This facile access to $\gamma,\delta$-unsaturated methyl ketones represents a synthetic alternative to an enolate allylation reaction or a Claisen/Carroll-type rearrangement.[17]

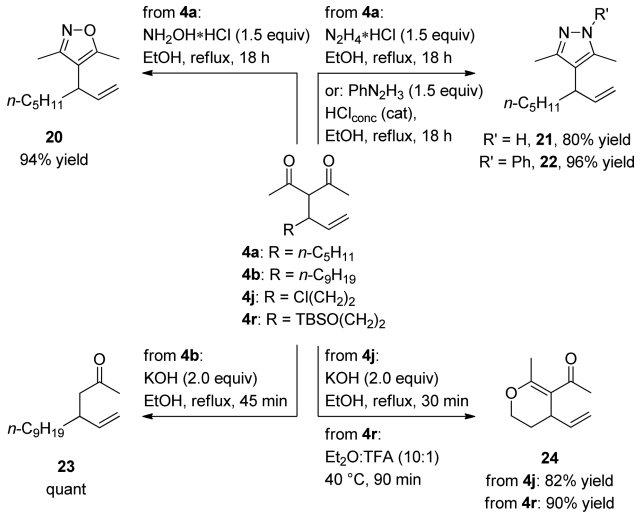
Furthermore, treatment of either chlorine or silylether functionalized substrates **4j** and **4r** under basic or acidic conditions, respectively, led to the formation of the dihydropyran system **24** in good yields (Scheme 4).[18]

In order to attain first insights into the reaction mechanism, the following control experiments were performed. Subjecting the allylic benzoic ester **25** to the reaction conditions furnished **4a**, the product of an allylic substitution reaction. This indicates that **25** might be an intermediate during the course of this



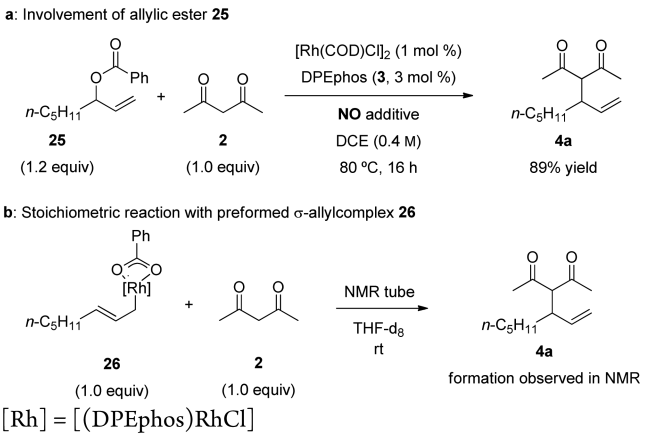
DOI: 10.1021/acs.orglett.5b03391
Org. Lett. XXXX, XXX, XXX−XXX

**Scheme 4. Applications in the Synthesis of Trisubstituted Oxazoles, Tri- or Tetra-Substituted Pyrazoles, Deacetylation, and Cyclization**




reaction (Scheme 5). However, from our previous mechanistic studies on the rhodium-catalyzed addition of benzoic acid to

**Scheme 5. Control Experiments**



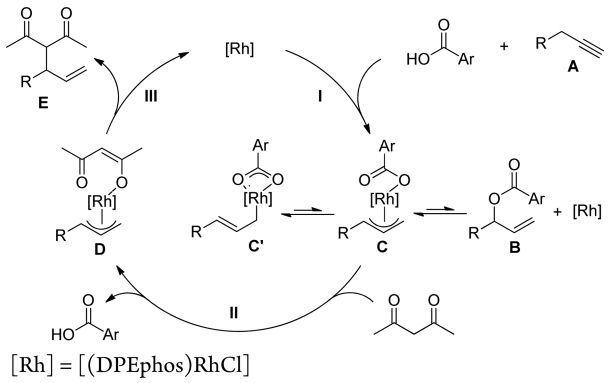

terminal alkynes furnishing branched allylic benzoates, it is known that allylic esters can undergo reaction with the rhodium catalyst to furnish $\sigma$-allyl rhodium complex **26**, which has been isolated previously representing the resting state of the catalyst.

Hence, to clarify whether the $\sigma$-allyl rhodium complex **26** is an intermediate in the reaction with acetylacetone as a nucleophile, a stoichiometric reaction with the preformed rhodium complex **26** was monitored in an NMR experiment. Indeed, formation of the allylic addition product **4a** could be observed suggesting the rhodium complex **26** to be an intermediate of the catalytic cycle. Additionally, isotope-labeling experiments with deuterated substrate showed deuterium incorporation in all positions of the alkene function of the product,[19] which is in agreement with previously made observations for the rhodium-catalyzed addition of different pronucleophiles to allenes[1a,b,j] and alkynes.[2a]

Based on these experiments and previous results, we propose the following catalytic cycle (Scheme 6).

Starting step **I** is the known formation of the $\sigma$-allyl complex **C′**, obtained by reaction of the alkyne and the aryl carboxylic acid. **C′** is presumably in equilibrium with $\pi$-allyl complex **C** and

**Scheme 6. Proposed Catalytic Cycle**




the allylic ester **B**. Anion exchange of **C** with acetylacetone would provide allyl complex **D**. Reductive elimination from **D** would release the allylic addition product **E**.

To conclude, starting from simple terminal alkynes and 1,3-dicarbonyls we have developed a highly regioselective rhodium-catalyzed C−C bond forming reaction furnishing valuable branched $\alpha$-allylated 1,3-dicarbonyl compounds in good to excellent yields. The utility of the obtained products was demonstrated through one step transformations to heterocyclic systems of medicinal interest. Furthermore, hydroxide mediated deacetylation provided products of a formal methylketone enolate allylation or Claisen/Carroll-type rearrangement. Further attempts regarding extensions of this method to the formation of quaternary centers, other (carbon-) nucleophiles as well as the development of an asymmetric variant are ongoing in our laboratories.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b03391.

Experimental procedures and analytical data for synthesized alkynes, diarylpropane-1,3-diones, and $\alpha$-allylated 1,3-dicarbonyl compounds, including $^{1}$H NMR and $^{13}$C NMR (PDF)

## ■ AUTHOR INFORMATION

### Corresponding Author

*E-mail: bernhard.breit@chemie.uni-freiburg.de.

### Notes

The authors declare no competing financial interest.

## ■ ACKNOWLEDGMENTS

We thank DFG (Deutsche Forschungsgemeinschaft) for generous support of our program. Anne Aßmann (University Freiburg) is acknowledged for technical support.

## ■ REFERENCES

(1) (a) Koschker, P.; Lumbroso, A.; Breit, B. *J. Am. Chem. Soc.* **2011**, *133*, 20746. (b) Cooke, M. L.; Xu, K.; Breit, B. *Angew. Chem., Int. Ed.* **2012**, *51*, 10876. (c) Li, C.; Breit, B. *J. Am. Chem. Soc.* **2014**, *136*, 862. (d) Xu, K.; Thieme, N.; Breit, B. *Angew. Chem., Int. Ed.* **2014**, *53*, 2162. (e) Xu, K.; Thieme, N.; Breit, B. *Angew. Chem., Int. Ed.* **2014**, *53*, 7268. (f) Li, C.; Kähny, M.; Breit, B. *Angew. Chem., Int. Ed.* **2014**, *53*, 13780. (g) Xu, K.; Gilles, T.; Breit, B. *Nat. Commun.* **2015**, *6*, 7616. (h) Xu, K.; Raimondi, W.; Bury, T.; Breit, B. *Chem. Commun.* **2015**, *51*, 10861.



DOI: 10.1021/acs.orglett.5b03391
*Org. Lett.* XXXX, XXX, XXX−XXX

(i) Pritzius, A. B.; Breit, B. *Angew. Chem., Int. Ed.* **2015**, *54*, 3121. (j) Haydl, A. M.; Xu, K.; Breit, B. *Angew. Chem., Int. Ed.* **2015**, *54*, 7149. (k) Pritzius, A. B.; Breit, B. *Angew. Chem., Int. Ed.* **2015**, *54*, 15818.

(2) (a) Lumbroso, A.; Koschker, P.; Vautravers, N. R.; Breit, B. *J. Am. Chem. Soc.* **2011**, *133*, 2386. (b) Xu, K.; Khakyzadeh, V.; Bury, T.; Breit, B. *J. Am. Chem. Soc.* **2014**, *136*, 16124. (c) Koschker, P.; Kähny, M.; Breit, B. *J. Am. Chem. Soc.* **2015**, *137*, 3131.

(3) For selected reviews on transition metal-catalyzed allylic substitution, see: (a) Trost, B. M.; Van Vranken, D. L. *Chem. Rev.* **1996**, *96*, 395. (b) Trost, B. M.; Crawley, M. L. *Chem. Rev.* **2003**, *103*, 2921. (c) Tsuji, J.; Minami, I. *Acc. Chem. Res.* **1987**, *20*, 140. (d) Lu, Z.; Ma, S. *Angew. Chem., Int. Ed.* **2008**, *47*, 258. (e) Helmchen, G.; Dahnz, A.; Dübon, P.; Schelwies, M.; Weihofen, R. *Chem. Commun.* **2007**, 675.

(4) For selected examples on Pd-catalyzed allylic alkylation to achieve branched products, see: (a) Trost, B. M.; Malhotra, S.; Chan, W. H. *J. Am. Chem. Soc.* **2011**, *133*, 7328. (b) Chen, J.-P.; Peng, Q.; Lei, B.-L.; Hou, X.-L.; Wu, Y.-D. *J. Am. Chem. Soc.* **2011**, *133*, 14180. (c) Chen, J.-P.; Ding, C.-H.; Liu, W.; Hou, X.-L.; Dai, L.-X. *J. Am. Chem. Soc.* **2010**, *132*, 15493. (d) Zhang, P.; Brozek, L. A.; Morken, J. P. *J. Am. Chem. Soc.* **2010**, *132*, 10686.

(5) For selected examples on Ir-catalyzed allylic alkylation to achieve branched products, see: (a) Chen, W.; Hartwig, J. F. *J. Am. Chem. Soc.* **2013**, *135*, 2068. (b) Hartwig, J. F.; Stanley, L. M. *Acc. Chem. Res.* **2010**, *43*, 1461. (c) Krautwald, S.; Sarlah, D.; Schafroth, M. A.; Carreira, E. M. *Science* **2013**, *340*, 1065. (d) Hamilton, J. Y.; Sarlah, D.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2013**, *52*, 7532. (e) Lipowsky, G.; Miller, N.; Helmchen, G. *Angew. Chem., Int. Ed.* **2004**, *43*, 4595.

(6) For selected examples on Rh-catalyzed allylic alkylation to achieve branched products, see: (a) Tsuji, J.; Minami, I.; Shimizu, I. *Tetrahedron Lett.* **1984**, *25*, 5157. (b) Hayashi, T.; Okada, A.; Suzuka, T.; Kawatsura, M. *Org. Lett.* **2003**, *5*, 1713. (c) Kazmaier, U.; Stolz, D. *Angew. Chem., Int. Ed.* **2006**, *45*, 3072. (d) Evans, P. A.; Nelson, J. D. *J. Am. Chem. Soc.* **1998**, *120*, 5581. (e) Ashfeld, B. L.; Miller, K. A.; Martin, S. F. *Org. Lett.* **2004**, *6*, 1321. (f) Evans, P. A.; Oliver, S.; Chae, J. *J. Am. Chem. Soc.* **2012**, *134*, 19314.

(7) For selected examples on other metal-catalyzed allylic alkylation to achieve branched products, see: (a) For Fe: Plietker, B. *Angew. Chem., Int. Ed.* **2006**, *45*, 1469. (b) For Co: Bhatia, B.; Reddy, M. M.; Iqbal, J. *Tetrahedron Lett.* **1993**, *34*, 6301. (c) For Mo: Trost, B. M.; Miller, J. R.; Hoffman, C. M., Jr. *J. Am. Chem. Soc.* **2011**, *133*, 8165. (d) For Ru: Sundararaju, B.; Achard, M.; Demerseman, B.; Toupet, L.; Sharma, G. V. M; Bruneau, C. *Angew. Chem., Int. Ed.* **2010**, *49*, 2782. (e) For W: Lloyd-Jones, G. C.; Pfalz, A. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 462.

(8) For Pd-catalyzed allylic oxidation, see: Covell, D. J.; White, M. C. *Angew. Chem., Int. Ed.* **2008**, *47*, 6448.

(9) For Cu-catalyzed allylic oxidation, see: (a) Malkov, A. V.; Bella, M.; Langer, V.; Kocovsky, P. *Org. Lett.* **2000**, *2*, 3047. (b) Eames, J.; Watkinson, M. *Angew. Chem., Int. Ed.* **2001**, *40*, 3567. (c) Andrus, M. B.; Zhou, Z. J. *J. Am. Chem. Soc.* **2002**, *124*, 8806.

(10) For selected examples on the coupling of nucleophiles to allenes, see: (a) Zimmer, R.; Dinesh, C.; Nandanan, E.; Khan, A. F. *Chem. Rev.* **2000**, *100*, 3067. (b) Trost, B. M.; Jakel, C.; Plietker, B. *J. Am. Chem. Soc.* **2003**, *125*, 4438. (c) Nishina, N.; Yamamoto, Y. *Angew. Chem., Int. Ed.* **2006**, *45*, 3314. (d) Al-Masum, M.; Yamamoto, Y. *J. Am. Chem. Soc.* **1998**, *120*, 3809. (e) Trost, B. M.; Xie, J.; Sieber, J. D. *J. Am. Chem. Soc.* **2011**, *133*, 20611. (f) Moran, J.; Preetz, A.; Mesch, R. A.; Krische, M. *Nat. Chem.* **2011**, *3*, 287. (g) Kawamoto, T.; Hirabayashi, S.; Guo, X.; Nishimura, T.; Hayashi, T. *Chem. Commun.* **2009**, 3528. (h) Lalonde, R. L.; Sherry, B. D.; Kang, E. J.; Toste, F. D. *J. Am. Chem. Soc.* **2007**, *129*, 2452. (i) Butler, K. L.; Tragni, M.; Widenhoefer, R. A. *Angew. Chem., Int. Ed.* **2012**, *51*, 5175.

(11) For selected examples on the coupling of nucleophiles to alkynes, see: (a) Lutete, L. M.; Kadota, I.; Yamamoto, Y. *J. Am. Chem. Soc.* **2004**, *126*, 1622. (b) Trost, B. M.; Brieden, W. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 1335. (c) Kadota, I.; Shibuya, A.; Gyoung, Y. S.; Yamamoto, Y. *J. Am. Chem. Soc.* **1998**, *120*, 10262. (d) Patil, N. T.; Yamamoto, Y. *J. Org. Chem.* **2004**, *69*, 6478. (e) Chen, Q.-A.; Chen, Z.; Dong, V. M. *J. Am. Chem. Soc.* **2015**, *137*, 8392.

(12) Gellrich, U.; Meißner, A.; Steffani, A.; Kähny, M.; Drexler, H.; Heller, D.; Plattner, D. A.; Breit, B. *J. Am. Chem. Soc.* **2014**, *136*, 1097.

(13) Unfortunately, cyclic 1,3-dicarbonyl compounds and malonates did not show product formation in our hands.

(14) For further tested 1,3-dicarbonyl compounds, ligands, and acids, see Supporting Information.

(15) (a) El-Tombary, A. A.; Abdel-Ghany, Y. S.; Belal, A. S. F.; Shams El-Dine, S. A.; Soliman, F. S. G. *Med. Chem. Res.* **2011**, *20*, 865. (b) Natale, N. R.; Triggle, D. J.; Palmer, R. B.; Lefler, B. J.; Edwards, W. D. *J. Med. Chem.* **1990**, *33*, 2255.

(16) (a) Zamponi, G. W.; Stotz, S. C.; Staples, R. J.; Andro, T. M.; Nelson, J. K.; Hulubei, V.; Blumenfeld, A.; Natale, N. R. *J. Med. Chem.* **2003**, *46*, 87. (b) Verstovsek, S.; Mesa, R. A.; Gotlib, J.; Levy, R. S.; Gupta, V.; DiPersio, J. F.; Catalano, J. V.; Deininger, M.; Miller, C.; Silver, R. T.; Talpaz, M.; Winton, E. F.; Harvey, J. H.; Arcasoy, M. O.; Hexner, E.; Lyons, R. M.; Paquette, R.; Raza, A.; Vaddi, K.; Erickson-Viitanen, S.; Koumenis, I. L.; Sun, W.; Sandor, V.; Kantarjian, H. M. *N. Engl. J. Med.* **2012**, *366*, 799. (c) Mesa, R. A.; Yasothan, U.; Kirkpatrick, P. *Nat. Rev. Drug Discovery* **2012**, *11*, 103. (d) Koppikar, P.; Bhagwat, N.; Kilpivaara, O.; Manshouri, T.; Adli, M.; Hricik, T.; Liu, F.; Saunders, L. M.; Mullally, A.; Abdel-Wahab, O.; Leung, L.; Weinstein, A.; Marubayashi, S.; Goel, A.; Gonen, M.; Estrov, Z.; Ebert, B. L.; Chiosis, G.; Nimer, S. D.; Bernstein, B. E.; Verstovsek, S.; Levine, R. L. *Nature* **2012**, *489*, 155.

(17) (a) Claisen, L. *Ber. Dtsch. Chem. Ges.* **1912**, *45*, 3157. (b) Martin Castro, A. M. *Chem. Rev.* **2004**, *104*, 2939. (c) Carroll, M. F. *J. Chem. Soc.* **1940**, 704. (d) Shimizu, I.; Yamada, T.; Tsuji, J. *Tetrahedron Lett.* **1980**, *21*, 3199. (e) Wilson, S. R.; Price, M. F. *J. Org. Chem.* **1984**, *49*, 722.

(18) (a) Shimizu, M.; Hayashi, T.; Shimizu, K.; Morita, N. *Phytochemistry* **1982**, *21*, 245. (b) Banskota, A. H.; Tezuka, Y.; Midorikawa, K.; Matsushige, K.; Kadota, S. *J. Nat. Prod.* **2000**, *63*, 1277. (c) Macías, F. A.; Varela, R. M.; Torres, A.; Molinillo, J. G. *Tetrahedron Lett.* **1999**, *40*, 4725. (d) Tal, B.; Robeson, D.; Burke, B.; Aasen, A. *Phytochemistry* **1985**, *24*, 729. (e) Birch, A. J.; Dahl, C. J. *Aust. J. Chem.* **1974**, *27*, 331.

(19) For further details about deuterium labeling experiments, see Supporting Information.



DOI: 10.1021/acs.orglett.5b03391
*Org. Lett.* XXXX, XXX, XXX−XXX