Synthetic Methods

Deutsche Ausgabe: DOI: 10.1002/ange.201605130
Internationale Ausgabe: DOI: 10.1002/anie.201605130

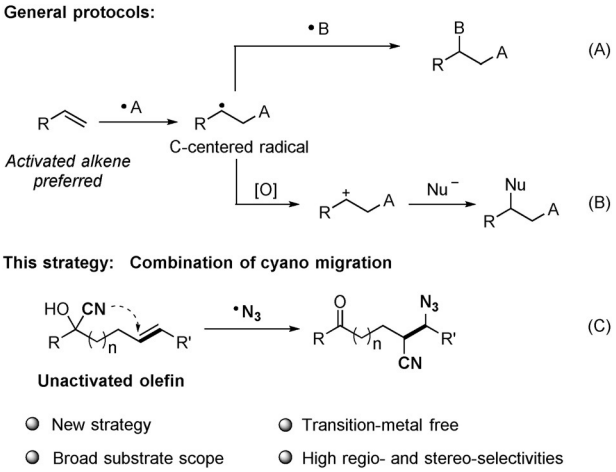
Combination of a Cyano Migration Strategy and Alkene Difunctionalization: The Elusive Selective Azidocyanation of Unactivated Olefins

*Zhen Wu, Rongguo Ren, and Chen Zhu**

Abstract: *A conceptually new, efficient, and metal-free approach for the challenging azidocyanation of unactivated alkenes is presented. The strategy of intramolecular distal cyano migration is combined with alkene difunctionalization for the first time. A variety of useful azido-substituted alkyl nitriles are prepared in good yields and, most importantly, with exquisite regio- and stereo-selectivities.*

The consecutive introduction of two functionalities into an alkene using a single operation, namely alkene difunctionalization, is a robust strategy for the manipulation of olefins and has a high synthetic efficiency.[1] Relying on the recent advances in chemo- and regio-selective radical reactions, the radical-mediated difunctionalization of alkenes has made great progress.[2] Mechanistically, this type of reactions is initiated by the free-radical addition to an olefin moiety and the generation of the C-centered radical intermediate. The C-centered radical can be subsequently coupled with an extrinsic radical donor (Scheme 1 A) or further single-electron oxidized to carbonium and trapped by a nucleophile (Scheme 1 B). In both cases, the reaction feasibility is largely dependent on the stability of the in situ formed radical or cation intermediate. In this scenario, activated alkenes such as aryl, carbonyl, and heteroatom-substituted alkenes become favorable substrates for alkene difunctionalization because of the p–π conjugate effect, which thus stabilizes the nascent radical intermediate.[3] In contrast, the reaction with unactivated olefins is more challenging and has received relatively less attention.

Alkyl nitriles are widely used for the preparation of carboxylic acids, amines, and many other useful products.[4] Thus, the production of alkyl nitriles is of great importance in both academia and industry.[5] The direct cyanation of alkenes provides efficient and divergent access to alkyl nitriles. However, the radical-promoted cyanofunctionalization of olefins remains underexplored.[6] In the current literature,



Scheme 1. Strategies for radical-promoted olefin difunctionalization.

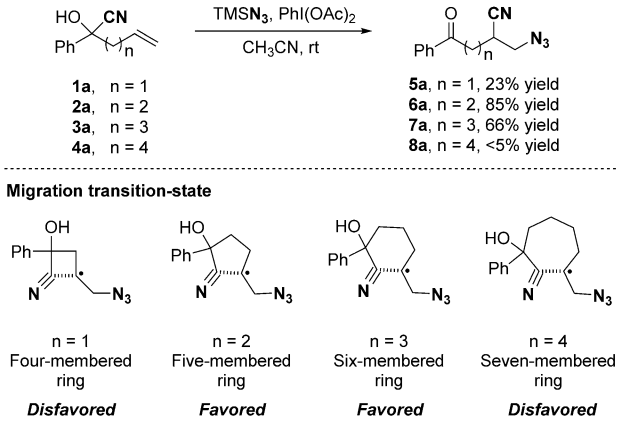
the substrate scope was severely limited to activated olefins, and unactivated olefins were only tolerated in the copper-catalyzed cyanotrifluoromethylation of alkenes.[6c,d] Thus, the establishment of a general method for cyanofunctionalization of unactivated olefins is highly desirable. Herein, we describe a transition-metal free, mild, and efficient protocol for the azidocyanation of unactivated alkenes (Scheme 1 C). A novel strategy of intramolecular cyano migration is introduced into alkene difunctionalization for the first time. A diverse array of vicinal azido-substituted alkyl nitriles are produced in good yields and with high regio- and stereo-selectivities.

Our investigations of the azidocyanation of alkenes began with the addition of an azido radical to a selection of cyanohydrins **1a**–**4a** (Scheme 2). After a brief survey of reaction conditions, the combination of $TMSN_3$ and PIDA was selected as the azido source.[7,8] While the reaction of homoallylic cyanohydrin **1a** ($n=1$) resulted in a low yield, that of bishomoallylic cyanohydrin **2a** ($n=2$) and the trishomoallylic analogue **3a** ($n=3$) gave the expected cyanated products **6a** and **7a** in good yields at room temperature. The cyanohydrin **4a,** with a longer chain ($n=4$), was not a suitable substrate. These results may be rationalized by the possible transition state involved in the cyano migration process. While the 1,4- (or 1,5-) cyano migration with **2a** (or **3a**) underwent the thermodynamically favored five- (or six-) membered cyclic transition state, the migration transition state of **1a** (or **4a**) via a four- (or seven-) membered ring was disfavored.

We then evaluated the generality of cyanohydrins. A variety of bishomoallylic cyanohydrins **2** were examined first

[*] Z. Wu, Dr. R. Ren, Prof. Dr. C. Zhu
Key Laboratory of Organic Synthesis of Jiangsu Province
College of Chemistry, Chemical Engineering and Materials Science
Soochow University
199 Ren-Ai Road, Suzhou, Jiangsu 215123 (China)
E-mail: chzhu@suda.edu.cn
Prof. Dr. C. Zhu
Key Laboratory of Synthetic Chemistry of Natural Substances
Shanghai Institute of Organic Chemistry
Chinese Academy of Sciences
345 Lingling Road, Shanghai 200032 (China)

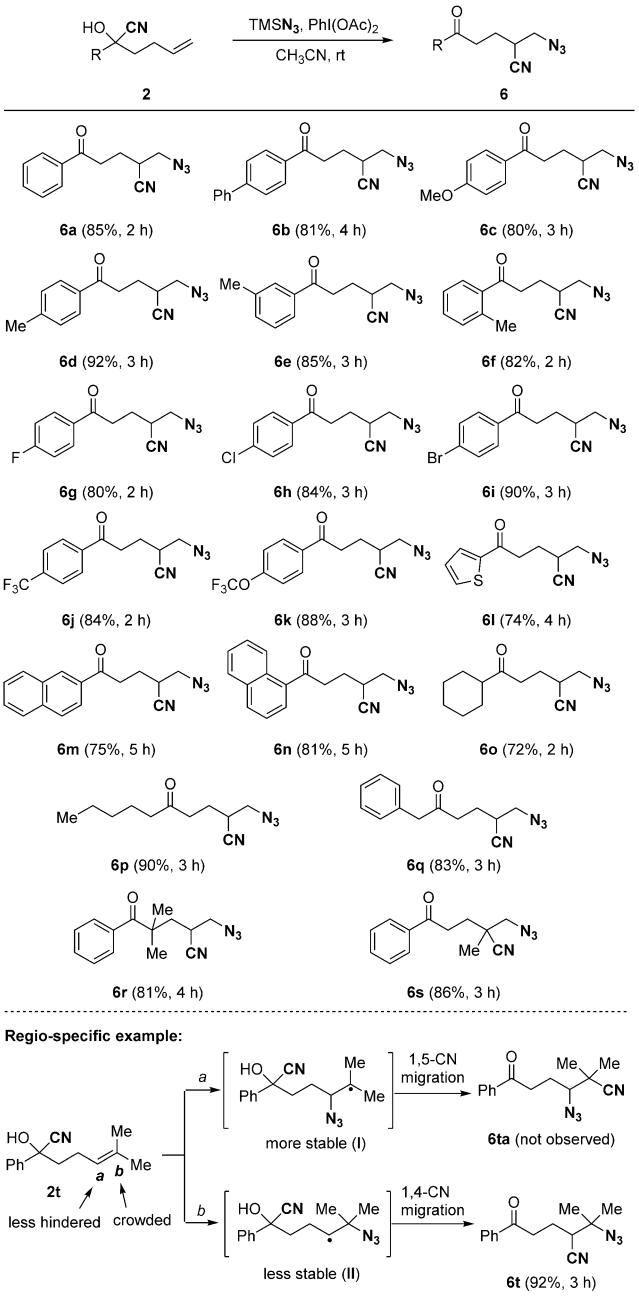
Supporting information for this article can be found under: http://dx.doi.org/10.1002/anie.201605130.



Scheme 2. Intramolecular cyano migration for azidocyanation of olefins.

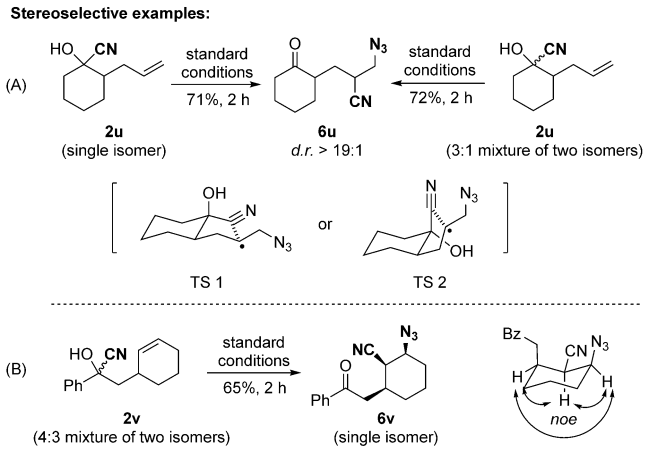
(Scheme 3). Broad functionality tolerance was demonstrated in the transformation, and many carbonyl and azido-containing alkyl nitriles **6** were readily generated at room temperature in a few hours. It should be noted that the synthesis of such distally cyano or azido-substituted ketones is usually difficult, yet it is our longstanding interest.[9] The cyanohydrins bearing various electron-rich aryl groups consistently delivered high yields (**6a**–**6f**). Steric hindrance did not exert an appreciable influence upon the reaction, as the substrates with *para*-, *meta*-, or *ortho*-substitution gave the corresponding products in comparable yields (**6d**–**6f**). The electron-deficient substrates were also converted into the desired products in good yields (**6g**–**6k**). The presence of bromide was valuable in the product (**6i**), because it allowed for the subsequent product manipulation during cross-coupling reactions. Naphthyl- and heteroaryl- (for example, thienyl) substituted cyanohydrins were also suitable substrates for the azidocyanation (**6l**–**6n**). Moreover, alkyl and benzyl substrates still gave synthetically useful yields (**6o**–**6q**). The placement of multiple substituents on the homoallylic chain did not impede the conversion (**6r** and **6s**). Remarkably, the reaction with 1,1-disubstituted olefin **2s** generated the expected product **6s**, in which a new cyano-substituted quaternary center was readily constructed in spite of the steric congestion, in good yield. The regiospecific reaction with trisubstituted cyanohydrin **2t** was noteworthy. There were two viable pathways for the reaction: 1) the addition of an N_3 radical to the less hindered carbon ***a*** to form a more stable tertiary C-radical **I**, followed by a 1,5-cyano migration to generate the product **6ta**; and 2) addition of an N_3 radical to the crowded carbon ***b*** to form a less stable secondary C-radical **II**, followed by a 1,4-cyano migration to afford the product **6t**. However, the reaction led to a unique positional product **6t** in high yield, and the regio-isomer **6ta** was not detected. The process might first generate the stable radical **I**, which was then transformed into radical **II** through an unusual 1,2-azidyl migration.[10]

Encouraged by the exclusive regioselectivity in the case of **6t**, we further investigated the stereochemistry of the cyano migration reaction. Although it was established that exquisite stereocontrol was usually difficult to obtain in radical-



Scheme 3. Azidocyanation of olefins via 1,4-cyano migration. Reaction conditions: **2** (0.20 mmol, 1.0 equiv), $TMSN_3$ (0.80 mmol, 4.0 equiv), and $PhI(OAc)_2$ (0.40 mmol, 2.0 equiv) in CH_3CN (2.0 mL) at RT under N_2. Yields of isolated products are given.

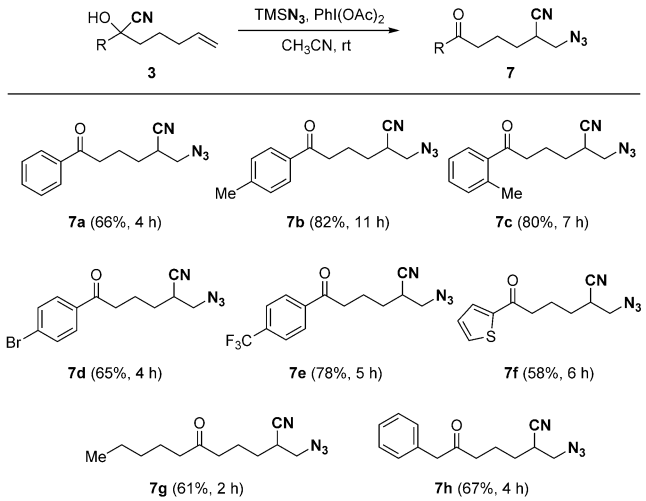
mediated transformations, we still anticipated to achieve the stereoselective cyano migration based on the cyclic transition states postulated in Scheme 2. A single isomer of **2u** was first examined under the standard reaction conditions. As expected, the reaction gave the corresponding product **6u** with high stereoselectivity (d.r. > 19:1). We then performed the same reaction with a 3:1 isomeric mixture of **2u**, and, interestingly, the product **6u** was also stereospecifically produced in similar yield (d.r. > 19:1) (Scheme 4 A). These results suggest that the configuration of cyanohydrin was of little importance and the stereochemistry of the product was



Scheme 4. Stereoselective 1,4-cyano migration.

mainly dictated by the cyclic transition-state. More evidence for the stereoselectivity was provided by the reaction of **2v**, a 4:3 mixture of two isomers. Remarkably, a single isomer of **6v** with all-*cis* 1,2,3-substituents was readily obtained in 65% yield, as indicated by the relative configuration assigned by the NMR analysis (Scheme 4B).

Afterward, we investigated the azidocyanation reaction with trishomoallylic cyanohydrins **3**. A set of representative cyanohydrins **3** were subjected to the standard reaction conditions (Scheme 5). Both electron-rich and deficient substrates were compatible with the reaction conditions, giving rise to the expected products **7** in synthetically useful yields. The reaction of *ortho*-substituted **3c** (for structure and characterization details, see the Supporting Information) afforded a similar yield to that of *para*-substituted **3b** (**7b** and **7c**). The cyanohydrins with a halide (for example, bromide) or a strong electron-withdrawing group (for example, CF_3) were also suitable substrates (**7d** and **7e**). Moreover, the reaction with heteroaryl (for example, thienyl) or alkyl



Scheme 5. Azidocyanation of olefins via 1,5-cyano migration. Reaction conditions: **3** (0.20 mmol, 1.0 equiv), $TMSN_3$ (0.80 mmol, 4.0 equiv), and $PhI(OAc)_2$ (0.40 mmol, 2.0 equiv) in CH_3CN (2.0 mL) at RT under N_2. Yields of isolated products are given.

substrates were also readily converted into the desired products (**7f–7h**).

Based on the experimental observations and inspired by previous reports, the plausible mechanistic pathways were depicted (Figure 1). The interaction of $PhI(OAc)_2$ with

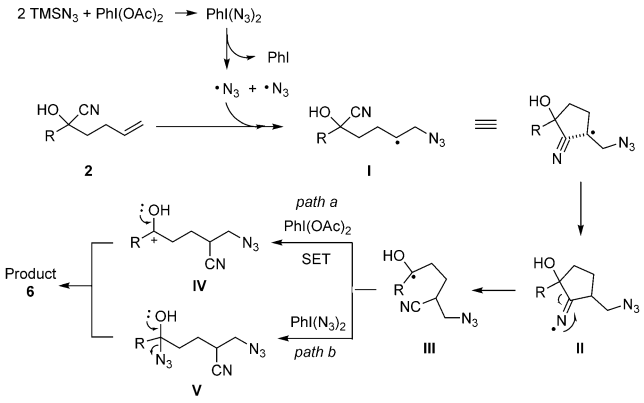
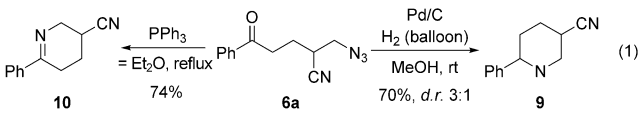


Figure 1. Proposed mechanism.

$TMSN_3$ generates the highly unstable acyclic azido hypoiodite, which decomposes immediately at room temperature to release an azido radical.[7] Then, the addition of an azidyl radical to cyanohydrin **2** gives rise to the metastable alkyl radical **I**. The efficient intramolecular interception of intermediate **I** by the cyanohydrin species through a five-membered ring cyclization is the key strategy for this synthesis, affording the cyclic iminium radical **II**.[11] The homolysis of **II** enables the 1,4-cyano migration and generates a more stable hydroxyalkyl radical **III**. There are two possible routes for the eventual conversion of radical **III** into the product **6**: a) the single-electron oxidation of radical **III** to the carbonium ion **IV** by $PhI(OAc)_2$ followed by deprotonation (path a), and b) the capture of radical **III** by a $PhI(N_3)_2$ intermediate followed by the collapse of the azidohydrin **V** to the final carbonyl (path b).

Multiply-substituted piperidines are found extensively in naturally occurring products and biologically active compounds.[12] Our method provides useful precursors for the construction of the piperidine skeleton. Under mild hydrogenation conditions, compound **6a** was readily converted into the 2,5-disubstituted piperidine **9** in good yield [Eq. (1), right]. Furthermore, compound **6a** could be selectively transformed into the cyclic imine **10** by means of the Staudinger ligation [Eq. (1), left].[13]



In summary, we have described a novel, efficient, and metal-free approach for the elusive azidocyanation of unactivated alkenes. A variety of synthetically useful alkyl nitriles are readily prepared in good yields, and, most importantly,

with exquisite regio- and stereo-selectivities. The intramolecular cyano migration strategy is combined with alkene difunctionalization for the first time, opening up new vistas for this area. The application of this strategy to other cyanofunctionalization of unactivated alkenes is ongoing in our laboratory.

Acknowledgements

C.Z. is grateful for the financial support from Soochow University, the National Natural Science Foundation of China (Grant no. 21402134), the Natural Science Foundation of Jiangsu Province (Grant no. BK20140306), and the Priority Academic Program Development of Jiangsu Higher Education Institutions (PAPD).

Keywords: alkene difunctionalization · alkyl nitrile · azidocyanation · cyano migration · radical reaction

How to cite: *Angew. Chem. Int. Ed.* **2016**, *55*, 10821 – 10824
Angew. Chem. **2016**, *128*, 10979 – 10982

[1] For selected reviews, see: a) G. Li, S. R. S. S. Kotti, C. Timmons, *Eur. J. Org. Chem.* **2007**, 2745 – 2758; b) S. R. Chemler, *Org. Biomol. Chem.* **2009**, *7*, 3009 – 3019; c) R. I. McDonald, G. Liu, S. S. Stahl, *Chem. Rev.* **2011**, *111*, 2981 – 3019; d) S. E. Allen, R. R. Walvoord, R. Padilla-Salinas, M. C. Kozlowski, *Chem. Rev.* **2013**, *113*, 6234 – 6458; e) Y. Shimizu, M. Kanai, *Tetrahedron Lett.* **2014**, *55*, 3727 – 3737; f) H. Egami, M. Sodeoka, *Angew. Chem. Int. Ed.* **2014**, *53*, 8294 – 8308; *Angew. Chem.* **2014**, *126*, 8434 – 8449; g) R. M. Romero, T. H. Wöste, K. Muñiz, *Chem. Asian J.* **2014**, *9*, 972 – 983.

[2] For selected reviews, see: a) T. Pintauer, K. Matyjaszewski, *Chem. Soc. Rev.* **2008**, *37*, 1087 – 1097; b) W. T. Eckenhoff, T. Pintauer, *Catal. Rev.* **2010**, *52*, 1 – 59; c) M.-Y. Cao, X. Ren, Z. Lu, *Tetrahedron Lett.* **2015**, *56*, 3732 – 3742; d) A. J. Clark, *Eur. J. Org. Chem.* **2016**, 2231 – 2243; e) S. Kindt, M. R. Heinrich, *Synthesis* **2016**, 1597 – 1606.

[3] For selected reviews, see: a) J.-R. Chen, X.-Y. Yu, W.-J. Xiao, *Synthesis* **2015**, 604 – 629; b) R.-J. Song, Y. Liu, Y.-X. Xie, J.-H. Li, *Synthesis* **2015**, 1195 – 1209; c) C.-C. Li, S.-D. Yang, *Org. Biomol. Chem.* **2016**, *14*, 4365 – 4377.

[4] For selected reviews, see: a) R. A. Michelin, M. Mozzon, R. Bertani, *Coord. Chem. Rev.* **1996**, *147*, 299 – 338; b) V. Y. Kukushkin, A. J. L. Pombeiro, *Chem. Rev.* **2002**, *102*, 1771 – 1802; c) S. J. Collier, P. Langer, *Science of Synthesis, Vol. 19*, Georg Thieme, Stuttgart, **2004**, pp. 403 – 425; d) V. Y. Kukushkin, A. J. L. Pombeiro, *Inorg. Chim. Acta* **2005**, *358*, 1 – 21; e) M.-X. Wang, *Top. Catal.* **2005**, *35*, 117 – 130.

[5] For selected reviews, see: a) D. T. Mowry, *Chem. Rev.* **1948**, *42*, 189 – 283; b) G. P. Ellis, I. L. Thomas, *Prog. Med. Chem.* **1974**, *10*, 245 – 285.

[6] For examples of the cyanofunctionalization of olefins, see: a) H. Zhang, W. Pu, T. Xiong, Y. Li, X. Zhou, K. Sun, Q. Liu, Q. Zhang, *Angew. Chem. Int. Ed.* **2013**, *52*, 2529 – 2533; *Angew. Chem.* **2013**, *125*, 2589 – 2593; b) N. O. Ilchenko, P. G. Janson, K. J. Szabó, *J. Org. Chem.* **2013**, *78*, 11087 – 11091; c) Y.-T. He, L.-H. Li, Y.-F. Yang, Z.-Z. Zhou, H.-L. Hua, X.-Y. Liu, Y.-M. Liang, *Org. Lett.* **2014**, *16*, 270 – 273; d) Z. Liang, F. Wang, P. Chen, G. Liu, *J. Fluorine Chem.* **2014**, *167*, 55 – 60; e) L. Xu, X.-Q. Mou, Z.-M. Chen, S.-H. Wang, *Chem. Commun.* **2014**, *50*, 10676 – 10679.

[7] For selected examples of the use of PIDA and $TMSN_3$ as azido sources, see: a) P. Magnus, J. Lacour, P. A. Evans, M. B. Roe, C. Hulme, *J. Am. Chem. Soc.* **1996**, *118*, 3406 – 3418; b) K. Matcha, R. Narayan, A. P. Antonchick, *Angew. Chem. Int. Ed.* **2013**, *52*, 7985 – 7989; *Angew. Chem.* **2013**, *125*, 8143 – 8147; c) X.-F. Xia, Z. Gu, W. Liu, H. Wang, Y. Xia, H. Gao, X. Liu, Y.-M. Liang, *J. Org. Chem.* **2015**, *80*, 290 – 295; d) Y. Su, J. L. Petersen, T. L. Gregg, X. Shi, *Org. Lett.* **2015**, *17*, 1208 – 1211; e) R. Zhu, S. L. Buchwald, *J. Am. Chem. Soc.* **2015**, *137*, 8069 – 8077; f) A.-F. Wang, Y.-L. Zhu, S.-L. Wang, W.-J. Hao, G. Li, S.-J. Tu, B. Jiang, *J. Org. Chem.* **2016**, *81*, 1099 – 1105.

[8] For selected examples of the azidation of alkenes, see: a) J. Waser, H. Nambu, E. M. Carreira, *J. Am. Chem. Soc.* **2005**, *127*, 8294 – 8295; b) J. Waser, B. Gaspar, H. Nambu, E. M. Carreira, *J. Am. Chem. Soc.* **2006**, *128*, 11693 – 11712; c) F. C. Sequeira, B. W. Turnpenny, S. R. Chemler, *Angew. Chem. Int. Ed.* **2010**, *49*, 6365 – 6368; *Angew. Chem.* **2010**, *122*, 6509 – 6512; d) K. Weidner, A. Giroult, P. Panchaud, P. Renaud, *J. Am. Chem. Soc.* **2010**, *132*, 17511 – 17515; e) A. Kapat, A. König, F. Montermini, P. Renaud, *J. Am. Chem. Soc.* **2011**, *133*, 13890 – 13893; f) B. Zhang, A. Studer, *Org. Lett.* **2013**, *15*, 4548 – 4551; g) B. Zhang, A. Studer, *Org. Lett.* **2014**, *16*, 1790 – 1793; h) F. Wang, X. Qi, Z. Liang, P. Chen, G. Liu, *Angew. Chem. Int. Ed.* **2014**, *53*, 1881 – 1886; *Angew. Chem.* **2014**, *126*, 1912 – 1917; i) X. Sun, X. Li, S. Song, Y. Zhu, Y. Liang, N. Jiao, *J. Am. Chem. Soc.* **2015**, *137*, 6059 – 6066.

[9] For reviews on the synthesis of distally-substituted ketones, see: a) R. Ren, C. Zhu, *Synlett* **2016**, 1139 – 1144; b) X. Fan, H. Zhao, C. Zhu, *Acta Chim. Sin.* **2015**, *73*, 979 – 983. For examples from our group, see: c) H. Zhao, X. Fan, J. Yu, C. Zhu, *J. Am. Chem. Soc.* **2015**, *137*, 3490 – 3493; d) R. Ren, H. Zhao, L. Huan, C. Zhu, *Angew. Chem. Int. Ed.* **2015**, *54*, 12692 – 12696; *Angew. Chem.* **2015**, *127*, 12883 – 12887; e) X. Fan, H. Zhao, J. Yu, X. Bao, C. Zhu, *Org. Chem. Front.* **2016**, *3*, 227 – 232; f) R. Ren, Z. Wu, Y. Xu, C. Zhu, *Angew. Chem. Int. Ed.* **2016**, *55*, 2866 – 2869; *Angew. Chem.* **2016**, *128*, 2916 – 2919; g) R. Ren, Z. Wu, C. Zhu, *Chem. Commun.* **2016**, *52*, 8160 – 8163.

[10] L. Hu, C. Mick-Lichtenfeld, T. Wang, G. He, M. Gao, J. Zhao, *Chem. Eur. J.* **2016**, *22*, 911 – 915.

[11] a) J. Kalvoda, *J. Chem. Soc. Chem. Commun.* **1970**, 1002 – 1003; b) D. S. Watt, *J. Am. Chem. Soc.* **1976**, *98*, 271 – 273; c) R. W. Freerksen, W. E. Pabst, M. L. Raggio, S. A. Sherman, R. R. Wroble, D. S. Watt, *J. Am. Chem. Soc.* **1977**, *99*, 1536 – 1542; d) G. W. Holbert, J. O. Johnston, B. W. Metcalf, *Tetrahedron Lett.* **1985**, *26*, 1137 – 1140; e) A. L. J. Beckwith, D. M. O'Shea, S. Gerba, S. W. Westwood, *J. Chem. Soc. Chem. Commun.* **1987**, 666 – 667; f) A. L. J. Beckwith, D. M. O'Shea, S. W. Westwood, *J. Am. Chem. Soc.* **1988**, *110*, 2565 – 2575; g) T. Kawamoto, S. J. Geib, D. P. Curran, *J. Am. Chem. Soc.* **2015**, *137*, 8617 – 8622; h) E. Doni, J. A. Murphy, *Org. Chem. Front.* **2014**, *1*, 1072 – 1076.

[12] For a review, see: a) H.-P. Husson, J. Royer, *Chem. Soc. Rev.* **1999**, *28*, 383 – 394; For selected examples, see: b) T. J. Wilkinson, N. W. Stehle, P. Beak, *Org. Lett.* **2000**, *2*, 155 – 158; c) X. Wang, Y. Dong, J. Sun, X. Xu, R. Li, Y. Hu, *J. Org. Chem.* **2005**, *70*, 1897 – 1900; d) J. C. G. González-Gómez, M. Medjahdi, F. Foubelo, M. Yus, *J. Org. Chem.* **2010**, *75*, 6308 – 6311; e) N. Gouault, M. L. Roch, G. C. Pinto, M. David, *Org. Biomol. Chem.* **2012**, *10*, 5541 – 5546.

[13] M. Kavala, F. Mathia, J. Kozisek, P. Szolcsanyi, *J. Nat. Prod.* **2011**, *74*, 803 – 808.

Received: May 26, 2016
Revised: July 11, 2016
Published online: August 4, 2016

