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Access to *Z*-Selective 1,3-Enynes via Ni-Catalyzed Intermolecular Cross-Alkylalkynylation of Terminal Alkynes

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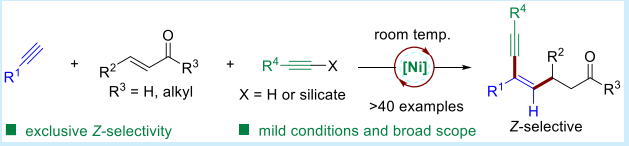
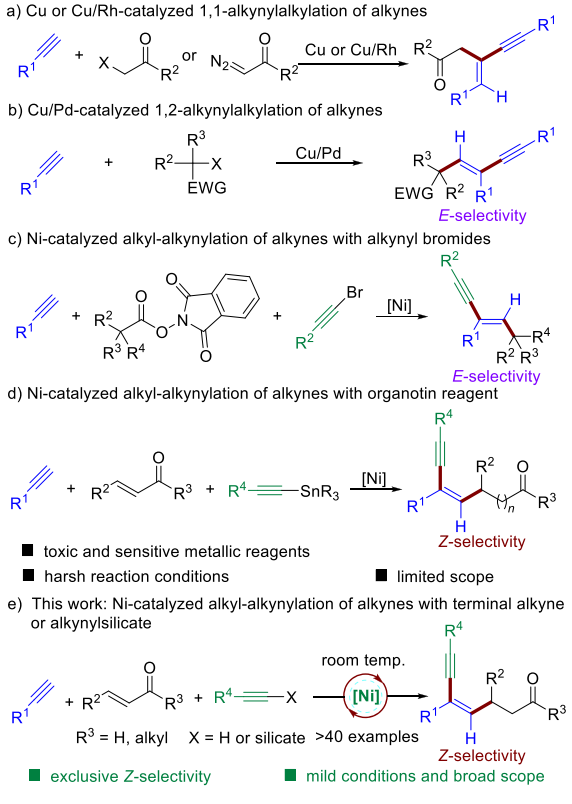
ABSTRACT: Access to 1,3-conjugated enynes with defined stereoselectivity is highly desirable and challenging. Herein, we report a facile synthesis of stereodefined 1,3-conjugated enynes via Ni-catalyzed intermolecular cross-alkylalkynylation of alkynes with unsaturated carbonyl compounds and alkynes or alkynyl silicates. The operational simple protocol proceeds at room temperature and tolerates a wide range of functional groups, providing an attractive alternative to carbonyl-tethered trisubstituted conjugated 1,3-enynes from easily accessible starting materials.



Conjugated 1,3-enynes are widely found substructures in natural products, pharmaceuticals, and functional materials.[1] They also serve as precursors for diverse functional groups and versatile intermediates to build molecular complexity.[2] To date, significant advances have been achieved in the synthesis of 1,3-enynes,[3] such as the Wittig reaction or Horner−Wadsworth−Emmons (HWE) reaction,[4] transition-metal-catalyzed cross-couplings of alkynes with alkenes,[5] cross-dimerization of alkynes,[6] dehydration of propargylic alcohols,[7] and others.[8] However, the existing methods suffer from several drawbacks, such as harsh reaction conditions, inconvenience of accessing advanced starting materials, difficulty to control the regio- or/and stereoselectivity, and the use of expensive and toxic precious metal catalysts. To this regard, the direct synthesis of 1,3-enynes from readily available and stable starting materials in a stereodefined manner is challenging and highly desirable. Transition-metal-catalyzed carbo-alkynylation of alkynes has emerged as one of the promising ways to construct conjugated 1,3-enynes. Jiang and co-workers developed a rhodium-/copper-catalyzed 1,1-alkylalkynylation of terminal alkynes with α-diazoketones via a dediazotized carbene C−H insertion process to access 1,3-enynes in an *E*-selectivity (Scheme 1a).[9] Lv group reported a copper-catalyzed 1,1-alkylalkynylation of alkynes with α-haloacetamides to give *E*-1,3-enynes (Scheme 1a).[10] Zhu and co-workers reported a tandem *trans*-carbohalogenation/Sonogashira coupling reaction, furnishing substituted 1,3-enynes with *E*-selectivity (Scheme 1b).[11] Unfortunately, the above-mentioned methods are limited to the homodimerization of alkynes to give 1,3-enynes with two identical substituents. Moreover, only *E*-1,3-enynes were accessible. On the other hand, nickel-catalyzed intermolecular dicarbofunctionalizations of alkynes have become one of the most straightforward and effective ways to synthesize multisubstituted alkenes.[12] However, few examples utilizing this strategy to construct 1,3-enynes have been developed, probably due to the competitive oligomeriza-

Scheme 1. Strategies to Access Stereodefined 1,3-Enynes by Difunctionalization of Alkynes



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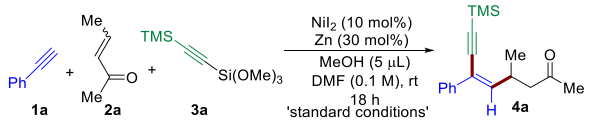
tion of alkynes. Recently, Koh and Zhao[13] reported a nickel-catalyzed three-component reductive alkylalkynylation of terminal alkynes with alkyl precursors and alkynyl bromides to deliver *E*-1,3-enynes (Scheme 1c). The Ikeda group reported a three-component reaction of nickel-catalyzed cross-coupling of alkynes, enones with organostannane, organozinc, or organoaluminum reagents, providing access to 1,3-enynes in *Z*-selectivity.[14] However, the methods required employing a stoichiometric amount of toxic and sensitive reagents, such as DIBAL-H, organometallic reagents (organotin/zinc/aluminum), and TMSCl, under harsh conditions, resulting in limited scope with narrow functional group tolerance (Scheme 1d). As our interest continued in earth-abundant metal-catalyzed selective transformations,[15] we envisioned building stereodefined 1,3-enynes via intermolecular oxidative cyclometalation of alkynes and enones, followed by a selective cross-coupling reaction with an easily available and user-friendly alkynyl precursor. Herein, we reported the regio- and stereoselective synthesis of 1,3-enynes by Ni-catalyzed intermolecular cross-coupling of alkynes with enones and alkynyl silicates/alkynes at room temperature (Scheme 1e), enabling the access to 1,3-enynes with exclusive *Z*-configuration under mild conditions with user-friendly reagents.

To test the feasibility of the reaction, we set out to evaluate the reaction conditions using phenylacetylene (**1a**), pent-3-en-2-one (**2a**, mixture of isomers), and trimethylsilylacetylene silicate (**3a**) as the prototype substrates. After extensive optimization of the reaction parameters, we defined the use of NiI_2 (10 mol %) as catalyst, zinc (30 mol %) as reductant, and methanol (5 μL) as additive in DMF (0.1 M) at room temperature as the standard conditions, affording the three-component cross-coupling product 4,5-enynone **4a** in 89% isolated yield (Table 1, entry 1). The reaction proceeded smoothly in the absence of methanol to give **4a** in 81% yield (Table 1, entry 2). Alternating the amount of methanol decreased the efficiency of the reaction, delivering **4a** in 83% and 90% yields, respectively (Table 1, entries 3 and 4). No desired product was obtained without zinc (Table 1, entry 5). Decreasing the amount of zinc led to lower yield of **4a** (Table 1, entry 6). Comparable yield of **4a** was obtained with higher loading of zinc (Table 1, entry 7). The use of Mn instead of Zn delivered **4a** in 11% yield (Table 1, entry 8). The selection of nickel precatalyst is also crucial to the reaction (Table 1, entries 9−13). The reaction proceeded smoothly in DMA, giving the desired product **4a** in 75% yield (Table 1, entry 14). Other solvents, such as tetrahydrofuran, acetonitrile, and dioxane, were not suitable for this sequential three-component transformation (Table 1, entries 15−17). Alternating the concentration and stoichiometry of **3a** delivered inferior results (Table 1, entries 18−20).[16] Conducting the reaction at higher concentration led to a heterogeneous mixture, which significantly decreased the yield of **4a** (Table 1, entry 18). Diluting the concentration of the reaction led to slower reaction rate, delivering **4a** in 39% yield (Table 1, entry 19).

With the optimized conditions in hand, we turned to evaluate the scope of this reaction (Figure 1). The reaction tolerated a wide range of functional groups with different substitution patterns for alkynes, enones, and alkynyl silicates. First, the scope of the terminal alkyne was tested. Electron-donating- and electron-withdrawing-substituted aryl alkynes were all good substrates for this transformation. Aryl terminal alkynes with *para*-, *meta*-, or *ortho*-substitution patterns could

Table 1. Evaluation of the Reaction Conditions[a]



entry	variation from "standard conditions"	yield of **4a**
1	none	94% (89%)[b]
2	no MeOH	81%
3	3 μL of MeOH	83%
4	8 μL of MeOH	90%
5	no Zn	0%
6	10 mol % of Zn	27%
7	50 mol % of Zn	91%
8	Mn instead of Zn	11%
9	no NiI_2	0%
10	$NiBr_2$ instead of NiI_2	23%
11	$NiBr_2$·glyme instead of NiI_2	26%
12	$NiCl_2$ instead of NiI_2	20%
13	$Ni(OAc)_2$ instead of NiI_2	0%
14	DMA instead of DMF	75%
15	THF instead of DMF	2%
16	MeCN instead of DMF	trace
17	dioxane instead of DMF	0%
18	DMF (0.2 M)	11%
19	DMF (0.05 M)	39%
20	**3a** (2 equiv)	77%

[a]The reaction was carried out using **1a** (0.15 mmol), **2a** (0.1 mmol), and **3a** (0.3 mmol) under indicated conditions. Yield was determined by GC using *n*-dodecane as the internal standard. [b]Isolated yield after flash chromatography. TMS = trimethylsilyl.

be converted to corresponding ketone-tethered *Z*-1,3-enynes in moderate to good yields (**4b**−**4o**). It is noteworthy that alkynyl arylhalides were compatible in this reaction with halides intact (**4f**, **4g**, **4j**, **4m**, and **4n**), leaving halides as a chemical handle for further elaboration. Multisubstituted aryl and fused aromatic alkynes were successfully transformed to corresponding *Z*-1,3-enynes (**4p** and **4q**) in 68% and 76% yields, respectively. Heteroaryl alkynes were also good subtrates for this reaction, delivering heteroaromatic-containing *Z*-1,3-enynes (**4r** and **4s**) in 62% and 68% yields. The *Z*-configuration of the product was confirmed by the NOE of **4p**. Unfortunately, the use of aliphatic alkynes failed to deliver the desired enyne products. Next, the scope of unsaturated alkenes was examined. Acyclic 2,3-enones with different substitution patterns were all well-tolerated under the reaction conditions, giving the desired products (**5a**−**5d**) in 75%−85% yields. Five-, six-, and seven-membered cyclic 2,3-enones were good substrates in the reaction, furnishing cyclic ketone tethered conjugated *Z*-1,3-enynes (**5e**−**5g**) in 55−70% yields. Then, the scope of alkynyl silicates was investigated. Aliphatic alkyne, silyl alkyne, and aryl alkyne derived silicates could be coupled with terminal alkynes and enones to deliver diverse conjugated 2,3-enynes with exclusive *Z*-selectivity in 60%−94% yields (**6a**−**6g**). Notably, this protocol provides direct access to 1,3-enynes with similar substituents at 2- and 4-positions (**6e**−**6g**), which are difficult to access using other methods.

Next, we tested the reactions of alkylalkynylation of alkynes with enones using terminal alkynes as both alkene and alkyne equivalents (Figure 2). Transition-metal-catalyzed dimerization of terminal alkynes provided efficient and atom-economic synthetic routes to 1,3-enynes.[6] However, the regio- and

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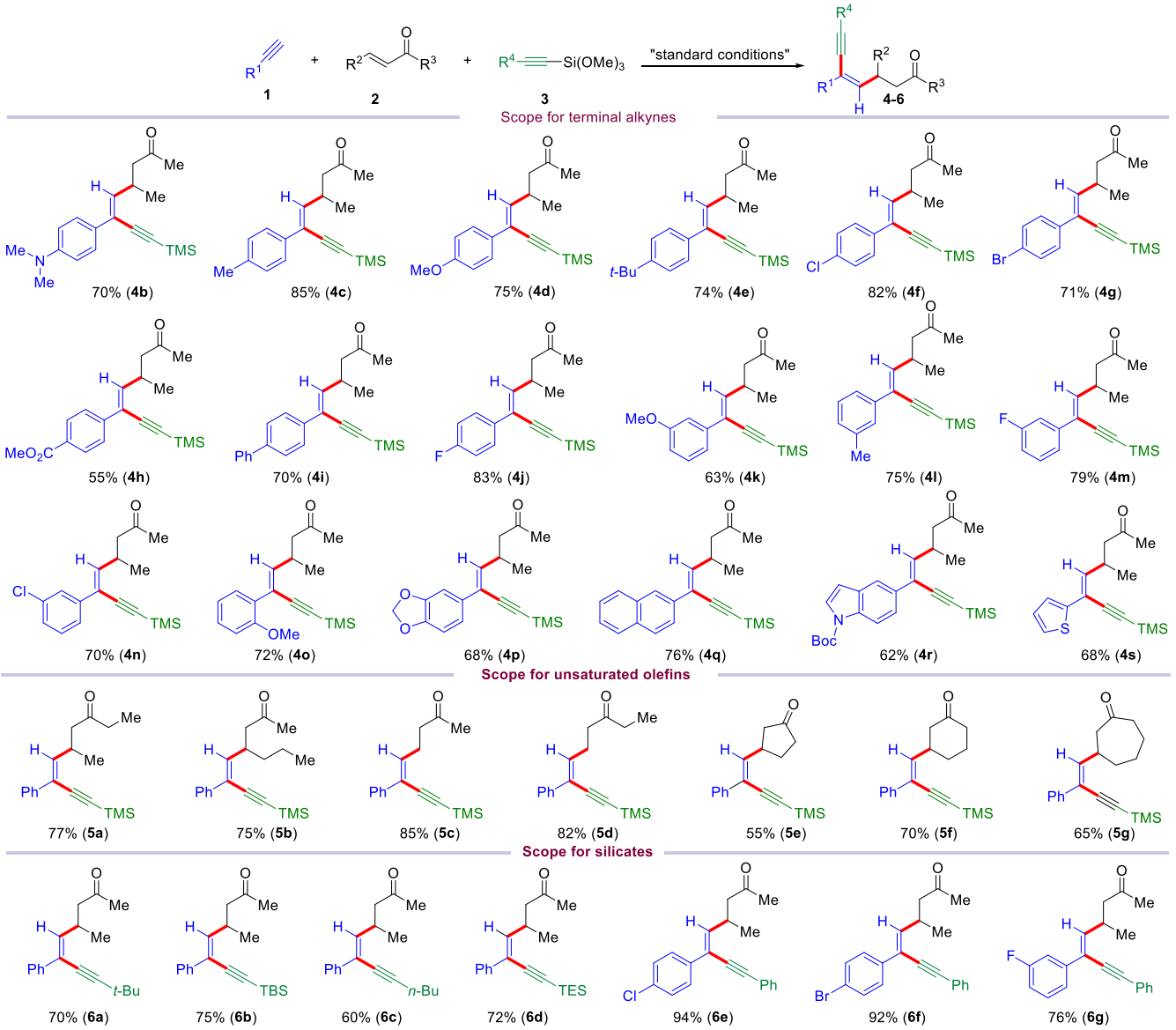

Figure 1. Scope for the stereodefined synthesis of 1,3-enynes from alkynyl silicates. The reaction was run on a 0.2 mmol scale. For detailed reaction conditions, see Table 1 (entry 1). Isolated yield after flash chromatography is shown. TBS = *tert*-butyldimethylsilyl, TES = triethylsilyl.

stereoselectivity control remains challenging, and the homodimerization of terminal alkynes may lead to different regioisomers. It is noteworthy that 2 equiv of alkynes underwent sequential coupling with 1 equiv of enones to give ketone-tethered conjugated 1,3-enynes with good functional group tolerance. Terminal aryl alkynes with electron-donating or electron-withdrawing substituents were all tolerated in this transformation, furnishing a wide range of conjugated 1,3-enynes with *Z*-selectivity in moderate to good yields (**7a**–**7j**). The *Z*-configuration of the product was further confirmed by the NOE of **7b** and X-ray diffraction analysis of **7l**. Cyclic enones with different ring size were all compatible under the reaction conditions, furnishing the desired 1,3-enyne products in synthetic useful yields (**7k** and **7l**). Conjugated enals with diverse α- or β-substitution patterns could be converted to the corresponding aldehydes with conjugated *Z*-enynes (**7m** and **7n**) in 55% and 61% yields, respectively.

To shed light on the mechansim of this reaction, we set up a series of control experiments to probe the reaction mechanism (Figure 3). First, deuterium-labeling experiments for three-component reaction were investigated. Reactions of an alkyne and an enone with an alkynyl silicate in the presence of deuterated methanol under otherwise standard conditions were conducted (Figures 3a and b). The reactions proceeded smoothly to deliver the desired 1,3-dienynes (**8** and **9**) in 68% and 77% yields, respectively. The reaction of a deuterated alkyne, an enone, and an alkynyl silicate in the presence of methanol was conducted to give **10** in 62% yield (Figure 3c). Deuterium was found at the α-position of the carbonyl group in the presence of CD_3OD, while no deuterium was detected at the α-position of the carbonyl group when CH_3OH was used as the additive. Deuterium was detected on alkene when deuterated alkyne was used, while no deuterium was involved on alkenes using regular alkynes. Next, a deuterium-labeling experiment for a two-component reaction was conducted (Figure 3d). The reaction of a deuterated alkyne with an enone delivered the desired product **11** in 88% yield with 95% deuterium incorporation on the alkene moiety and partial deuterium incorporation at the α-proton of the carbonyl group. These results indicated the proton on an alkene moiety

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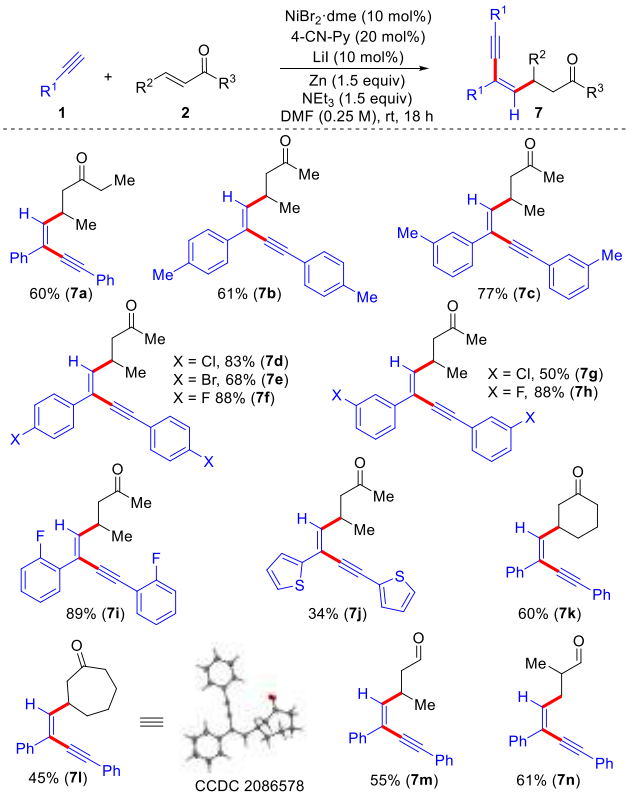

Figure 2. Scope for the stereodefined synthesis of 1,3-enynes from terminal alkynes. The reaction was conducted using alkyne **1** (0.8 mmol) and enone **2** (0.2 mmol) under the indicated conditions.

exclusively originated from the terminal alkyne, and the α-proton of the carbonyl group was exchangeable with the surroundings.

Based on the mechanistic results and the literature,[14] a plausible mechanism of this reaction is depicted in Figure 3e. First, Ni(0) species from Ni(II) by reduction initiated metallacyclic intermediate **A** via cross-oxidative cyclometalation between an alkyne and an enone. C-Bound intermediate **A** could equilibriate with O-bound intermediate **B**. In the presence of a proton source (methanol or terminal alkyne), intermediate **C** was formed via protonation, which could further undergo transmetalation with an alkynyl silcate or a teminal alkyne to give intermediate **D**. In the case of an alkynyl silicate, the formation of a pentavalent silicate intermediate might be essential to transfer the alkynyl group to nickel. In the case of a terminal alkyne, a deprotonated acetylide might directly attack a Ni(II) center. **D** underwent reductive elimination to form the final product along with the Ni(0) intermediate to complete the catalytic cycle.

In summary, an efficient synthesis of conjugated 1,3-enynes via Ni-catalyzed intermolecular cross-coupling reaction between terminal alkynes, α,β-unsaturated carbonyl compounds, and alkynes or alkynyl silicates was reported. The reaction features intermolecular regio- and stereoselective alkylalkynylation of alkyne from easily available and user-friendly starting materials, providing a highly flexible method for introduction of trisubstituted 1,3-enynes to the β-C of carbonyls in exclusive *Z*-selectivity from easily available starting materials.

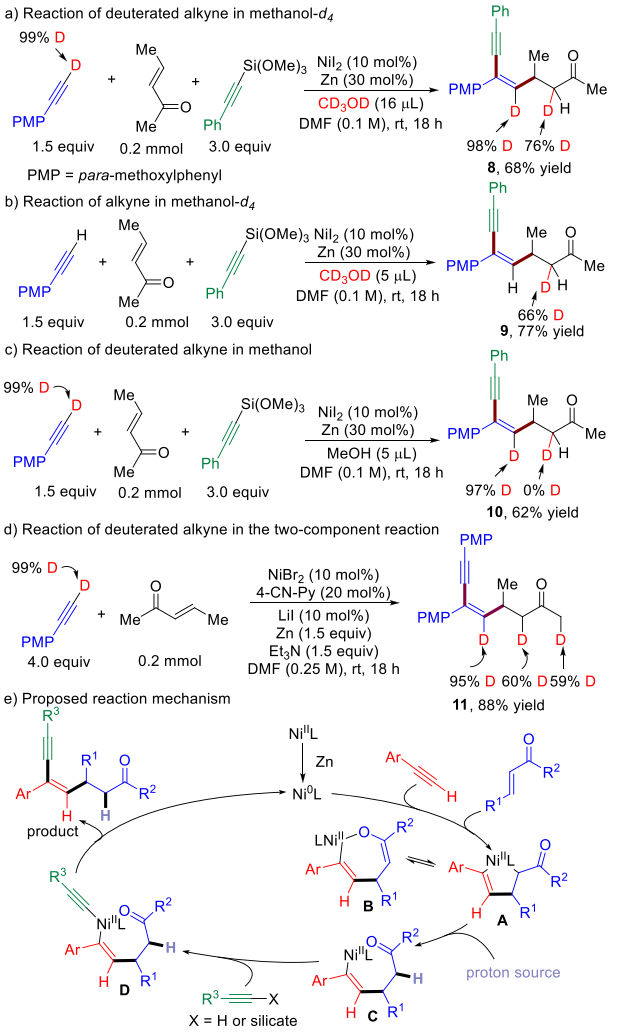

Figure 3. Mechanistic study and proposed mechanism for the reaction.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c01728.

General procedures, characterization of new compounds, and copies of NMR spectra (PDF)

Accession Codes

CCDC 2086578 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

[‖]N.X., Y.-Z.Z., and H.M. contributed equally.

Notes

The authors declare no competing financial interest.

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■ DEDICATION

This paper is dedicated to the memory of Prof. Ei-ichi Negishi.

■ REFERENCES

(1) (a) Rudi, A.; Schleyer, M.; Kashman, Y. Clathculins A and B, Two Novel Nitrogen-Containing Metabolites from the Sponge *Clathrina aff. Reticulum*. *J. Nat. Prod.* **2000**, *63*, 1434−1436. (b) Fontana, A.; D'Ippolito, G.; D'Souza, L.; Mollo, E.; Parameswaram, P. S.; Cimino, G. New Acetogenin Peroxides from the Indian Sponge *Acarnus bicladotylota*. *J. Nat. Prod.* **2001**, *64*, 131−133. (c) Liu, Y.; Nishiura, M.; Wang, Y.; Hou, Z. π-Conjugated Aromatic Enynes as a Single-Emitting Component for White Electroluminescence. *J. Am. Chem. Soc.* **2006**, *128*, 5592−5593. (d) Lan, P.; White, L. E.; Taher, E. S.; Guest, P. E.; Banwell, M. G.; Willis, A. C. Chemoenzymatic Synthesis of (+)-Asperpentyn and the Enantiomer of the Structure Assigned to Aspergillusol A. *J. Nat. Prod.* **2015**, *78*, 1963−1968.

(2) (a) Trost, B. M.; Masters, J. T. Transition Metal-Catalyzed Couplings of Alkynes to 1,3-Enynes: Modern Methods and Synthetic Applications. *Chem. Soc. Rev.* **2016**, *45*, 2212−2238. and references cited therein. (b) Zhu, X.; Deng, W.; Chiou, M.-F.; Ye, C.; Jian, W.; Zeng, Y.; Jiao, Y.; Ge, L.; Li, Y.; Zhang, X.; Bao, H. Copper-Catalyzed Radical 1,4-Difunctionalization of 1,3-Enynes with Alkyl Diacyl Peroxides and *N*-Fluorobenzenesulfonimide. *J. Am. Chem. Soc.* **2019**, *141*, 548−559. (c) Kuang, Z.; Chen, H.; Qiu, J.; Ou, Z.; Lan, Y.; Song, Q. Cu-Catalyzed Regio- and Stereodivergent Chemoselective sp^2/sp^3 1,3- and 1,4-Diborylations of CF_3-Containing 1,3-Enynes. *Chem.* **2020**, *6*, 2347−2363. (d) Dherbassy, D.; Manna, S.; Talbot, F. J. T.; Prasitwatcharakorn, W.; Perry, G. J. P.; Procter, D. J. Copper-Catalyzed Functionalization of Enynes. *Chem. Sci.* **2020**, *11*, 11380−11393. (e) Fu, L.; Greßies, S.; Chen, P.; Liu, G. Recent Advances and Perspectives in Transition Metal-Catalyzed 1,4-Functionalizations of Unactivated 1,3-Enynes for the Synthesis of Allenes. *Chin. J. Chem.* **2020**, *38*, 91−100. (f) Zhou, Y.; Zhou, L.; Jesikiewicz, L. T.; Liu, P.; Buchwald, S. L. Synthesis of Pyrroles through the CuH-Catalyzed Coupling of Enynes and Nitriles. *J. Am. Chem. Soc.* **2020**, *142*, 9908−9914.

(3) Zhou, Y.; Zhang, Y.; Wang, J. Recent Advances in Transition-Metal-Catalyzed Synthesis of Conjugated Enynes. *Org. Biomol. Chem.* **2016**, *14*, 6638−6650.

(4) Wadsworth, W. S., Jr.; Emmons, W. D. The Utility of Phosphonate Carbanions in Olefin Synthesis. *J. Am. Chem. Soc.* **1961**, *83*, 1733−1738.

(5) (a) Miyaura, N.; Yamada, K.; Suginome, H.; Suzuki, A. Novel and Convenient Method for the Stereo- and Regiospecific Synthesis of Conjugated Alkadienes and Alkenynes via the Palladium-Catalyzed Cross-Coupling Reaction of 1-Alkenylboranes with Bromoalkenes and Bromoalkynes. *J. Am. Chem. Soc.* **1985**, *107*, 972−980. (b) Stang, P. J.; Kitamura, T. Novel and Convenient Method for the Stereo- and Regiospecific Synthesis of Conjugated Alkadienes and Alkenynes via the Palladium-Catalyzed Cross-Coupling Reaction of 1-Alkenylboranes with Bromoalkenes and Bromoalkynes. *J. Am. Chem. Soc.* **1987**, *109*, 7561−7563. (c) Sorg, A.; Brückner, R. Total Synthesis of Xerulinic Acid. *Angew. Chem., Int. Ed.* **2004**, *43*, 4523−4526. (d) Bates, C. G.; Saejueng, P.; Venkataraman, D. Copper-Catalyzed Synthesis of 1,3-Enynes. *Org. Lett.* **2004**, *6*, 1441−1444. (e) Doucet, H.; Hierso, J.-C. Palladium-Based Catalytic Systems for the Synthesis of Conjugated Enynes by Sonogashira Reactions and Related Alkynylations. *Angew. Chem., Int. Ed.* **2007**, *46*, 834−871. (f) Liu, F.; Ma, D. Assembly of Conjugated Enynes and Substituted Indoles via CuI/Amino Acid-Catalyzed Coupling of 1-Alkynes with Vinyl Iodides and 2-Bromotrifluoroacetanilides. *J. Org. Chem.* **2007**, *72*, 4844−4850. (g) Hatakeyama, T.; Yoshimoto, Y.; Gabriel, T.; Nakamura, M. Iron-Catalyzed Enyne Cross-Coupling Reaction. *Org. Lett.* **2008**, *10*, 5341−5344.

(6) (a) Ogoshi, S.; Ueta, M.; Oka, M. A.; Kurosawa, H. Dimerization of Terminal Alkynes Catalyzed by a Nickel Complex Having a Bulky Phosphine Ligand. *Chem. Commun.* **2004**, 2732−2733. (b) Suginome, M.; Shirakura, M.; Yamamoto, A. Nickel-Catalyzed Addition of Alkynylboranes to Alkynes. *J. Am. Chem. Soc.* **2006**, *128*, 14438−14439. (c) Tsukada, N.; Ninomiya, S.; Aoyama, Y.; Inoue, Y. Palladium-Catalyzed Selective Cross-Addition of Triisopropylsilylacetylene to Internal and Terminal Unactivated Alkynes. *Org. Lett.* **2007**, *9*, 2919−2921. (d) Xu, H. D.; Zhang, R. W.; Li, X.; Huang, S.; Tang, W.; Hu, W.-H. Rhodium-Catalyzed Chemo- and Regioselective Cross-Dimerization of Two Terminal Alkynes. *Org. Lett.* **2013**, *15*, 840−843. (e) Rivada-Wheelaghan, O.; Chakraborty, S.; Shimon, L. J. W.; Ben-David, Y.; Milstein, D. *Z*-Selective (Cross-)Dimerization of Terminal Alkynes Catalyzed by an Iron Complex. *Angew. Chem., Int. Ed.* **2016**, *55*, 6942−6945. (f) Gorgas, N.; Alves, L. G.; Stöger, B.; Martins, A. M.; Veiros, L. F.; Kirchner, K. Stable, Yet Highly Reactive Nonclassical Iron(II) Polyhydride Pincer Complexes: *Z*-Selective Dimerization and Hydroboration of Terminal Alkynes. *J. Am. Chem. Soc.* **2017**, *139*, 8130−8133. (g) Liang, Q.; Hayashi, K.; Song, D. Catalytic Alkyne Dimerization without Noble Metals. *ACS Catal.* **2020**, *10*, 4895−4905. (h) Ueda, Y.; Tsurugi, H.; Mashima, K. Cobalt-Catalyzed *E*-Selective Cross-Dimerization of Terminal Alkynes: A Mechanism Involving Cobalt(0/II) Redox Cycles. *Angew. Chem., Int. Ed.* **2020**, *59*, 1552−1556.

(7) (a) Nishibayashi, Y.; Shinoda, A.; Miyake, Y.; Matsuzawa, H.; Sato, M. Ruthenium-Catalyzed Propargylic Reduction of Propargylic Alcohols with Silanes. *Angew. Chem., Int. Ed.* **2006**, *45*, 4835−4839. (b) Yan, W.; Ye, X.; Akhmedov, N. G.; Petersen, J. L.; Shi, X. 1,2,3-Triazole: Unique Ligand in Promoting Iron-Catalyzed Propargyl Alcohol Dehydration. *Org. Lett.* **2012**, *14*, 2358−2361. (c) Ye, C.; Qian, B.; Li, Y.; Su, M.; Li, D.; Bao, H. Iron-Catalyzed Dehydrative Alkylation of Propargyl Alcohol with Alkyl Peroxides to Form Substituted 1,3-Enynes. *Org. Lett.* **2018**, *20*, 3202−3205.

(8) (a) Schreib, B. S.; Fadel, M.; Carreira, E. M. Palladium-Catalyzed C-H Alkynylation of Unactivated Alkenes. *Angew. Chem., Int. Ed.* **2020**, *59*, 7818−7822. (b) Cembellín, S.; Dalton, T.; Pinkert, T.; Schäfers, F.; Glorius, F. Highly Selective Synthesis of 1,3-Enynes,

Pyrroles, and Furans by Manganese(I)-Catalyzed C-H Activation. *ACS Catal.* **2020**, *10*, 197−202. (c) Barsu, N.; Leutzsch, M.; Fürstner, A. Ruthenium-Catalyzed *trans*-Hydroalkynylation and *trans*-Chloroalkynylation of Internal Alkynes. *J. Am. Chem. Soc.* **2020**, *142*, 18746−18752.

(9) Wang, N.-N.; Huang, L.-R.; Hao, W.-J.; Zhang, T.-S.; Li, G.; Tu, S.-J.; Jiang, B. Synergistic Rhodium/Copper Catalysis: Synthesis of 1,3-Enynes and N-Aryl Enaminones. *Org. Lett.* **2016**, *18*, 1298−1301.

(10) Lv, Y.; Wang, Y.; Pu, W.; Zhu, X.; Wu, N.; Zhao, Y. Copper-Catalyzed 1,1-Alkynylalkylation of Alkynes: Access toward Conjugated Enynes. *Org. Chem. Front.* **2020**, *7*, 2752−2756.

(11) Che, C.; Zheng, H.; Zhu, G. Copper-Catalyzed *trans*-Carbohalogenation of Terminal Alkynes with Functionalized Tertiary Alkyl Halides. *Org. Lett.* **2015**, *17*, 1617−1620.

(12) Liu, W.; Kong, W. Ni-Catalyzed Stereoselective Difunctionalization of Alkynes. *Org. Chem. Front.* **2020**, *7*, 3941−3955.

(13) Jiang, Y.; Pan, J.; Yang, T.; Zhao, Y.; Koh, M.-J. Nickel-Catalyzed Site- and Stereoselective Reductive Alkylalkynylation of Alkynes. *Chem.* **2021**, *7*, 993−1005.

(14) (a) Ikeda, S.; Sato, Y. Synthesis of Stereodefined Enynes by the Nickel-Catalyzed Coupling Reaction of Alkynyltins, Alkynes, and Enones. *J. Am. Chem. Soc.* **1994**, *116*, 5975−5976. (b) Ikeda, S.; Yamamoto, H.; Kondo, K.; Sato, Y. Nickel-Catalyzed Tandem Coupling of Chlorotrimethylsilane, α,β-Enones, Alkynes, and Dimethylzinc. *Organometallics* **1995**, *14*, 5015−5016. (c) Ikeda, S.; Kondo, K.; Sato, Y. Nickel-Catalyzed Tandem Coupling of α,β-Enones, Alkynes, and Alkynyltins for the Regio- and Stereoselective Synthesis of Conjugated Enynes. *J. Org. Chem.* **1996**, *61*, 8248−8255. (d) Ikeda, S.; Cui, D.-M.; Sato, Y. Nickel-Catalyzed Asymmetric Multiple-Component Tandem Coupling. Effects of Simple Monodentate Oxazolines as Chiral Ligands. *J. Am. Chem. Soc.* **1999**, *121*, 4712−4713. (e) Cui, D.-M.; Yamamoto, H.; Ikeda, S.; Hatano, K.; Sato, Y. Nickel-Catalyzed Diastereodifferentiative Tandem Coupling of α,β-Enones, Norbornenes, and Organometallics. *J. Org. Chem.* **1998**, *63*, 2782−2784.

(15) (a) Zhan, Y.-Z.; Xiao, N.; Shu, W. Ni-Catalyzed Regio- and Stereo-Defined Intermolecular Cross-Electrophile Dialkylation of Alkynes without Directing Group. *Nat. Commun.* **2021**, *12*, 928. (b) Shi, L.; Xing, L.-L.; Hu, W.-B.; Shu, W. Regio- and Enantioselective Ni-Catalyzed Formal Hydroalkylation, Hydrobenzylation and Hydropropargylation of Acrylamides to α-Tertiary Amides. *Angew. Chem., Int. Ed.* **2021**, *60*, 1599−1604. (c) Wang, S.; Zhang, J.-X.; Zhang, T.-Y.; Meng, H.; Chen, B.-H.; Shu, W. Enantioselective Access to Chiral Aliphatic Amines and Alcohols via Ni-Catalyzed Hydroalkylations. *Nat. Commun.* **2021**, *12*, 2771.

(16) For more details on condition optimization, see the Supporting Information.

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