Multicomponent Reactions

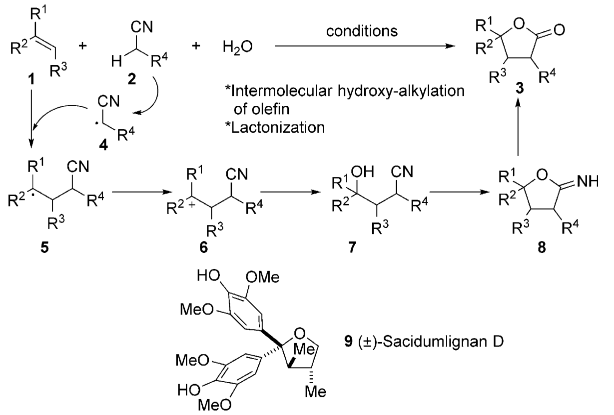
International Edition: DOI: 10.1002/anie.201604528
German Edition: DOI: 10.1002/ange.201604528

Copper-Catalyzed Formal [2+2+1] Heteroannulation of Alkenes, Alkylnitriles, and Water: Method Development and Application to a Total Synthesis of (±)-Sacidumlignan D

*Tu M. Ha, Claire Chatalova-Sazepin, Qian Wang, and Jieping Zhu**

Abstract: *A copper-catalyzed three-component reaction of alkenes, alkylnitriles, and water affords γ-butyrolactones in good yields. The domino process involves an unprecedented hydroxy-cyanoalkylation of alkenes and subsequent lactonization with the creation of three chemical bonds and a quaternary carbon center. The synthetic potential of this novel [2+2+1] heteroannulation reaction was illustrated by a concise total synthesis of (±)-sacidumlignan D.*

Copper-catalyzed difunctionalization of unactivated alkenes involving a C−C and a C−X bond formation is one of the most attractive transformations in organic chemistry. Although copper-mediated and copper-catalyzed carboamidation,[1] carbooxygenation,[2] carboboration,[3] and other difunctionalization reactions of alkenes have been intensively investigated,[4] most of them involve the intramolecular formation of a C(sp^2)−C(sp^3) bond using substrates in which one of the reaction partners is tethered to the alkene. The copper-catalyzed intermolecular carbooxygenation of alkenes are limited mainly to those reactions initiated by aryl radicals[5] and the CF_3 radical.[6,7] In this regard, one notable and important exception involving the formation of a C(sp^3)−C(sp^3) bond is the manganese(III) acetate mediated annulation of olefins with acetic acid, thus leading to γ-butyrolactones [2.0 equiv of $Mn(OAc)_3$ in refluxing acetic acid].[8] γ-Butyrolactone is an important core structure found in many biologically active natural products[9] and is also a useful synthetic building block.[10] It is therefore not surprising that many different strategies have been developed for the efficient synthesis of this heterocycle. For example, Jiang and co-workers have recently reported a copper-catalyzed formal [3+2] heteroannulation of terminal alkenes with acetic anhydride for the synthesis of γ-butyrolactones.[11,12]



Scheme 1. Difunctionalization of alkenes to γ-butyrolactones: A copper-catalyzed three-component reaction of alkenes, alkylnitriles, and water.

Our group has recently initiated a research program aimed at developing copper-catalyzed alkylative difunctionalization of alkenes using alkylnitriles as a key reactant.[13–15] As a continuation of this project, we became interested in developing a novel synthesis of γ-lactones (**3**) by a copper-catalyzed three-component [2+2+1] heteroannulation of alkenes (**1**), alkylnitriles (**2**), and water (Scheme 1). The underlying principle is outlined in Scheme 1. Addition of the in situ generated α-cyanoalkyl radical **4** to an alkene **1** would afford the adduct radical **5**, which could be further oxidized to the carbenium ion **6**.[16] Trapping of the latter by water would afford the γ-hydroxy alkylnitrile **7**, which, upon intramolecular cyclization, would provide the cyclic imidate **8**. Acidic work-up would then convert **8** into the γ-butyrolactone **3**. For the desired domino sequence to proceed towards the formation of **3**, the catalytic conditions should satisfy the following mechanistic criteria: a) selective generation of **4**, which adds rapidly to the double bond of **1**, b) fast oxidation of the resulting nucleophilic radical **5** to **6** to avoid the dimerization of the former, c) rapid addition of water to **6** to avoid its cationic polymerization with the remaining alkene, and d) proper activation of the cyano group to accelerate the lactonization process. The realization of this synthetic scheme and its application to the total synthesis of (±)-sacidumlignan D (**9**)[17] is reported herein.

Using α-methyl styrene (**1a**) and acetonitrile (**2a**) as test substrates, the reaction conditions were surveyed by varying the copper sources, the ligands, the oxidants, the bases, and the additives (for details, see the Supporting Information). Preliminary results indicated that the reaction can indeed take place, thus providing, after acidic treatment (1.0 N HCl, 80 °C), the lactone **3a** in 60 % yield (NMR; Table 1, entry 1). Since the intermediate **7a** ($R^1 = Ph$, $R^2 = Me$, $R^3 = R^4 = H$; Scheme 1) was detected before the acidic treatment, various Lewis acids were tested to accelerate the lactonization step.

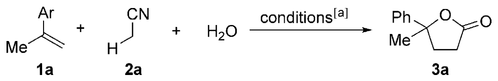
---

[*] T. M. Ha, Dr. C. Chatalova-Sazepin, Dr. Q. Wang, Prof. Dr. J. Zhu
Laboratory of Synthesis and Natural Products
Institute of Chemical Sciences and Engineering
Ecole Polytechnique Fédérale de Lausanne
EPFL-SB-ISIC-LSPN, BCH 5304, 1015 Lausanne (Switzerland)
E-mail: jieping.zhu@epfl.ch
Homepage: http://lspn.epfl.ch

Dr. C. Chatalova-Sazepin
Visiting Ph.D. student from Department of Chemistry, University of British Columbia (Canada)

Supporting information for this article can be found under: http://dx.doi.org/10.1002/anie.201604528.

Table 1: Copper-catalyzed formal [2+2+1] annulation of **1a**, **2a**, and water to **3a**: optimization of reaction conditions.

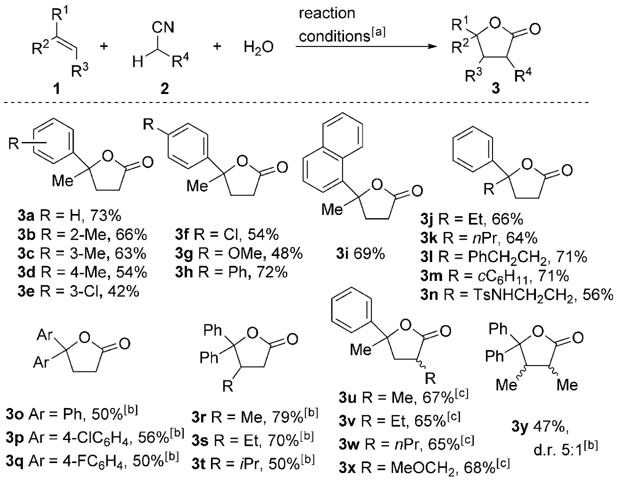


Entry	Base (equiv)	Lewis acid (equiv)	Yield [%][b]
1	K_3PO_4 (0.1)	none	60
2	K_3PO_4 (0.1)	$In(OTf)_3$ (0.2)	66
3	K_3PO_4 (0.1)	$Yb(OTf)_3$ (0.2)	69
4	K_3PO_4 (0.1)	$Mg(OTf)_2$ (0.2)	68
5	K_3PO_4 (0.1)	$Ca(ClO_4)_2$ (0.2)	65
6	K_3PO_4 (0.1)	$Mg(ClO_4)_2$ (0.2)	79
7	K_3PO_4 (0.1)	$Zn(OTf)_2$ (0.2)	75
8	K_3PO_4 (0.1)	$Ca(OTf)_2$ (0.2)	81 (69)[c]
9	K_3PO_4 (0.2)	$Ca(OTf)_2$ (0.2)	74
10	Na_3PO_4 (0.2)	$Ca(OTf)_2$ (0.2)	75
11	KO*t*Bu (0.1)	$Ca(OTf)_2$ (0.2)	56
12	LiO*t*Bu (0.1)	$Ca(OTf)_2$ (0.2)	54
13	DBU (0.15)	$Ca(OTf)_2$ (0.2)	89 (73)[c]
14	DBN (0.15)	$Ca(OTf)_2$ (0.2)	79
15	*N*-methylimidazole (0.15)	$Ca(OTf)_2$ (0.2)	79
16	2,6-lutidine (0.15)	$Ca(OTf)_2$ (0.2)	56

[a] Reaction was performed in a sealed tube: **1a** (0.1 mmol), $Cu(BF_4)_2 \cdot 6H_2O$ (0.2 equiv), H_2O (30 equiv), Bipy (0.6 equiv), DTBP (4.0 equiv), base and Lewis acid in MeCN (0.025 M), N_2 atmosphere, 140 °C, 3.5 h, then 1.0 N HCl, 80 °C, 45 min. [b] Yield was determined by ^1H NMR spectroscopy with CH_2Br_2 as an internal standard. [c] Yield of isolated product. Bipy = 2,2′-bipyridine, DBN = 1,5-diazabicyclo-[4.3.0]non-5-ene, DTBP = di-*tert*-butyl peroxide, DBU = 1,8-diazabicyclo-[5.4.0]undec-7-ene, Tf = trifluoromethanesulfonyl.

Some representative results are summarized in Table 1. Adding lanthanide triflates (entries 2 and 3), $Mg(OTf)_2$ (entry 4), and $Ca(ClO_4)_2$ (entry 5) to the reaction mixture slightly increased the yield of **3a**. A significant improvement was observed by performing the reaction in the presence of a catalytic amount of either $Mg(ClO)_4$, $Zn(OTf)_2$, or $Ca(OTf)_2$ (entries 6–9),[18] with the latter furnishing the cleaner reaction.[19] Including $Ca(OTf)_2$ as a Lewis acid, the influence of base on the reaction outcome was re-investigated. Na_3PO_4 (entry 10), DBN and *N*-methylimidazole (entries 14 and 15) were as efficient as K_3PO_4, whereas a lower yield of **3a** was isolated when KO*t*Bu, LiO*t*Bu, and 2,6-lutidine (entries, 11, 12, and 16) were used as bases. Gratefully, a clear improvement of the reaction efficiency was observed when the reaction was performed in the presence of DBU (entry 13). Overall, under optimum reaction conditions, **3a** was isolated in 73 % yield. We note that the reaction proceeded equally well in the dark.[19] Since three chemical bonds were created in this domino process, the average yield per chemical bond formation is around 90 %.

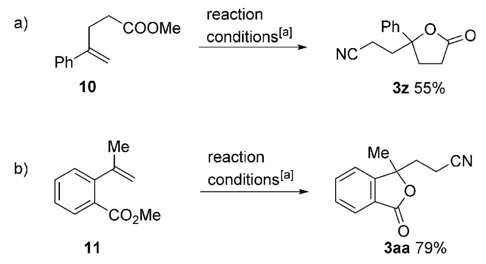
With the optimized reaction conditions [$Cu(BF_4)_2 \cdot 6H_2O$, (0.2 equiv), Bipy (0.6 equiv), DBU (0.15 equiv), H_2O (30 equiv), $Ca(OTf)_2$ (0.2 equiv), DTBP (4.0 equiv), 3.5 h, N_2 atmosphere, MeCN, 140 °C, then 1.0 N HCl, 80 °C, 45 min], the scope of this copper-catalyzed, formal [2+2+1] heteroannulation was investigated. As shown in Scheme 2, the α-methyl styrenes with both electron-donating (Me, OMe) and electron-withdrawing (Cl) substituents on the aromatic ring, regardless of their positions, afforded the γ-butyrolactones **3b–i** in good yields. Methyl, ethyl, isopropyl, phenethyl, and functionalized alkyl-substituted styrenes participated in the reaction without event to provide the corresponding γ-butyrolactones (**3j–n**). 1,1-Diaryl-substituted alkenes are excellent substrates leading to the corresponding lactones (**3o–t**). Importantly, trisubstituted alkenes participated in the reaction equally well to efficiently give the 3,4,4-trisubstituted γ-butyrolactones **3r–t**. Propionitrile, butyronitrile, valeronitrile, and 3-methoxypropionitrile are competent alkylating agents to initiate the domino process leading to the corresponding γ-butyrolactones **3u–3x** as a mixture of two diastereomers. Pleasingly, reaction of trisubstituted alkenes with propionitrile afforded the 2,3,4,4-tetrasubstituted γ-butyrolactone **3y**, albeit in a slightly reduced yield (47 %).



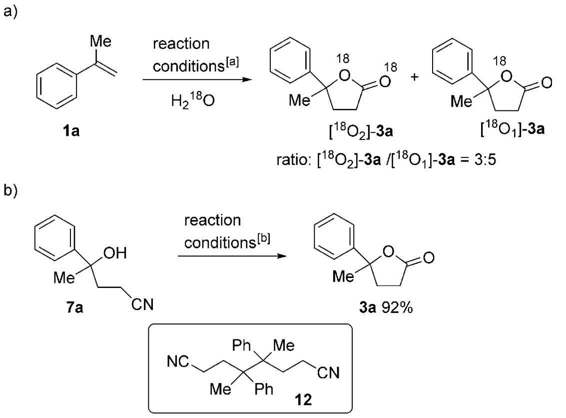
Scheme 2. Substrate scope. [a] Standard reaction conditions. [b] DTBP (2.5 equiv) under otherwise identical conditions. [c] d.r. = 1:1.

The reaction of methyl-4-phenylpent-4-enoate (**10**) with acetonitrile under standard reaction conditions afforded the lactone **3z** in which the cyano group remained untouched (Scheme 3a). Similarly, methyl 2-(prop-1-en-2-yl)benzoate (**11**) was converted, under identical reaction conditions, into the lactone **3aa** (Scheme 3b). The observed highly chemoselective cyclization could be accounted for by the direct interception of the benzylic cation by the tethered methoxycarbonyl function.

Performing the reaction of **1a** in MeCN under an oxygen atmosphere with or without DTBP led only to the decomposition of the alkenes. In contrast, performing the same reaction under strictly inert atmosphere afforded **3a** in 73 % yield. An isotope-labelling experiment was conducted to gain further mechanistic insights. Reaction of **1a** with acetonitrile



Scheme 3. Additional examples on the synthesis of functionalized γ-lactones. [a] Standard reaction conditions.

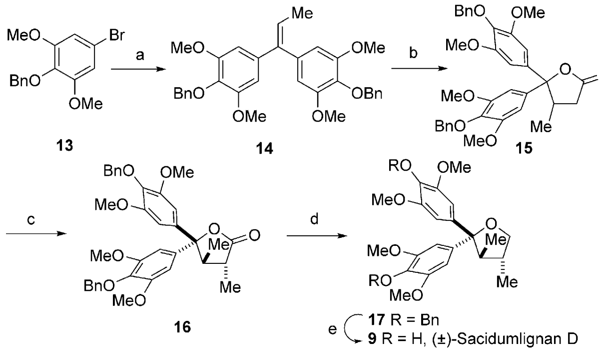


Scheme 4. ^{18}O-Labeling and control experiments. [a] $H_2{}^{18}O$ (30 equiv), under otherwise standard reaction conditions. [b] Standard reaction conditions.

(**2a**) in the presence of $H_2{}^{18}O$ (^{18}O content 97%) under otherwise standard reaction conditions afforded the double and mono ^{18}O-labeled products $[^{18}O_2]$-**3a** and $[^{18}O_1]$-**3a**, respectively (Scheme 4a). The upfield shift of ^{13}C NMR signals of C1 and C4 in $[^{18}O_2]$-**3a**/$[^{18}O_1]$-**3a** relative to those of **3a** $[\Delta\delta_{(C=O)}{}^{16}O\text{-}{}^{18}O = +2.5$ Hz, $[\Delta\delta_{(C4)}{}^{16}O\text{-}{}^{18}O = +4.9$ Hz] is in agreement with literature reports.[20] The results of these control experiments indicated that the oxygen atoms in the lactones **3** came from water rather than from adventitious oxygen or DTBP (Scheme 1). Furthermore, submitting an authentic sample of the tertiary alcohol **7a** to the standard reaction conditions afforded **3a** in 92% yield, thus indicating that the tertiary alcohol **7** could indeed be an intermediate on the way to lactone **3** (Scheme 4b).

In the absence of $Cu(BF_4)_2{\cdot}6H_2O$ or Bipy, only a trace amount of **3a** was formed. In contrast, without DTBP, **1a** was converted into **3a** in 39% yield (NMR) in the presence of a stoichiometric amount of $Cu(BF_4)_2$. These observations are in accord with our previous conclusion that the copper catalyst played a key role in the generation of the acetonitrile radical **4** and that DTBP served mainly as an oxidant to regenerate the copper(II) species.[21] In our initial survey of reaction conditions, we isolated the dimer **12**, resulting most probably from the dimerization of the benzylic radical **5a** (see Scheme 1; $R^1 = Ph$, $R^2 = Me$, $R^3 = R^4 = H$) because of its inefficient oxidation to **6a**. Therefore, the copper catalyst played a dual role in this transformation, that is, to generate the cyanoalkyl radical and to selectively oxidize the adduct radical to the carbenium ion.

(±)-Sacidumlignan D (**9**) was isolated by Yue and coworkers from the plant *Sarcostemma acidum* (Roxb.) collected from Hainan island, China, where the local people use it for the treatment of chronic cough and postnatal hypogalactia.[17,22] To illustrate the synthetic potential of our heteroannulation process, a total synthesis of **9** was undertaken (Scheme 5). Lithium–halogen exchange of the arylbromide **13**, readily synthesized in two steps from 2,6-dimethoxyphenol, followed by nucleophilic addition of the resulting aryllithium species to propionyl chloride furnished a tertiary alcohol, which, without purification, was dehydrated under acidic conditions to give the alkene **14**. The key [2+2+1] heteroannulaton of **14** with acetonitrile and water under our standard reaction conditions proceeded smoothly to afford the lactone **15** in 60% yield. Treatment of **15** with LHMDS followed by methylation of the lithium enolate provided the 2,3-*trans* disubstituted lactone **16** as an only isolable stereoisomer. Reduction of **16** with $LiAlH_4$ afforded the tetrahydrofuran **17**, which was converted into **9** in 93% yield under hydrogenolysis conditions.



Scheme 5. Total synthesis of (±)-sacidumlignan D (**9**): a) *n*BuLi, EtCOCl, THF, 60 °C, then PTSA, toluene, reflux, 56%; b) $Cu(BF_4)_2{\cdot}6H_2O$ (0.2 equiv), Bipy (0.6 equiv), DBU (0.15 equiv), H_2O (30 equiv), $Ca(OTf)_2$ (0.2 equiv), DTBP (2.5 equiv), 140 °C, in MeCN (0.025 M), 3.5 h; then 1.0 N HCl, 80 °C, 45 min, 60%; c) LHMDS (5 equiv), MeOTf (4 equiv), THF, −78 °C, 12 h, 89%; d) $LiAlH_4$, then TFA, CH_2Cl_2, 91% (2 steps); e) H_2, Pd/C, MeOH/EtOAc (1:1), 93%. LHMDS = lithium hexamethyldisilazide, PTSA = *p*-toluene sulfonic acid, TFA = trifluoroacetic acid, THF = tetrahydrofuran.

In summary, we have developed the first examples of copper-catalyzed three-component reactions of alkenes with alkylnitriles and water. The domino process involved an unprecedented copper-catalyzed hydroxy-cyanoalkylation of alkenes and subsequent cyclization leading to γ-butyrolactones with concomitant formation of one $C(sp^3)-C(sp^3)$ bond and two C−O bonds. This novel [2+2+1] heteroannulation reaction was featured as the key step in a concise total synthesis of (±)-sacidumlignan D.

Acknowledgments

Financial support from the EPFL (Switzerland), the Swiss National Science Foundation (SNSF), and Swiss National Centers of Competence in Research NCCR-Chemical Biology are gratefully acknowledged.

Keywords: alkenes · copper · heterocycles · multicomponent reactions · total synthesis

---

[1] a) E. S. Sherman, S. R. Chemler, T. B. Tan, O. Gerlits, *Org. Lett.* **2004**, *6*, 1573; b) P. H. Fuller, S. R. Chemler, *Org. Lett.* **2007**, *9*, 5477; c) W. Zeng, S. R. Chemler, *J. Am. Chem. Soc.* **2007**, *129*, 12948; d) L. Miao, I. Haque, M. R. Manzoni, W. S. Tham, S. R. Chemler, *Org. Lett.* **2010**, *12*, 4739; e) T. W. Liwosz, S. R. Chemler, *J. Am. Chem. Soc.* **2012**, *134*, 2020; f) K. Kaneko, T.

Yoshino, S. Matsunaga, M. Kanai, *Org. Lett.* **2013**, *15*, 2502; g) H. Zhang, W. Pu, T. Xiong, Y. Li, X. Zhou, K. Sun, Q. Liu, Q. Zhang, *Angew. Chem. Int. Ed.* **2013**, *52*, 2529; *Angew. Chem.* **2013**, *125*, 2589.

[2] a) Y. Miller, L. Miao, A. S. Hosseini, S. R. Chemler, *J. Am. Chem. Soc.* **2012**, *134*, 12149; b) M. T. Bovino, T. W. Liwosz, N. E. Kendel, Y. Miller, N. Tyminska, E. Zurek, S. R. Chemler, *Angew. Chem. Int. Ed.* **2014**, *53*, 6383; *Angew. Chem.* **2014**, *126*, 6501; c) Y. Wang, H. Du, *J. Org. Chem.* **2010**, *75*, 3503; d) K. K. Toh, Y.-F. Wang, E. P. Jian, S. Chiba, *J. Am. Chem. Soc.* **2011**, *133*, 13942.

[3] a) D. S. Laitar, E. Y. Tsui, J. P. Sadighi, *Organometallics* **2006**, *25*, 2405; b) H. Ito, Y. Kosaka, K. Nonoyama, Y. Sasaki, M. Sawamura, *Angew. Chem. Int. Ed.* **2008**, *47*, 7424; *Angew. Chem.* **2008**, *120*, 7534; c) C. Zhong, S. Kunii, Y. Kosaka, M. Sawamura, H. Ito, *J. Am. Chem. Soc.* **2010**, *132*, 11440; d) H. Ito, T. Toyoda, M. Sawamura, *J. Am. Chem. Soc.* **2010**, *132*, 5990; e) K. Kubota, E. Yamamoto, H. Ito, *J. Am. Chem. Soc.* **2013**, *135*, 2635.

[4] a) S. R. Chemler, P. H. Fuller, *Chem. Soc. Rev.* **2007**, *36*, 1153; b) Y. Shimizu, M. Kanai, *Tetrahedron Lett.* **2014**, *55*, 3727.

[5] a) M. R. Heinrich, A. Wetzel, M. Kirschstein, *Org. Lett.* **2007**, *9*, 3833; b) S. Kirchberg, R. Fröhlich, A. Studer, *Angew. Chem. Int. Ed.* **2010**, *49*, 6877; *Angew. Chem.* **2010**, *122*, 7029; c) A. D. Melhado, W. E. Brenzovich, Jr., A. D. Lackner, F. D. Toste, *J. Am. Chem. Soc.* **2010**, *132*, 8885; d) M. Hartmann, Y. Li, A. Studer, *J. Am. Chem. Soc.* **2012**, *134*, 16516; e) G. Fumagalli, S. Boyd, M. F. Greaney, *Org. Lett.* **2013**, *15*, 4398; f) M. N. Hopkinson, B. Sahoo, F. Glorius, *Adv. Synth. Catal.* **2014**, *356*, 2794; g) W. Guo, H.-G. Cheng, L.-Y. Chen, J. Xuan, Z.-J. Feng, J.-R. Chen, L.-Q. Lu, W.-J. Xiao, *Adv. Synth. Catal.* **2014**, *356*, 2787; h) T. Itoh, Y. Shimizu, M. Kanai, *Org. Lett.* **2014**, *16*, 2736; For a review, see: i) M. R. Heinrich, *Chem. Eur. J.* **2009**, *15*, 820.

[6] a) A. T. Parsons, S. L. Buchwald, *Angew. Chem. Int. Ed.* **2011**, *50*, 9120; *Angew. Chem.* **2011**, *123*, 9286; b) J. Xu, Y. Fu, D.-F. Luo, Y.-Y. Jiang, B. Xiao, Z.-J. Liu, T.-J. Gong, L. Liu, *J. Am. Chem. Soc.* **2011**, *133*, 15300; c) X. Wang, Y. Ye, S. Zhang, J. Feng, Y. Xu, Y. Zhang, J. Wang, *J. Am. Chem. Soc.* **2011**, *133*, 16410; d) R. Zhu, S. L. Buchwald, *J. Am. Chem. Soc.* **2012**, *134*, 12462; e) L. Chu, F.-L. Qing, *Org. Lett.* **2012**, *14*, 2106; f) P. G. Janson, I. Ghoneim, N. O. Ilchenko, K. Szabó, *Org. Lett.* **2012**, *14*, 2882; g) R. Zhu, S. L. Buchwald, *Angew. Chem. Int. Ed.* **2013**, *52*, 12655; *Angew. Chem.* **2013**, *125*, 12887; h) H. Egami, R. Shimizu, S. Kawamura, M. Sodeoka, *Angew. Chem. Int. Ed.* **2013**, *52*, 4000; *Angew. Chem.* **2013**, *125*, 4092; i) H. Egami, S. Kawamura, A. Miyazaki, M. Sodeoka, *Angew. Chem. Int. Ed.* **2013**, *52*, 7841; *Angew. Chem.* **2013**, *125*, 7995; j) for a highlight, see: A. Studer, *Angew. Chem. Int. Ed.* **2012**, *51*, 8950; *Angew. Chem.* **2012**, *124*, 9082.

[7] From α-bromoacetonitriles, see: Z. Liao, H. Yi, Z. Li, C. Fan, X. Zhang, J. Liu, Z. Deng, A. Lei, *Chem. Asian J.* **2015**, *10*, 96.

[8] a) J. B. Bush, Jr., H. Finkbeiner, *J. Am. Chem. Soc.* **1968**, *90*, 5903; b) E. I. Heiba, R. M. Dessau, W. J. Koehl, Jr., *J. Am. Chem. Soc.* **1968**, *90*, 5905; c) E. I. Heiba, R. M. Dessau, P. G. Rodewald, *J. Am. Chem. Soc.* **1974**, *96*, 7977; d) W. E. Fristad, J. R. Peterson, *J. Org. Chem.* **1985**, *50*, 10; e) E. J. Corey, M.-C. Kang, *J. Am. Chem. Soc.* **1984**, *106*, 5384; f) B. B. Snider, *Tetrahedron* **2009**, *65*, 10738.

[9] J. D. Connolly, R. A. Hill, *Dictionary of Terpenoids*; Chapman and Hall: London, **1991**; Vol. 1, pp. 476.

[10] a) S. S. C. Koch, A. R. Chamberlin, *J. Org. Chem.* **1993**, *58*, 2725; For reviews, see: b) I. Collins, *J. Chem. Soc. Perkin Trans. 1* **1998**, 1869; c) I. Collins, *J. Chem. Soc. Perkin Trans. 1* **1999**, 1377.

[11] L. Huang, H. Jiang, C. Qi, X. Liu, *J. Am. Chem. Soc.* **2010**, *132*, 17652.

[12] From α-bromoacetate, see: X.-J. Wei, D.-T. Yang, L. Wang, T. Song, L.-Z. Wu, Q. Liu, *Org. Lett.* **2013**, *15*, 6054.

[13] a) A. Bunescu, Q. Wang, J. Zhu, *Chem. Eur. J.* **2014**, *20*, 14633; b) A. Bunescu, Q. Wang, J. Zhu, *Angew. Chem. Int. Ed.* **2015**, *54*, 3132; *Angew. Chem.* **2015**, *127*, 3175; c) C. Chatalova-Sazepin, Q. Wang, G. M. Sammis, J. Zhu, *Angew. Chem. Int. Ed.* **2015**, *54*, 5443; *Angew. Chem.* **2015**, *127*, 5533; d) A. Bunescu, Q. Wang, J. Zhu, *Org. Lett.* **2015**, *17*, 1890.

[14] Other groups' contributions, see: a) J. Li, Z. Wang, N. Wu, G. Gao, J. You, *Chem. Commun.* **2014**, *50*, 15049; b) D. Zhou, Z.-H. Li, J. Li, S.-H. Li, M.-W. Wang, X.-L. Luo, G.-L. Ding, R.-L. Sheng, M.-J. Fu, S. Tang, *Eur. J. Org. Chem.* **2015**, 1606; c) Z. Li, Y. Xiao, Z.-Q. Liu, *Chem. Commun.* **2015**, *51*, 9969; d) X.-Q. Chu, X.-P. Xu, H. Meng, S.-J. Ji, *RSC Adv.* **2015**, *5*, 67829; e) S. Tang, S.-H. Li, Z.-H. Li, D. Zhou, R.-L. Sheng, *Tetrahedron Lett.* **2015**, *56*, 1423; f) J. Shen, D. Yang, Y. Liu, S. Qin, J. Zhang, J. Sun, C. Liu, C. Liu, X. Zhao, C. Chu, R. Liu, *Org. Lett.* **2014**, *16*, 350; For metal-free conditions: g) Y. Li, B. Liu, H.-B. Li, Q. Wang, J.-H. Li, *Chem. Commun.* **2015**, *51*, 1024; For iron-catalyzed: h) C. Pan, H. Zhang, C. Zhu, *Org. Biomol. Chem.* **2015**, *13*, 361; For Mn^{III} mediated: i) X. Li, J. Xu, Y. Gao, H. Fang, G. Tang, Y. Zhao, *J. Org. Chem.* **2015**, *80*, 2621; Pd/Cu-catalyzed: j) Y. Liu, K. Yang, H. Ge, *Chem. Sci.* **2016**, *7*, 2804.

[15] Addition of acetonitrile to polarized double bond: copper-catalyzed: a) Y. Suto, N. Kumagai, S. Matsunaga, M. Kanai, M. Shibasaki, *Org. Lett.* **2003**, *5*, 3147; b) Y. Suto, R. Tsuji, M. Kanai, M. Shibasaki, *Org. Lett.* **2005**, *7*, 3757; c) G.-W. Wang, A.-X. Zhou, J.-J. Wang, R.-B. Hu, S.-D. Yang, *Org. Lett.* **2013**, *15*, 5270; ruthenium-catalyzed: d) N. Kumagai, S. Matsunaga, M. Shibasaki, *J. Am. Chem. Soc.* **2004**, *126*, 13632; e) N. Kumagai, S. Matsunaga, M. Shibasaki, *Tetrahedron* **2007**, *63*, 8598; nickel-catalyzed: f) S. Chakraborty, Y. J. Patel, J. A. Krause, H. Guan, *Angew. Chem. Int. Ed.* **2013**, *52*, 7523; *Angew. Chem.* **2013**, *125*, 7671.

[16] a) C. L. Jenkins, J. K. Kochi, *J. Am. Chem. Soc.* **1972**, *94*, 843; b) B. Zhang, A. Studer, *Org. Lett.* **2014**, *16*, 1790; For a recent review: c) A. E. Wendlandt, A. M. Suess, S. S. Stahl, *Angew. Chem. Int. Ed.* **2011**, *50*, 11062; *Angew. Chem.* **2011**, *123*, 11256.

[17] L.-S. Gan, S.-P. Yang, C.-Q. Fan, J.-M. Yue, *J. Nat. Prod.* **2005**, *68*, 221.

[18] M. Niggemann, M. J. Meel, *Angew. Chem. Int. Ed.* **2010**, *49*, 3684; *Angew. Chem.* **2010**, *122*, 3767.

[19] Reaction of **1a** in ethyl acetate under optimized reaction conditions afforded **3a** in 18 % yield upon isolation. In contrast, the same reaction in *tert*-butyl acetate and in pinacolone led to a complex mixture. This result indicated that it might be possible to generate $EtOOCCH_2^{\bullet}$ and to engage it in subsequent domino processes. We thank the referee for suggesting these experiments.

[20] a) J. C. Vederas, *J. Am. Chem. Soc.* **1980**, *102*, 374; b) Y. Odabachian, S. Tong, Q. Wang, M.-X. Wang, J. Zhu, *Angew. Chem. Int. Ed.* **2013**, *52*, 10878; *Angew. Chem.* **2013**, *125*, 11078; c) T. Buyck, Q. Wang, J. Zhu, *J. Am. Chem. Soc.* **2014**, *136*, 11524.

[21] a) G. E. Morris, D. Oakley, D. A. Pippard, D. J. H. Smith, *J. Chem. Soc. Chem. Commun.* **1987**, 411; b) R. T. Gephart III, C. L. McMullin, N. G. Sapiezynski, E. S. Jang, M. J. B. Aguila, T. R. Cundari, T. H. Warren, *J. Am. Chem. Soc.* **2012**, *134*, 17350.

[22] For the synthesis of sacidumlignans: a) D. S. K. Pandey, C. V. Ramana, *J. Org. Chem.* **2011**, *76*, 2315; b) J. K. Rout, C. V. Ramana, *J. Org. Chem.* **2012**, *77*, 1566; c) J.-J. Zhang, C.-S. Yan, Y. Peng, Z.-B. Luo, X.-B. Xu, Y.-W. Wang, *Org. Biomol. Chem.* **2013**, *11*, 2498; d) C. Xie, D. Bai, S.-H. Huang, X. Jia, R. Hong, *Asian J. Org. Chem.* **2014**, *3*, 277.

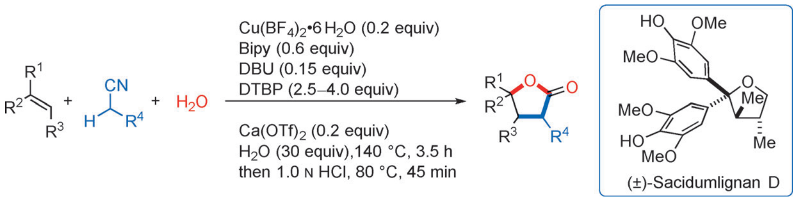
Received: May 10, 2016

Communications

Multicomponent Reactions

T. M. Ha, C. Chatalova-Sazepin, Q. Wang, J. Zhu* ______ ■■■■–■■■■

Copper-Catalyzed Formal [2+2+1] Heteroannulation of Alkenes, Alkylnitriles, and Water: Method Development and Application to a Total Synthesis of (±)-Sacidumlignan D



Water connections: The title reaction affords γ-butyrolactones with the creation of three chemical bonds and a quaternary carbon center. The domino process involves an unprecedented copper-catalyzed hydroxy-cyanoalkylation of alkenes. A total synthesis of (±)-sacidumlignan D was accomplished featuring this heteroannulation as a key step.