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Tuning of Copper-Catalyzed Multicomponent Reactions toward 3-Functionalized Oxindoles

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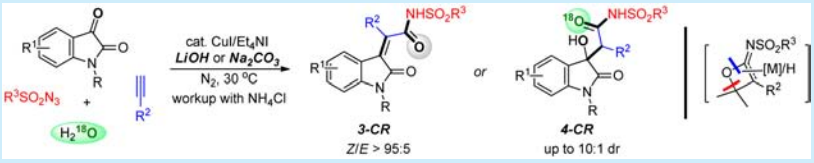
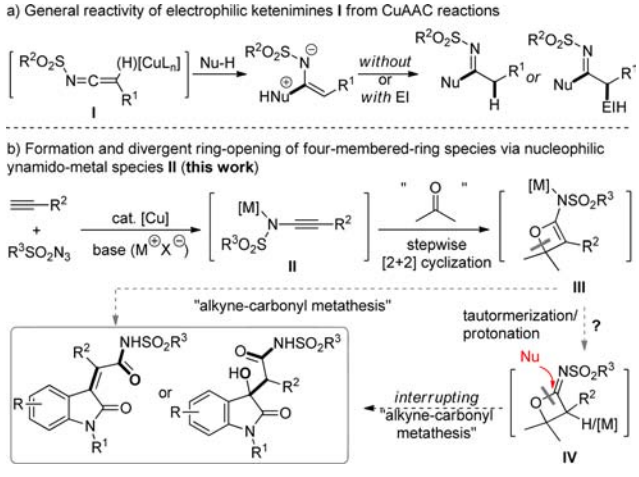
Supporting Information



ABSTRACT: A tunable copper-catalyzed azide−alkyne cycloaddition (CuAAC)-initiated multicomponent reaction strategy for the construction of 3-functionalized indolin-2-ones is reported. Upon controlling the ring opening of four-membered *O*-heterocyclic intermediates, this unique method enables the divergent derivatization of *N*-protected isatins to give three-component (3-CR) and four-component (4-CR) adducts, respectively.

Construction of molecular diversity, especially those involving privileged scaffolds in natural products and biologically active molecules, is of great interest.[1] The rational employment of sulfonyl azide in the CuAAC reaction,[2] pioneered by Chang and co-workers in 2005,[3] has led to the establishment of CuAAC-initiated three-component reactions toward the synthesis of complex molecules via electrophilic ketenimines **I** (Scheme 1a).[4,5] As an alternative to forging electrophilic ketenimine, we have reported a mild and direct access to nucleophilic ynamido-metal intermediates[6] by using stoichiometric inorganic bases in CuAAC reactions.[7] The resulting alkali metal ynamidates **II** proved sufficiently effective to accomplish a formal alkyne−carbonyl metathesis[8,9] with aldehydes that yielded (*E*)-*N*-sulfonylacrylamides[7a−c] probably through the intermediacy of an oxetene intermediates **III**. Based on these results, we have envisioned that the oxetene species **III** might be capable of converting to oxetane **IV** via tautormerization or protonation, as a result, providing extra potentiality in generating versatile molecules upon the subsequent transformation of species **IV** (Scheme 1b).

Scheme 1. Copper-Catalyzed Multicomponent Reactions of Ketenimines I or Ynamidates II



Unfortunately, whereas oxetanes constitute versatile elements in drug discovery and organic synthesis,[10] the construction and evolution of α-iminooxetanes, particularly of those bearing an electron-withdrawing group at the nitrogen atom, has rarely been accomplished.[11] Furthermore, to the best our knowledge, the nucleophilic ring-opening reaction of 2-sulfonyliminooxetanes remains uncovered despite the apparent merits in greatly expanding the diversity of products.[12] Herein, we wish to present our preliminary results on a tunable base-mediated CuAAC-triggered multicomponent strategy for the divergent derivatization of isatins,[13] resulting in the formation of two sorts of 3-functionalized oxindole compounds. Notably, both oxindole[14] and acylsulfonamide[15] are privileged scaffolds in natural products and biologically active molecules.

The reaction of isatin **1a**, ethynylbenzene (**2a**), and tosyl azide (**3a**) was initially investigated in the presence of CuI (10 mol %), Et_4NI (10 mol %), and a base (1.2 equiv) in anhydrous CH_2Cl_2 at 30 °C under N_2 (Table 1). To our delight, (*Z*)-3-alkenyloxindole **4a** was afforded in 77% yield with high *Z*-selectivity by using LiOH as the base (Table 1, entry 1) because the stereoselective construction of tetrasubstituted alkenes remains a challenging task in organic synthesis by classical carbonyl olefination.[16] While a relative low yield of **4a** was found using Cs_2CO_3 or K_2CO_3 instead, some tertiary amines like DBU and Et_3N turned out to be completely ineffective in

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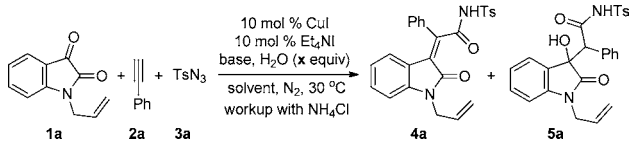
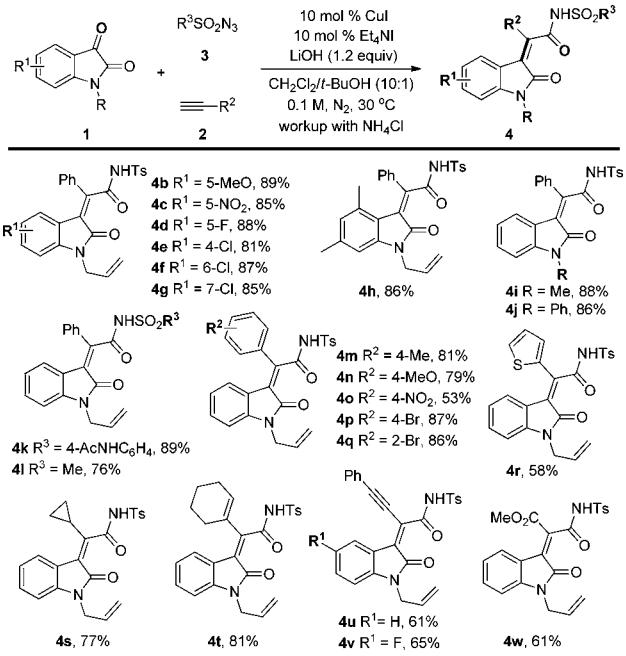
Table 1. Optimization of Reaction Conditions[a]



entry	base	solvent	H_2O (equiv)	yield **4a**/**5a**[b] (%)
1	LiOH	CH_2Cl_2		77/–
2	Cs_2CO_3	CH_2Cl_2		66/–
3	K_2CO_3	CH_2Cl_2		61/–
4[c]	DBU	CH_2Cl_2		<3/–
5[c]	Et_3N	CH_2Cl_2		<3/–
6	LiOH	DCE		68/–
7	LiOH	THF		56/–
8	LiOH	CH_3CN		17/–
9	LiOH	CH_2Cl_2:*t*-BuOH[d]		92/–
10	LiOH	CH_2Cl_2:*t*-BuOH[d]	10	76/5
11	LiOH	THF	10	65/5
12	LiOH	DMF	10	62/11
13	K_3PO_4	DMF	10	18/45
14	Na_2CO_3	DMF	10	31/51
15	NaOAc	DMF	10	29/38
16	Na_2CO_3	DMF	30	<3/72
17	Na_2CO_3	DMF	60	16/56
18[e]	DBU	DMF	10	–/–

[a]Unless otherwise noted, the reactions were carried out on a 0.3 mmol scale of **1a** with **2a** (0.45 mmol), **3a** (0.45 mmol), base (1.2 equiv), CuI (0.03 mmol), and Et_4NI (0.03 mmol) in anhydrous solvent (3.0 mL) under N_2 at 30 °C; quenched by saturated aqueous NH_4Cl. [b]Isolated yield. [c]50% of **1a** was recovered. [d]v/v = 10:1. [e]**1a** was recovered in 80% yield.

Scheme 2. Substrate Scopes in the Synthesis of 4[a]



[a]Reaction conditions: **1** (0.3 mmol), **2** (0.45 mmol), **3** (0.45 mmol), CuI (0.03 mmol), Et_4NI (0.03 mmol), and LiOH (0.36 mmol) in CH_2Cl_2/*t*-BuOH (v/v = 10:1) under N_2 at 30 °C; quenched by saturated aqueous NH_4Cl. The yields are of the isolated products. For all products **4**, *Z*/*E* > 95:5 of newly formed C=C bond, detected by the ^1H NMR spectra.

yielding the targeted product (Table 1, entries 2–5). It was found that solvent had a dramatic effect on reaction outcomes. When CH_2Cl_2 was switched to DCE or THF, respectively, alkene **4a** was isolated in 68% and 56% yield; however, acetonitrile led to a sharply decreasing yield (Table 1, entries 6–8). Among those solvents examined, a mixed solvent of CH_2Cl_2/*t*-BuOH (10:1) proved to be optimal and gave **4a** in 92% yield (Table 1, entry 9). On the other hand, when 10 equiv of H_2O was added to the reaction mixture, a four-component adduct **5a** (5%) was isolated besides **4a**, and a slight increase in the yield of **5a** was achieved in DMF (Table 1, entries 11 and 12). Given the possible effect of their basicity as well as the oxophilicity and coordination ability of alkali metal cations,[17] we tested a set of alkali metal salts in DMF to improve the reaction selectivity to **5a** (Table 1, entries 13–17). It appeared that not only the base used but the amount of H_2O was critical to selectively completing this conversion. The use of Na_2CO_3 and 30 equiv of H_2O enabled the formation of **5a** in 72% yield (dr = 1:8), along with less than 3% of **4a**; while further increasing the amount of H_2O to 60 equiv resulted in a reduced yield (entries 16 versus 17). Nevertheless, DBU still could not afford any desired products, and the substrate **1a** was recovered in 80% yield after 6 h (Table 1, entry 18).

The substrate scopes of the reaction to 3-alkenyloxindoles **4** were investigated (Scheme 2). A variety of *N*-protected isatins **1** carrying different substitution partners at the benzene moiety or the nitrogen atom all reacted with ethynylbenzene (**2a**) and tosyl azide (**3a**) efficiently, giving the corresponding products **4b–j** in high yield. Installation of a protecting group at the nitrogen atom of isatins appeared indispensable to this transformation; otherwise, no any desired products **4** were detected. Variation of sulfonyl azides **3** (R^3 = 4-$AcNHC_6H_4$ and Me) was also tolerated to form the desired **4k** and **4l** in 89 and 76% yield, respectively. Next, a set of terminal alkynes **2** was examined for this formal metathesis reaction. Aryl acetylenes bearing both electron-donating (–OMe and –Me) and electron-withdrawing ($-NO_2$) groups as well as a bromine atom at either the *para* or *ortho* position of the benzene ring achieved the reaction easily, delivering products **4m–q** with consistently high stereoselectivities. However, 1-ethynyl-4-nitrobenzene was found to be less efficient and gave **4o** in lower yield, probably due to the poor nucleophilicity of related ynamido metal intermediates. 2-Ethynylthiophene was also a tolerable substrate, leading to the formation of **4r** (58%). In addition, these reaction conditions were completely compatible with various aliphatic alkynes like alkyl-, alkenyl-, and alkynyl-substituted substrates and produced tetrasubstituted alkenes **4s–v** in good yields. Pleasingly, methyl propiolate could also be employed in this reaction to construct **4w** with a retained ester group.

Next, the substrate scopes for the synthesis of oxindoles **5** were examined (Scheme 3). Whereas nonprotected isatins (R = H) could not conduct this reaction, variation of the substituent at the nitrogen atom of isatins **1** was tolerable to give oxindoles **5a–c**. A set of available 1-allylindoline-2,3-diones **1** underwent this reaction smoothly, delivering the targeted products **5d–f** in reasonable good yields. The scope of terminal alkynes **2** was also examined. Aryl alkynes bearing electron-donating groups (–OMe and –NHAc) and a fluorine atom performed this reaction readily, affording **5g–k** in 52–77% yields. Whereas this reaction proceeded with varying dr values,[18] some positive effect of steric hindrance arising from the alkyne component

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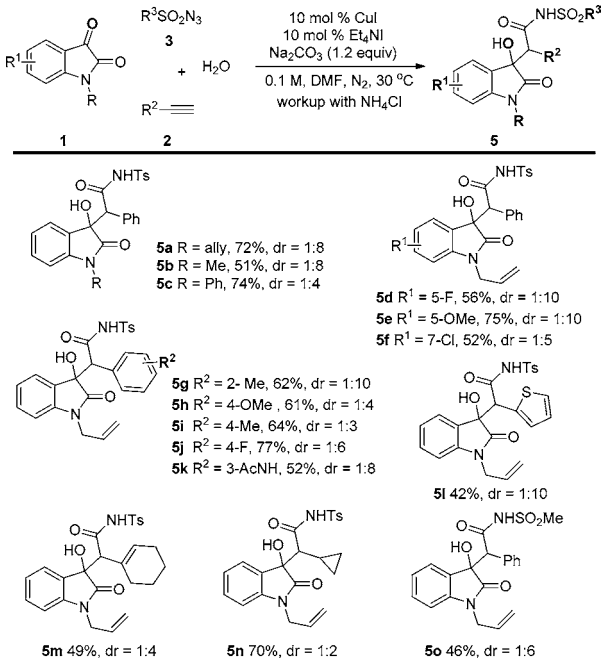
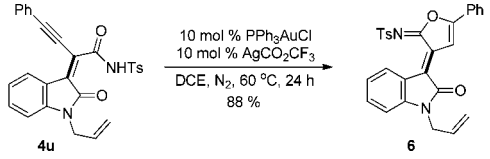
Scheme 3. Substrate Scopes in the Synthesis of 5[a]



[a]Reaction conditions: **1** (0.3 mmol), **2** (0.45 mmol), **3** (0.45 mmol), CuI (0.03 mmol), Et_4NI (0.03 mmol), H_2O (9 mmol) and Na_2CO_3 (0.36 mmol) in anhydrous DMF under N_2 at 30 °C; quenched by aqueous NH_4Cl. The yields are of the isolated products. The dr values were determined by ^1H NMR spectra. The phenyl and hydroxyl groups of the major diastereoisomer of **5a** were arranged in an *anti*-configuration according to X-ray crystallographic analysis.

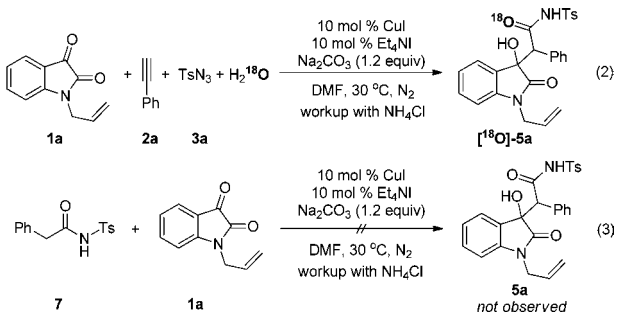
(R^2) was found. While 1-ethynyl-2-methylbenzene gave **5g** in 62% with a good dr value (1:10), the 4-methyl counterpart furnished **5i** in a similar yield but with poor diastereoselectivity (dr = 1:3). Unfortunately, a strongly electron-deficient alkyne ($R^2 = NO_2$) only forged some *N*-tosylacetamide compounds deriving from the coupling of alkyne, sulfonyl azide, and H_2O,[5c,d] and the isatin substrate was recovered in 80% yield. This result demonstrated the differentiating reactivity of the corresponding intermediates rendered by Na_2CO_3 or LiOH, respectively. Pleasingly, 2-thienyl-substituted acetylene and aliphatic terminal alkynes could be used to assemble the desired products **5l–m**; switching tosyl azide to methanesulfonyl azide formed **5o**, albeit in lower yield compared with the tosyl product **5a**.

The (*Z*)-3-alkenyloxindoles **4** represented a useful platform for further manipulations.[18] Treated by $PPh_3AuCl/AgCO_2CF_3$, the cycloisomerization of **4u** proceeded smoothly along with the *E*/*Z* configuration interconversion of the enyne scaffold, giving furan **6**, an analogue of isoindigo,[19] in 88% yield (eq 1).



(1)

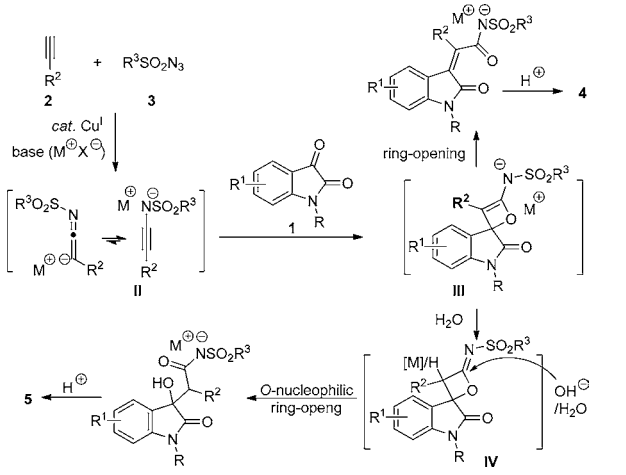
While subjecting oxindole **5a** to $H_2{}^{18}O$ (30 equiv) under standard conditions did not give obvious ^{18}O-labeled products, the reaction in the presence of $H_2{}^{18}O$ led to [^{18}O]-**5a** as detected by HRMS (eq 2). These isotopic-labeling results clearly indicated that the oxygen atom in the newly created



carbonyl group of **5a** is from H_2O. Furthermore, the exposure of 2-phenyl-*N*-tosylacetamide (**7**) and isatin **1a** to the standard conditions could not yield any detectable **5a**, thus excluding imide **7** or its conjugated base as the possible intermediate for the synthesis of oxindole **5** (eq 3).

A proposed reaction pathway is depicted in Scheme 4. Initial CuI-catalyzed reaction of terminal alkyne **2** and azide **3** in the

Scheme 4. Proposed Reaction Pathway



presence of stoichiometric amounts of inorganic base forges metal ynamidate **II**, which undergoes stepwise cyclization with isatin **1** to form [2 + 2] cycloadduct **III**. When LiOH was used as the base, the torquoselective electrocyclic ring opening of oxetene **III** followed by acidification afforded alkene product **4**. On the other hand, Na_2CO_3 allowed the conversion of **III** to oxetane species **IV** via tautomerization or a protonation sequence. A subsequent *O*-nucleophilic ring-opening cascade of **IV** triggered by the attack of hydroxide ion or water at the imidate group gave 3-hydroxyindole **5**.

In summary, we have developed a new, flexible protocol for the construction of 3-functionalized oxindoles from accessible isatins by a distinct CuAAC-initiated multicomponent reaction strategy. This tandem process can be manipulated to proceed in three-component and four-component fashion, respectively, yielding a range of (*Z*)-3-alkenyloxindole or 3-substituted 3-hydroxyoxindole compounds. Investigations aimed at exploring the synthetic application of this method as well as the detailed mechanism are currently underway.

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■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00964.

Experimental procedures and characterization data of new compounds (PDF)

X-ray crystallographic data of products **4d**, **4u**, **5a-major**, and **6** (CIF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) For selected reviews, see: (a) Costantino, L.; Barlocco, D. *Curr. Med. Chem.* **2006**, *13*, 65. (b) Welsch, M. E.; Snyder, S. A.; Stockwell, B. R. *Curr. Opin. Chem. Biol.* **2010**, *14*, 347.

(2) (a) Rostovtsev, V. V.; Green, L. G.; Fokin, V. V.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2002**, *41*, 2596. (b) Tornøe, C. W.; Christensen, C.; Meldal, M. *J. Org. Chem.* **2002**, *67*, 3057. For a review, see: (c) Meldal, M.; Tornøe, C. W. *Chem. Rev.* **2008**, *108*, 2952.

(3) Bae, I.; Han, H.; Chang, S. *J. Am. Chem. Soc.* **2005**, *127*, 2038.

(4) For recent reviews on multicomponent reactions, see: (a) Dömling, A.; Wang, W.; Wang, K. *Chem. Rev.* **2012**, *112*, 3083. (b) de Graaff, C.; Ruijter, E.; Orru, R. V. A. *Chem. Soc. Rev.* **2012**, *41*, 3969. (c) Rotstein, B. H.; Zaretsky, S.; Rai, V.; Yudin, A. K. *Chem. Rev.* **2014**, *114*, 8323.

(5) For reviews, see: (a) Kim, S. H.; Park, S. H.; Choi, J. H.; Chang, S. *Chem. - Asian J.* **2011**, *6*, 2618. (b) Lu, P.; Wang, Y. G. *Chem. Soc. Rev.* **2012**, *41*, 5687. For selected examples, see: (c) Cho, S. H.; Yoo, E. J.; Bae, I.; Chang, S. *J. Am. Chem. Soc.* **2005**, *127*, 16046. (d) Cassidy, M.; Raushel, J.; Fokin, V. V. *Angew. Chem., Int. Ed.* **2006**, *45*, 3154. (e) Cui, S.-L.; Lin, X.-F.; Wang, Y.-G. *Org. Lett.* **2006**, *8*, 4517. (f) Cui, S.-L.; Wang, J.; Wang, Y.-G. *Org. Lett.* **2007**, *9*, 5023. (g) Yoo, E. J.; Park, S. H.; Lee, S. H.; Chang, S. *Org. Lett.* **2009**, *11*, 1155. (h) Cano, I.; Álvarez, E.; Nicasio, M. C.; Pérez, P. J. *J. Am. Chem. Soc.* **2011**, *133*, 191. (i) Chen, Z.; Zheng, D.; Wu, J. *Org. Lett.* **2011**, *13*, 848. (j) Li, B.-S.; Yang, B.-M.; Wang, S.-H.; Zhang, Y.-Q.; Cao, X.-P.; Tu, Y.-Q. *Chem. Sci.* **2012**, *3*, 1975. (k) Lee, I.-H.; Kim, H.; Choi, T.-L. *J. Am. Chem. Soc.* **2013**, *135*, 3760. (l) Xu, H.-D.; Jia, Z.-H.; Xu, K.; Han, M.; Jiang, S.-N; Cao, J.; Wang, J.-C.; Shen, M.-H. *Angew. Chem., Int. Ed.* **2014**, *53*, 9284. (m) Kiran Kumar, Y. K.; Ranjith Kumar, G. R.; Sridhar Reddy, M. S. *J. Org. Chem.* **2014**, *79*, 823.

(6) Fokin first reported the generation of lithium ynamidates from isolated 1-sulfonyl-4-phenyltriazole by *n*-BuLi; see: (a) Whiting, M.; Fokin, V. V. *Angew. Chem., Int. Ed.* **2006**, *45*, 3157. For leading examples, see: (b) Raap, R. *Can. J. Chem.* **1971**, *49*, 1792. (c) Sung, K. *J. Chem. Soc., Perkin Trans. 2* **1999**, 1169. For a recent formation of ynamidates by Me_2Zn, see: (d) Hu, Y.; Zhou, B.; Wang, C. *Org. Biomol. Chem.* **2016**, *14*, 3022. For reviews on ynamide chemistry, see: (e) DeKorver, K. A.; Li, H.; Lohse, A. G.; Hayashi, R.; Lu, Z.; Zhang, Y.; Hsung, R. P. *Chem. Rev.* **2010**, *110*, 5064. (f) Evano, G.; Coste, A.; Jouvin, K. *Angew. Chem., Int. Ed.* **2010**, *49*, 2840.

(7) (a) Cheng, D.; Ling, F.; Li, Z.; Yao, W.; Ma, C. *Org. Lett.* **2012**, *14*, 3146. (b) Li, Z.; Ling, F.; Cheng, D.; Ma, C. *Org. Lett.* **2014**, *16*, 1822. (c) Wu, J.; Wang, D.; Wan, Y.; Ma, C. *Chem. Commun.* **2016**, *52*, 1661. For our related work, see: (d) Yao, W.; Pan, L.; Zhang, Y.; Wang, G.; Wang, X.; Ma, C. *Angew. Chem., Int. Ed.* **2010**, *49*, 9210. (e) Yan, X.; Ling, F.; Zhang, Y.; Ma, C. *Org. Lett.* **2015**, *17*, 3536.

(8) For leading examples, see: (a) Harding, C. E.; Hanack, M. *Tetrahedron Lett.* **1971**, *12*, 1253. (b) Balf, R. J.; Rao, B.; Weiler, L. *Can. J. Chem.* **1971**, *49*, 3135.

(9) Heteroatom-substituted alkyne−carbonyl metathesis: for ynolates, see: (a) Shindo, M. *Tetrahedron* **2007**, *63*, 10. (b) Shindo, M.; Sato, Y.; Shishido, K. *Tetrahedron Lett.* **1998**, *39*, 4857. (c) Shindo, M.; Sato, Y.; Yoshikawa, T.; Koretsune, R.; Shishido, K. *J. Org. Chem.* **2004**, *69*, 3912. For Lewis acid/transition-metal-mediated reaction of *N*-substituted ynamides, see: (d) Hsung, R. P.; Zificsak, C. A.; Wei, L.-L.; Douglas, C. J.; Xiong, H.; Mulder, J. A. *Org. Lett.* **1999**, *1*, 1237. (e) Kurtz, K. C. M.; Hsung, R. P.; Zhang, Y. *Org. Lett.* **2006**, *8*, 231. (f) You, L.; Al-Rashid, Z. F.; Figueroa, R.; Ghosh, S. K.; Li, G.; Lu, T.; Hsung, R. P. *Synlett* **2007**, *2007*, 1656. (g) Aikawa, K.; Hioki, Y.; Shimizu, N.; Mikami, K. *J. Am. Chem. Soc.* **2011**, *133*, 20092.

(10) For reviews, see: (a) Burkhard, J. A.; Wuitschik, G.; Rogers-Evans, M.; Müller, K.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2010**, *49*, 9052. (b) Carreira, E. M.; Fessard, T. C. *Chem. Rev.* **2014**, *114*, 8257.

(11) Chi reported an elegant (*Z*)-olefination of isatins using aliphatic alkynes and azides by a copper/NHC relay catalysis strategy via the formation and spontaneous conversion of oxetane species, see: Namitharan, K.; Zhu, T.; Cheng, J.; Zheng, P.; Li, X.; Yang, S.; Song, B.-A.; Chi, Y. R. *Nat. Commun.* **2014**, *5*, 3982.

(12) For *N*-alkyl/aryl-substituted 2-iminooxetanes, see: (a) Barbaro, G.; Battaglia, A.; Giorgianni, P. *J. Org. Chem.* **1992**, *57*, 5128. (b) Barbaro, G.; Battaglia, A.; Giorgianni, P. *J. Org. Chem.* **1994**, *59*, 906. (c) Barbaro, G.; Battaglia, A.; Giorgianni, P. *J. Org. Chem.* **1995**, *60*, 1020.

(13) For selected reviews, see: (a) Singh, G. S.; Desta, Z. Y. *Chem. Rev.* **2012**, *112*, 6104. (b) Zhou, F.; Liu, Y.-L.; Zhou, J. *Adv. Synth. Catal.* **2010**, *352*, 1381. For selected examples, see: (c) Guo, X.; Huang, H.; Yang, L.; Hu, W. *Org. Lett.* **2007**, *9*, 4721. (d) Jing, C.; Shi, T.; Xing, D.; Guo, X.; Hu, W. *Green Chem.* **2013**, *15*, 620. (e) Jiang, B.; Tu, X.-J.; Wang, X.; Tu, S.-J.; Li, G. *Org. Lett.* **2014**, *16*, 3656. (f) Horwitz, M. A.; Tanaka, N.; Yokosaka, T.; Uraguchi, D.; Johnson, J. S.; Ooi, T. *Chem. Sci.* **2015**, *6*, 6086. (g) Wang, X.-N.; Zhang, Y.-Y.; Ye, S. *Adv. Synth. Catal.* **2010**, *352*, 1892. (h) Liu, Y.-L.; Wang, B.-L.; Cao, J.-J.; Chen, L.; Zhang, Y.-X.; Wang, C.; Zhou, J. *J. Am. Chem. Soc.* **2010**, *132*, 15176. (i) Zheng, K.; Yin, C.; Liu, X.; Lin, L.; Feng, X. *Angew. Chem., Int. Ed.* **2011**, *50*, 2573. (j) Zhu, B.; Zhang, W.; Lee, R.; Han, Z.; Yang, W.; Tan, D.; Huang, K.-W.; Jiang, Z. *Angew. Chem., Int. Ed.* **2013**, *52*, 6666.

(14) For selected reviews, see: (a) Dalpozzo, R.; Bartoli, G.; Bencivenni, G. *Chem. Soc. Rev.* **2012**, *41*, 7247. (b) Millemaggi, A.; Taylor, R. J. K. *Eur. J. Org. Chem.* **2010**, *2010*, 4527. (c) Peddibhotla, S. *Curr. Bioact. Compd.* **2009**, *5*, 20. (d) Mohammadi, S.; Heiran, R.; Herrera, R. P.; Marqués-López, E. *ChemCatChem* **2013**, *5*, 2131.

(15) For recent examples, see: (a) Asaki, T.; Kuwano, K.; Morrison, K.; Gatfield, J.; Hamamoto, T.; Clozel, M. *J. Med. Chem.* **2015**, *58*, 7128. (b) Pelz, N. F.; Bian, Z.; Zhao, B.; Shaw, S.; Tarr, J. C.; Belmar, J.; Gregg, C.; Camper, D. V.; Goodwin, C. M.; Arnold, A. L.; Sensintaffar, J. L.; Friberg, A.; Rossanese, O. W.; Lee, T.; Olejniczak, E. T.; Fesik, S. W. *J. Med. Chem.* **2016**, *59*, 2054. (c) Mizuhara, T.; Saha, K.; Moyano, D. F.; Kim, C. S.; Yan, B.; Kim, Y.-K.; Rotello, V. M. *Angew. Chem., Int. Ed.* **2015**, *54*, 6567.

(16) (a) *Modern Carbonyl Olefination: Methods and Applications*; Takeshi, T., Ed.; Wiley−VCH: Weinheim, 2004. For selected reviews, see:. (b) Flynn, A. B.; Ogilvie, W. W. *Chem. Rev.* **2007**, *107*, 4698. (c) Negishi, E.; Huang, Z.; Wang, G.; Mohan, S.; Wang, C.; Hattori, H. *Acc. Chem. Res.* **2008**, *41*, 1474.

(17) (a) Fromm, K. M. *Coord. Chem. Rev.* **2008**, *252*, 856. (b) Gokel, G. W.; Daschbach, M. M. *Coord. Chem. Rev.* **2008**, *252*, 886. (c) Dugal-Tessier, J.; O'Bryan, E. A.; Schroeder, T. B. H.; Cohen, D. T.; Scheidt, K. A. *Angew. Chem., Int. Ed.* **2012**, *51*, 4963.

(18) D'Souza, D. M.; Rominger, F.; Müller, T. J. J. *Angew. Chem., Int. Ed.* **2005**, *44*, 153.

(19) (a) Wrede, R. *Hoppe-Seyler's Z. Physiol. Chem.* **1934**, *223*, 113. (b) Strong, F. M. *Science* **1944**, *100*, 287.

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