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Authors: Ahmad A. Almasalma and Esteban Mejía

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Copper-Catalyzed Allylic C-H Alkynylation *via* Cross-Dehydrogenative Coupling

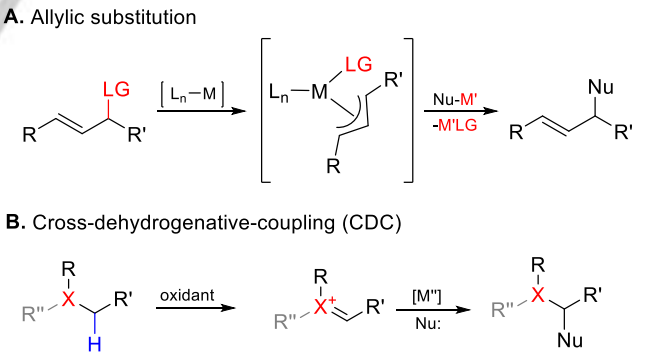
Ahmad A. Almasalma[a] and Esteban Mejía*[a]

Abstract: C-H bond functionalization is a well-developed concept that has been thoroughly studied and gives entry to rather complex molecules without the need of previous derivatization of the substrates, although the use of copper complexes for allylic C-H bond functionalization under oxidative conditions as an alternative to the well-established palladium-based methodologies remains largely underdeveloped. Here we show for the first time a selective cross-dehydrogenative coupling reaction between underivatized allylic substrates and terminal alkynes to produce 1,4-enynes in high yields in a single step, using an in situ synthesized copper catalyst and an oxidant.

Allylic substitution is currently one of the most important methods for the construction of C-C bonds and has been used as a key step to access pharma intermediates and complex target molecules like natural products.[1] It is usually carried out with palladium catalysts[2] even though several metals including copper, nickel, platinum, rhodium, iridium, ruthenium, molybdenum and tungsten have been also explored.[3] Almost invariably, the key intermediate of these reactions is a (π-allyl)metal complex which can undergo a wide range of regio-, chemo- , and stereoselective transformations (Scheme 1, A). An important drawback of all these methodologies is that they require electrophilic substrates with preinstalled leaving groups at the allylic position like halides, phosphonates acetoxy, amino, hydroxyl and carbonates.[1, 3b, 4] The installation of these functional groups requires additional synthetic steps, and narrows the scope of this transformation. Therefore, the direct utilization of allylic C–H bonds as C-C bond coupling substrates is of high interest. Transition-metal catalyzed C-H bond functionalization offers a good alternative to overcome these problems.[5] These processes are atom-economic, make synthesis protocols shorter and reduce the amount of produced waste (metal salts), leading to sustainable processes, an ultimate goal of our modern society in which environmental concerns are of highest priority.

Most of the developed C-H functionalization methodologies relies on the functionalization of C–H bonds at sp^2 carbons, especially from electron-rich heterocycles and directing group-containing arenes,[6] for both, kinetic and thermodynamic reasons, the metal-catalyzed C–H functionalization at sp^3 carbons devoid of functional groups is more challenging than that at its sp^2 hybridized congeners,[7] with the exception of C-H bonds at benzylic and allylic positions.[8] Although copper-based C-H functionalization is a fairly active research field,[9] when compared to the amount of research done on Pd systems, one can fairly say that is still underdeveloped. Most of the efforts on this area have been focused on aromatic sp^2 hetero-derivatization[10] and on the synthesis of heterocycles.[11] Reports on copper-catalyzed allylic C-H bond functionalization are still scarce, even though allylic oxidation with peresters is known for a long time (as the Kharash-Sosnovsky reaction).[12] Other allylic C-H heterofunctionalyzation reactions have being developed, namely aminations[13] and phosphonations.[14] Allylic trifluoromethylation is one of the few rare cases by which C-C bond formation has been achieved by means of Cu-catalyzed allylic C-H functionalization.[15]

Developed at the turn of the 21st century, the *cross-dehydrogenative coupling* reaction (CDC), is a powerful and elegant methodology for the formation of C-C bonds using two different C-H moieties.[16] Following this breakthrough, various efficient methods have been developed for sp^3 C–H bond functionalization and subsequent coupling with sp, sp^2 and sp^3 C–H bonds under relatively mild reaction conditions with good selectivity.[16a, 17] One apparent limitation of the CDC approach is that most derivatizations occur at α-C–H bond to heteroatoms such as nitrogen and oxygen due to the prompt formation of iminium and oxonium ions respectively, under oxidative conditions (Scheme 1, B).[18]



Scheme 1. C-C Bond forming methodologies relevant to this work (general scheme). R, R', R''= alkyl or aryl; LG= leaving group; Nu= nucleophile (organyl); M= Pt or Cu); M'= main group metal (Li, MgBr); X= O or N; M''= Cu, Zn or Ag

In a seminal report, Li and co-workers described the first catalytic allylic alkylation reaction coupling an allylic sp^3 carbon with a methylenic sp^3-C using a combination of CuBr and $CoCl_2$ as catalysts and a super-stoichiometric amount of tert-butyl hydroperoxide (TBHP) as the oxidant.[19] However, the extension of this methodology to terminal alkynes has, so far, remained elusive.

[a] A. A: Almasalma and Dr. E. Mejía
Leibniz Institute for Catalysis
Albert-Einstein-Straße 29a, 18059 Rostock, Germany
Esteban.Mejia@catalysis.de

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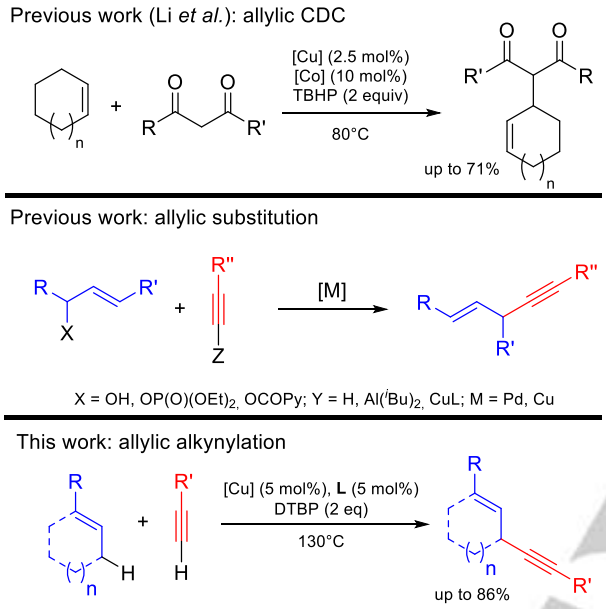
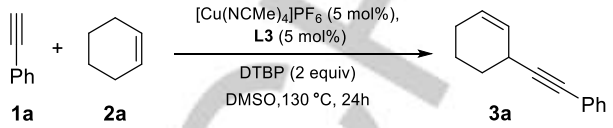
To the best of our knowledge, this work is the first example of a direct allylic C(sp^3)–H alkynylation reaction with terminal alkynes. Compared with the "classic" allylic substitution approaches (Scheme 2),[20] this new methodology gives a more straightforward access to 1,4-enynes, important structural scaffolds in organic synthesis[21] and core of several compounds of pharmaceutical relevance.[22] Thus, we hope, it might become a valuable addition to the organic chemist's toolbox.



Scheme 2. Allylic C-C coupling reactions. TBHP=tert-butyl hydroperoxide; DTBP=di-tert-butyl peroxide

We started our research by establishing the conditions for the representative CDC reaction between phenylacetylene (**1a**) and cyclohexene (**2a**) (Scheme 3). After an extensive screening of various oxidants (Table S1), catalysts precursors (Table S2), stoichiometric ratio of the reactants (Table S3), and ligands (Table 1), we selected as the best conditions: **1a** (1 equivalent), an excess of 2a (10 equivalents), $[Cu(NCMe)_4]PF_6$ as the catalyst precursor (5 mol%), 4'-(p-tolyl)-2,2':6',2''-terpyridine **L3** as ligand (5 mol%) and DTBP as oxidant (2 equivalents) in DMSO at 130 °C for 24 hours. Under these conditions product **3a** was afforded in 70 % within 5 hours, 75% after 16 hours, 78% after 24 hours without any further increase of the yield after 48 hours.

The use of TBHP as oxidant (as reported by Li *et al*.) [19] proved to be ineffective, as well as other common oxidants including benzoyl peroxide (BPO), 1,4 benzoquinone (BQ), $Cu(OAc)_2$ and oxygen. The chosen ligand also showed to play an important role on the reaction efficiency; selected examples are presented in Chart 1. The best results were obtained with terpyridine derivatives (**L1**-**L7**), which, compared to the commonly used bipyridins and phenantrolines (**L8**, **L9** and **L10**), can prevent more effectively the formation of metal aggregates and other inactive complexes by ligation of multiple substrate molecules.[23] Moreover, considering their strong σ-donating properties, a good stabilization of copper(II) and (III) intermediates can be anticipated (see mechanistic discussion below). Other ligands common in copper chemistry like bidentate phosphines, N-heterocyclic carbenes and phtalocyanine proved to be ineffective.



Scheme 3. Optimized conditions for the allylic alkynylation reaction *via* CDC: **1a** (1 equivalent), **2a** (10 equivalents), [Cu(NCMe)4]PF6 (5 mol%), **L3** (5 mol%), DTBP (2 equivalents), DMSO, 130 °C, 24 hours

Table 1. Effect of chelating pyridine ligands on the yield of **3a**.

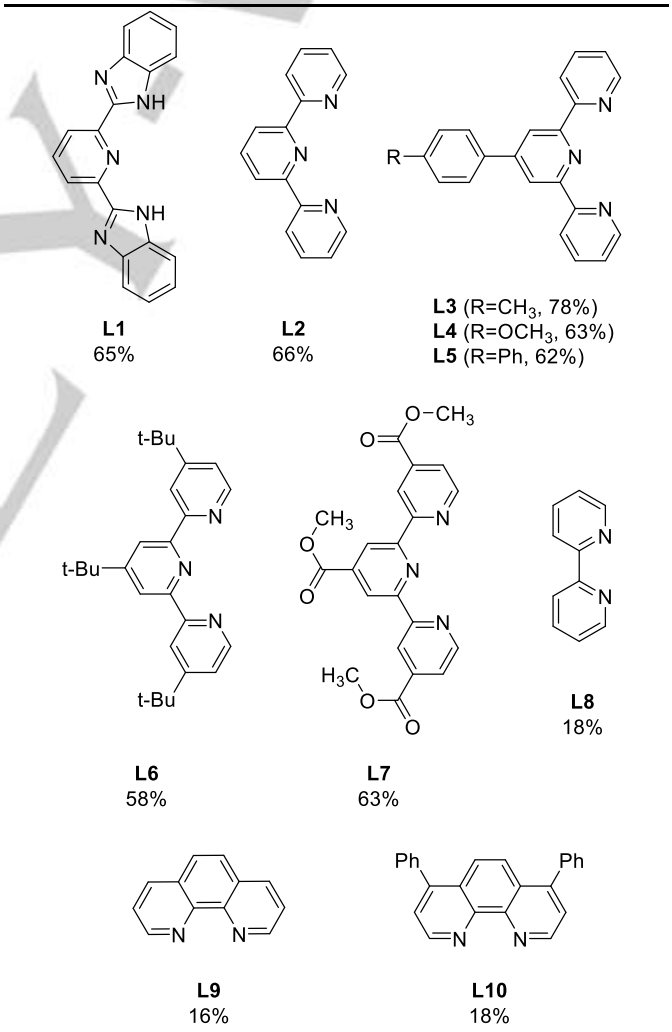
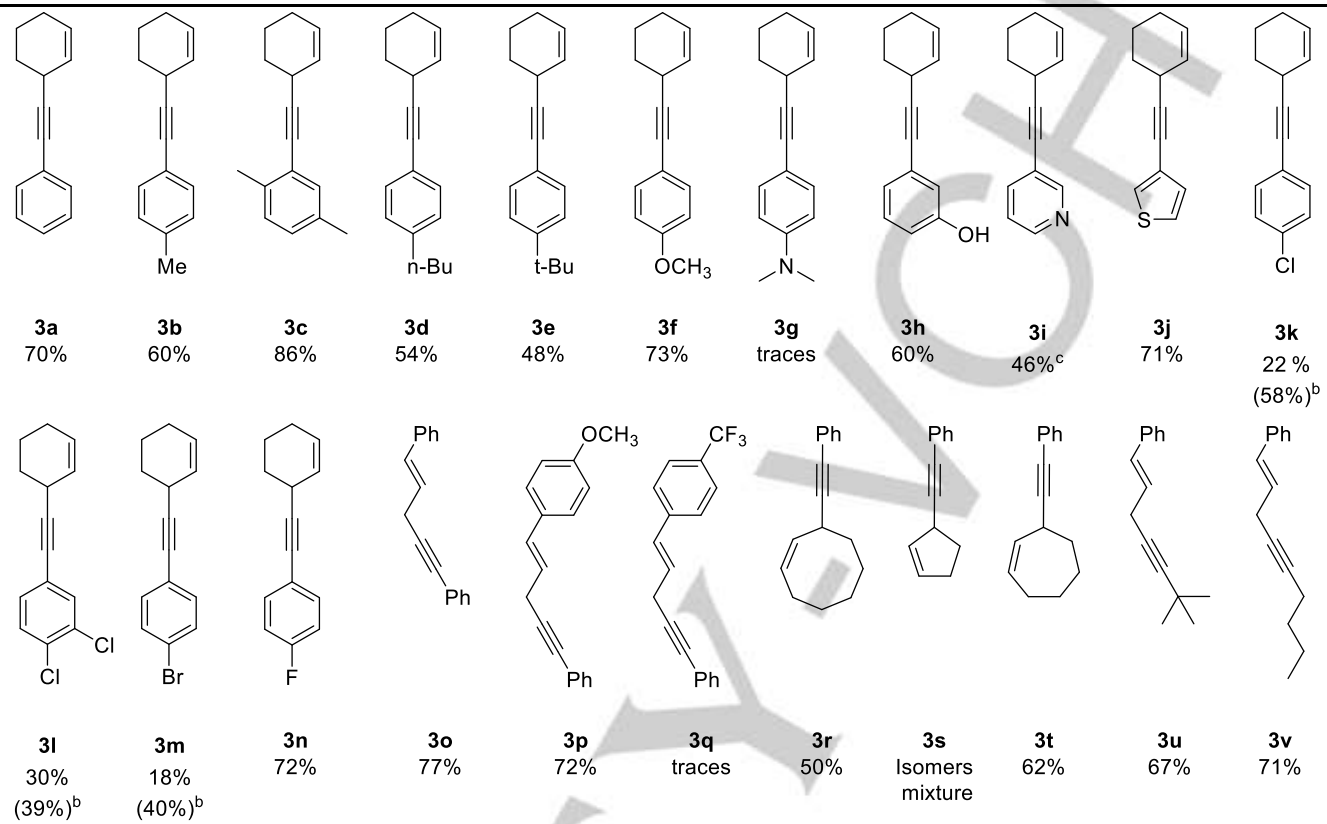


Table 2. Substrate scope for the allylic alkynylation reaction *via* CDC.[a]



[a] Isolated yield. [b] Using **L1**. [c] NMR yield …

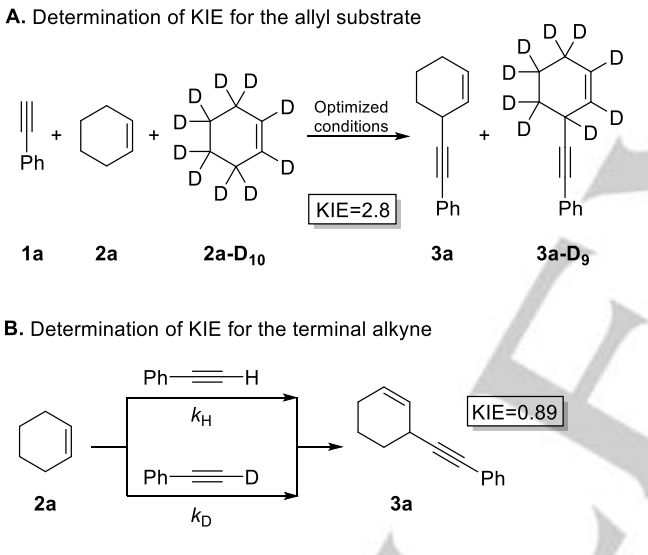
While direct C–H alkynylation (with terminal alkynes) has recently emerged as one of the preferred approaches to access substituted alkynes, this transformation is still challenging due to the facile Glaser-type homo-coupling and polymerization of terminal alkynes under oxidative conditions.[24] In our case, the use of a tenfold excess of cyclohexene **2a** was enough to effectively slow down the undesired dimerization of **1a** that results in the formation of 1,4-diphenylbuta-1,3-diyne (**4**, Table S3).

With the best conditions at hand, we decided to investigate the substrate scope of this transformation with different types of terminal acetylenes (Table 2). In all cases, the major by-product was the corresponding prop-1-yn-1-ylbenzene derivative, resulting from the methylation of the alkyne (vide infra). In general, phenylacetylene derivatives bearing electron-donating substituents on the phenyl ring showed good reactivity, furnishing the desired products in high yields (**3a**-**3f**), except from the 4-(N,N-dimethylamino)phenylacetylene, which led only to trace amounts of the coupling product (**3g**). A plausible explanation to this caveat might be the propensity of alkyl amines to form radicals in α-positions (to the nitrogen), resulting in uncontrolled side reactions.[25] Interestingly, *m*-hydroxy phenylacetylene could be successfully derivatized with our new methodology without previous protection of the hydroxyl functionality yielding the 1,4-enyne **3h** in 60% yield. Electron-deficient substrates were also reactive under these conditions, although lower yields of **3** were obtained (**3i**-**3n**). Electron-rich allylbenzene derivatives also proved to be effective substrates for the CDC reaction with phenyl acetylene producing the corresponding linear 1,4-enynes **3o** and **3p** in good yields and requiring only a five-fold excess. On the contrary, reaction of the electron-poor, CF_3-substituded allyl benzene resulted only in traces of the desired product (**3q**). The scope of the CDC coupling with phenylacetylene was extended successfully to other cycloalkanes. Although slightly lower yields were obtained for larger rings (cyclooctene, **3r** and cycloheptene, **3t**) only the desired product was observed. On the contrary, in spite of its high reactivity (resulting on 67% conversion of **1a**), the reaction with cyclopentene afforded a mixture of isomers of difficult separation (**3s**). The reaction was also successful when less reactive aliphatic alkynes were used (**3u** and **3v**).

In order to assess the nature of the radical species present in the reaction mixture, radical trapping experiments using TEMPO (2, 2, 6, 6–tetramethylpiperidin–1–yl)oxy were carried out (see Supporting Information, Scheme S1). By adding 1 equivalent of TEMPO to the reaction mixture 50 % of the expected product

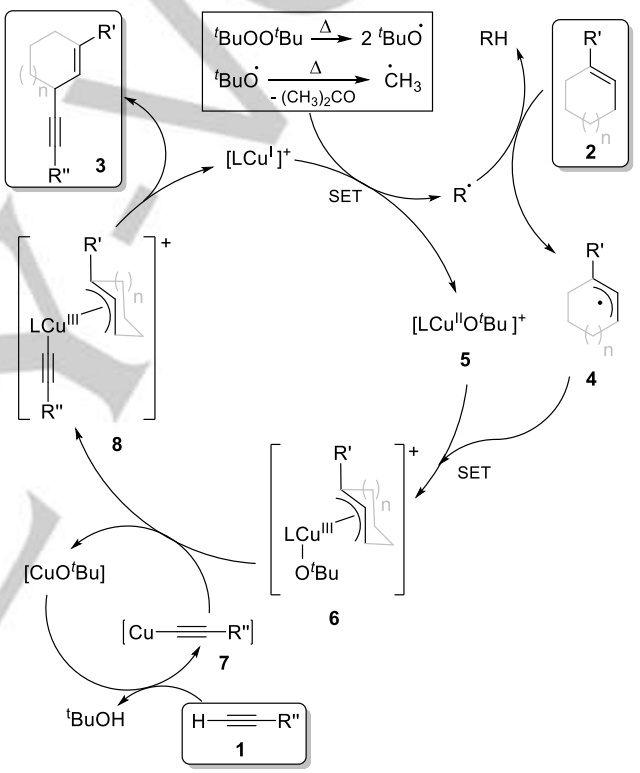
(**3a**) was obtained along with methylated TEMPO as the only TEMPO-derivative. The use of higher amounts of the radical trap (3 equivalents) resulted in complete inhibition of the cross-coupling reaction, being the methylated TEMPO the only product. These results underline the importance of the methyl radicals, not only as a side product of the decomposition of the tert-butoxy radicals, but as possible reaction partners for the deprotonation of the allyl substrate **2**.

A primary kinetic isotopic effect (see Supporting information) was observed for C(sp^3)-H bond cleavage (Scheme 4, A; [**3a**]/[**3a-D$_9$**] =2.8), suggesting that irreversible C(sp^3)–H bond cleavage in the cyclohexene occurs within the catalytic cycle, although with the available data it cannot be said if it is involved in the turnover-determining step of the overall transformation.[26] Moreover, while no obvious kinetic isotopic effect was observed for the C(sp)–H for phenyl acetylene (Scheme 5, B; k_H/k_D=0.89), it can be concluded that C-H bond cleavage at the terminal alkyne is not involved in the turnover-determining step (for a detailed description on the determination of the reaction rates, see Supporting information).



Scheme 4. Experiments for the determination of the kinetic isotope effects (KIE)

Although the exact underlying reaction mechanism remains unclear, we postulate the pathway depicted in Scheme 5. In a first step, DTBP (thermally) splits to generate two O-centered alkoxyl radicals.[27] The formed alkoxyl radicals can selectively abstract a hydrogen atom from the allylic position of **2** to generate the allyl radical **4**.[28] Comparison of the corresponding bond dissociation energies (BDE, kJ/mol) of both the O-H bond in *t*-BuOH ─produced when DTBP is used─ (444.9) and the allylic C-H of propylene (368.6),[29] shows that this radical abstraction is exergonic, hence thermodynamically favored. Nevertheless, under our reaction conditions the formed tert-butoxy radicals can decompose into methyl radicals and acetone(equation 2).[30] The produced open-shell species may then react with the copper(I) catalyst [LCuI]$^+$ in a reductive fashion to produce the oxidized copper(II) complex **5**.[31] This single electron transfer (SET) reaction should be feasible considering the inherent electrophilicity of the alkoxy radical[32] and the reductive power of [LCu^I]$^+$ (for reference: $E_{1/2}^{Cu(II)/Cu(I)}$ in water is -0.093 V vs. SCE).[33] Taking into account the known propensity of copper(II) complexes to react with organic radicals,[27, 34] the formation of the transient copper(III) intermediate **6** can be expected.[35] At the same time, the formation of organocuprates (**7**) under the reaction conditions is anticipated due to the inherent acidity of the protons of the substrate (**1**).[36] Finally, ligand exchange between **6** and **7** would lead to the formation of the copper(III) intermediate **8** which, upon reductive elimination of the coupling product **3,** shall regenerate the copper(I) catalyst [LCu^I]$^+$.



Scheme 5. Proposed reaction mechanism for the allylic alkynylation reaction via CDC

The cross-coupling of open-shell (radical) species have become a powerful and attractive way to create new C-C bonds. Yet, the hurdles associated with this process (even though the activation energy of radical−radical coupling reactions is nearly zero), have slowed down the development of radical C-H functionalization/cross coupling processes, compared with "classical" cross-coupling methodologies. [37] Herewith, we report a novel methodology to achieve oxidative C–H cross-coupling of underivatized allylic substrates (cyclic and linear) and terminal alkynes (aromatic and aliphatic). The utilization copper(I) and a trispyridyl ligand for this catalytic system was the key for controlling the reaction selectivity towards the allylic alkynylation (cross-coupling) versus the, commonly unsurmountable, alkynyl

homocoupling. It has to be noted that in order to do so, a tenfold excess of the allylic substrate is necessary. Various substituted 1,4 enynes were synthesized in good to high yields with a good functional group tolerance. Preliminary mechanistic studies suggest that the reaction proceeds through cross-dehydrogenative pathway with a primary KIE for the C-H bond braking on the allylic substrate and the involvement of CH_3 radicals from the decomposition of the oxidant DTBP. To the best of our knowledge, this work provides the first example of a direct allylic C(sp^3)–H alkynylation with terminal alkynes, giving access to 1,4-enynes under oxidative conditions without the need of preinstalled leaving groups or strong organometallic nucleophiles. Further studies towards the control of the stereochemical outcome of the reaction, the replacement of the oxidant and further optimization of the condition are currently undergoing in our laboratories and will be the subject of a separate report.

Acknowledgements

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Keywords: Copper • Cross Dehydrogenative Coupling • Allylic Alkynylation • Oxidation • C-H Functionalization

[1] B. M. Trost, M. L. Crawley, in Topics in Organometallic Chemistry, Vol. 38 (Ed.: U. Kazmaier), Springer Berlin, Heidelberg, 2012, pp. 321-340.

[2] a) S. Fan, F. Chen, X. Zhang, Angew. Chem., Int. Ed. 2011, 50, 5918-5923; b) G. Liu, Y. Wu, in Topics in Current Chemistry, Vol. 292 (Eds.: J.-Q. Yu, Z. Shi), Springer, Berlin, Heidelberg, 2010, pp. 195-209.

[3] a) B. L. Tran, M. Driess, J. F. Hartwig, J. Am. Chem. Soc. 2014, 136, 17292-17301; b) J.-M. Begouin, J. M. N. Klein, D. Weickmann, B. Plietker, in Topics in Organometallic Chemistry, Vol. 38 (Ed.: U. Kazmaier), Springer, Berlin, Heidelberg, 2012, pp. 269-320; c) Y. Nishibayashi, S. Uemura, in Comprehensive Organometallic Chemistry III, Vol. 11 (Eds.: R. H. Crabtree, D. M. P. Mingos), Elsevier, 2007, pp. 75-122; d) G. Helmchen, U. Kazmaier, S. Förster, in Catalytic Asymmetric Synthesis, Third ed. (Ed.: I. Ojima), John Wiley & Sons, Inc., 2010, pp. 437-770.

[4] a) N. A. Butt, W. Zhang, Chem. Soc. Rev. 2015, 44, 7929-7967; b) J.-B. Langlois, A. Alexakis, in Topics in Organometallic Chemistry, Vol. 38 (Ed.: U. Kazmaier), Springer Berlin, Heidelberg, 2012, pp. 235-268.

[5] H. M. L. Davies, J. Hansen, in Catalytic Asymmetric Synthesis (Ed.: I. Ojima), John Wiley & Sons, Inc., 2010, pp. 163-226.

[6] T. W. Lyons, M. S. Sanford, Chem. Rev. 2010, 110, 1147-1169.

[7] J. A. Labinger, J. E. Bercaw, Nature 2002, 417, 507-514.

[8] T. Jensen, P. Fristrup, Chem. Eur. J. 2009, 15, 9632-9636.

[9] a) H.-Q. Do, O. Daugulis, J. Am. Chem. Soc. 2011, 133, 13577-13586; b) J. Roane, O. Daugulis, J. Am. Chem. Soc. 2016, 138, 4601-4607; c) X. Chen, X.-S. Hao, C. E. Goodhue, J.-Q. Yu, J. Am. Chem. Soc. 2006, 128, 6790-6791.

[10] J.-L. Hu, J. Li, Y.-F. Zhou, Curr. Green Chem. 2015, 2, 170-191.

[11] a) X.-X. Guo, D.-W. Gu, Z. Wu, W. Zhang, Chem. Rev. 2015, 115, 1622-1651; b) O. Daugulis, in Topics in Current Chemistry, Vol. 292 (Eds.: J.-Q. Yu, Z. Shi), Springer, Berlin, Heidelberg, 2010, pp. 57-84.

[12] a) D. J. Rawlinson, G. Sosnovsky, Synthesis 1972, 1972, 1-28; b) G. Chelucci, A. Iuliano, D. Muroni, A. Saba, J. Mol. Catal. A: Chem. 2003, 191, 29-33.

[13] R. T. Gephart, T. H. Warren, Organometallics 2012, 31, 7728-7752.

[14] B. Yang, H.-Y. Zhang, S.-D. Yang, Org. Biomol. Chem. 2015, 13, 3561-3565.

[15] 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, 15300-15303.

[16] a) C.-J. Li, Acc. Chem. Res. 2009, 42, 335-344; b) C. Zhang, C. Tang, N. Jiao, Chem. Soc. Rev. 2012, 41, 3464-3484; c) S. A. Girard, T. Knauber, C.-J. Li, Angew. Chem., Int. Ed. 2014, 53, 74-100.

[17] Y. Xing, N.-X. Wang, W. Zhang, Synlett 2015, 26, 2088-2098.

[18] A. Gini, T. Brandhofer, O. G. Mancheno, Org. Biomol. Chem. 2017, 15, 1294-1312.

[19] Z. Li, C.-J. Li, J. Am. Chem. Soc. 2006, 128, 56-57.

[20] a) Y.-X. Li, Q.-Q. Xuan, L. Liu, D. Wang, Y.-J. Chen, C.-J. Li, J. Am. Chem. Soc. 2013, 135, 12536-12539; b) A. Harada, Y. Makida, T. Sato, H. Ohmiya, M. Sawamura, J. Am. Chem. Soc. 2014, 136, 13932-13939; c) Y. Makida, Y. Takayama, H. Ohmiya, M. Sawamura, Angew. Chem., Int. Ed. 2013, 52, 5350-5354; d) J. A. Dabrowski, F. Gao, A. H. Hoveyda, J. Am. Chem. Soc. 2011, 133, 4778-4781; e) Y. Kiyotsuka, Y. Kobayashi, J. Org. Chem. 2009, 74, 7489-7495.

[21] a) T. Sato, T. Onuma, I. Nakamura, M. Terada, Org. Lett. 2011, 13, 4992-4995; b) X. Shi, D. J. Gorin, F. D. Toste, J. Am. Chem. Soc. 2005, 127, 5802-5803; c) A. Buzas, F. Gagosz, J. Am. Chem. Soc. 2006, 128, 12614-12615; d) F. Erver, J. R. Kuttner, G. Hilt, J. Org. Chem. 2012, 77, 8375-8385; e) V. Hickmann, M. Alcarazo, A. Fürstner, J. Am. Chem. Soc. 2010, 132, 11042-11044.

[22] a) V. D. P. Nair, A. Dairam, A. Agbonon, J. T. Arnason, B. C. Foster, I. Kanfer, J. Agric. Food Chem. 2007, 55, 1707-1711; b) S. Drewes, R. W. Liebenberg; Roecar Holdings US4652636 A, 1987

[23] A. Kiyomori, J.-F. Marcoux, S. L. Buchwald, Tetrahedron Lett. 1999, 40, 2657-2660.

[24] a) S. Tang, P. Wang, H. Li, A. Lei, Nat. Commun. 2016, 7, 11676; b) X. Chen, H. Zhang, J. Chen, H. Gong, Chem. Lett. 2015, 44, 129-131.

[25] O. Kei, N. Takashi, F. Shunichi, Bull. Chem. Soc. Jpn. 2006, 79, 1489-1500.

[26] E. M. Simmons, J. F. Hartwig, Angew. Chem., Int. Ed. 2012, 51, 3066-3072.

[27] A. L. J. Beckwith, A. A. Zavitsas, J. Am. Chem. Soc. 1986, 108, 8230-8234.

[28] a) J. K. Kochi, P. J. Krusic, J. Am. Chem. Soc. 1968, 90, 7157-7159; b) P. C. Wong, D. Griller, J. C. Scaiano, J. Am. Chem. Soc. 1982, 104, 5106-5108.

[29] J. Hioe, H. Zipse, Org. Biomol. Chem. 2010, 8, 3609-3617.

[30] P. J. Jones, B. Riser, J. Zhang, J. Phys. Chem. A 2017, 121, 7846-7853.

[31] F. Chen, C. Qin, Y. Cui, N. Jiao, Angew. Chem., Int. Ed. 2011, 50, 11487-11491.

[32] B. P. Roberts, Chem. Soc. Rev. 1999, 28, 25-35.

[33] B. R. James, R. J. P. Williams, J. Chem. Soc. 1961, 0, 2007-2019.

[34] Y. L. Chow, G. E. Buono-Core, J. Am. Chem. Soc. 1986, 108, 1234-1239.

[35] A. Casitas, X. Ribas, Chem. Sci. 2013, 4, 2301-2318.

[36] Z. Li, C.-J. Li, J. Am. Chem. Soc. 2004, 126, 11810-11811.

[37] H. Yi, G. Zhang, H. Wang, Z. Huang, J. Wang, A. K. Singh, A. Lei, Chem. Rev. 2017, 117, 9016-9085.

10.1002/chem.201801772

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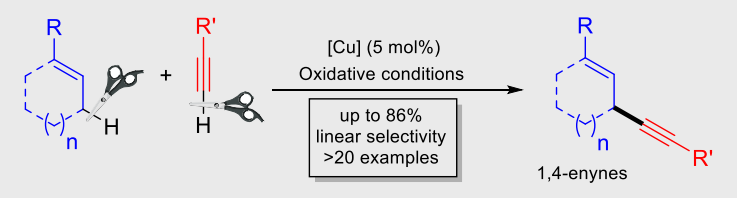

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