C–H functionalization | Hot Paper

DOI: 10.1002/ange.201407083

Practical and Highly Selective C–H Functionalization of Structurally Diverse Ethers**

*Miao Wan, Zhilin Meng, Hongxiang Lou, and Lei Liu**

Abstract: *A trityl ion mediated C–H functionalization of ethers with a wide range of nucleophiles at ambient temperature has been developed. The reaction displays high chemoselectivity and good functional group tolerance. The protocol also exhibits excellent regio- and diastereoselectivities for the unsymmetric ethers, thus stereoselectively generating highly functionalized disubstituted 2,5-trans tetrahydrofurans (THF), 2,6-trans tetrahydropyrans (THP), 2,6-trans dihydropyrans (DHP), and 1,3-trans isochromans, and highlighting the capacity of the protocol in complex molecule synthesis.*

Ethers are one of the most common structural motifs spread across bioactive natural products and synthetic pharmaceuticals (Figure 1).[1] Over 20% of the top 200 small-molecule

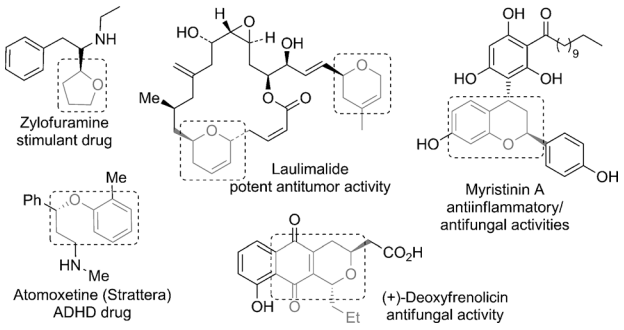


Figure 1. Representative bioactive molecules containing α-functionalized ethers.

pharmaceuticals and 75% of new chemical entities contain at least one α-substituted ether moiety.[1c] Therefore, the availability of efficient methods for the synthesis of structurally diverse α-substituted ethers is vital to the discovery of biologically interesting agents.

α-Substituted ether synthesis typically relies on the transformation of pre-existing functional groups such as heteroatoms and unsaturation in Williamson ether synthesis, hydroalkoxylation, Lewis acid mediated nucleophilic substituent of acetals, etc.[2] While the traditional methods are efficient, multiple and unproductive steps are usually involved for reactive functionality incorporation.[3] Moreover, the α-substituent is customarily installed early in the synthesis, and thus the starting materials are often dissimilar from the targets. Therefore, during the preparation of a series of compounds, multiple and distinct de novo sequences are required for each derivative. In contrast, selective and direct C(sp^3)–H functionalization of ethers with different carbon nucleophiles provides a straightforward approach to access multiple analogues from a common structural precursor by a structural-core diversification strategy.[4] The C–H functionalization of ethers has attracted great interest since the pioneering studies of Li and co-workers, and a number of oxidation systems have been developed.[5] However, the approaches lack broad generality. The scope is narrow, with the substrate largely restricted to activated benzyl ethers like isochroman derivatives. The functionalization of saturated ethers proved to be much more challenging, which might be ascribed to their inherent low reactivity.[6,7] The existing oxidation systems typically required high temperature, neat conditions, and long reaction times. Therefore, poor regio- and diastereoselectivity are always observed during the oxidation of unsymmetric ethers. The neat conditions call for a large excess of ether substrates as the solvent, lacks atom-economy, and limits the application in the late-stage synthesis of complex molecules because of the inaccessibility to solvent-scaled advanced ether intermediates. Moreover, each known method only focused on a single class of the nucleophile, and therefore, the integrated pattern of functionalities in the α-position is narrow. Therefore, the development of a mild and selective approach for direct C–H functionalization of a variety of ethers with a wide range of nucleophiles is highly desired.

Trityl ions have long been known to mediate the oxidation of oxygen-containing substrates.[8] For example, Ph_3CBF_4 was used to promote the deprotection of benzyl ethers,[8a] and induce the oxidation of trimethylsilyl ethers to ketones.[8b] Ph_3CBF_4 can also facilitate the C–H functionalization of acetal 1,3-dioxolane with MeLi or TMSCN in two steps, with the formation of the isolable 1,3-dioxolan-2-ylium cation as the first step.[8c,d] However, to the best of our knowledge, trityl ions have not been used to initiate the oxidative coupling of ethers with carbon nucleophiles to date.

Inspired by the predictable reactivity patterns and functional diversity of organoboranes, the coupling of the tetrahydrofuran (THF; **1a**) with the potassium trifluorobo-

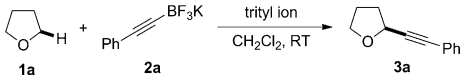
[*] M. Wan,[+] Z. Meng,[+] Prof. H. Lou, Prof. L. Liu
Key Lab of Chemical Biology of Ministry of Education
School of Pharmaceutical Sciences
Shandong University, Jinan 250012 (China)
E-mail: leiliu@sdu.edu.cn

[+] These authors contributed equally to this work.

[**] We are grateful to Dr. Paul E. Floreancig (University of Pittsburgh) and Dr. Armin R. Ofial (University of Munich) for helpful suggestion on the mechanism. This work was supported by the National Science Foundation of China (21202093, 21472112, and 21432003), the Program for New Century Excellent Talents in University (NCET-13-0346), and the Fundamental Research Funds of Shandong University (2014JC005).

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201407083.

Table 1: The exploration of trityl ion source.[a]

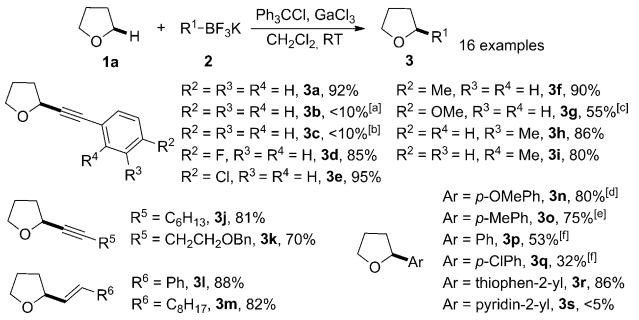


Entry	Trityl ion	Time [h]	Yield [%][b]
1	Ph_3CBF_4	1	31
2	Ph_3CClO_4	1	42
3	Ph_3CX[c]	1	< 20
4	Ph_3CCl/TMSOTf	1	20
5	$Ph_3CCl/FeCl_3$	1	50
6	$Ph_3CCl/InBr_3$	1	75
7	Ph_3CCl/LA[d]	1	< 40
8	$Ph_3CCl/GaCl_3$	1	92
9	$GaCl_3$ or Ph_3CCl	24	0
10	$Ph_3CClO_4/GaCl_3$	1	43
11	(*m*-F)$Ph_3CCl/GaCl_3$	1	76
12	(*p*-Me)$Ph_3CCl/GaCl_3$	1	81
13	(*p*-OMe)$Ph_3CCl/GaCl_3$	1	21
14	$Ph_2CHCl/GaCl_3$	24	0

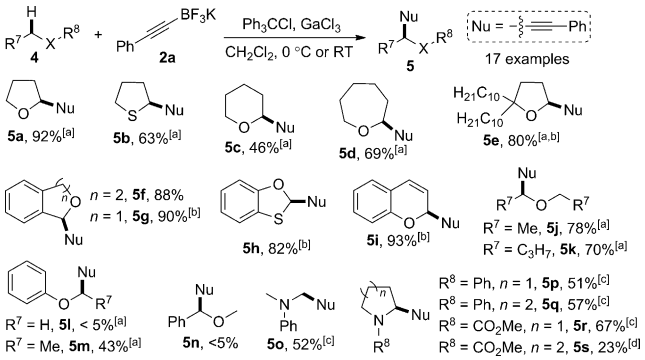
[a] The reaction was conducted with **1a** (4 mmol), **2a** (0.2 mmol), and oxidant (0.1 mmol) in CH_2Cl_2 (1.0 mL) at RT. [b] Yield of isolated product. [c] Ph_3COTf, Ph_3CSbCl_6, and Ph_3CPF_6 used. [d] Other Lewis acids: $TiCl_4$, $AlCl_3$, $InCl_3$, $Yb(OTf)_3$, $Sc(OTf)_3$, $Cu(OTf)_2$, and $BF_3{\cdot}OEt_2$. LA = Lewis acid, Tf = trifluoromethanesulfonyl, TMS = trimethylsilyl.

rate **2a** was selected as a model reaction for the optimization.[9] Initially, several commonly employed pre-prepared trityl salts were examined in CH_2Cl_2 at room temperature (Table 1, entries 1–3). The different efficiency observed for these oxidants prompted us to further explore the counter-ion effect on the coupling. Accordingly, a number of trityl salts were examined by mixing Ph_3CCl (1.0 equiv) with a variety of Lewis acids (1.0 equiv) in CH_2Cl_2 (entries 4–8; see also Table S1 in the Supporting Information). Delightedly, $GaCl_3$ was finally found to be the optimal choice, with the desired **3a** isolated in 92% yield (entry 8). No reaction took place if $GaCl_3$ or Ph_3CCl alone was used (entry 9). The combination of Ph_3CClO_4 with $GaCl_3$ did not give any improvement (entries 2 and 10). Then electronically varied trityl chlorides together with benzhydrylium ion were studied, and Ph_3CCl proved to be the best candidate (entries 10–14).

The reaction proved general for a broad range of structurally and electronically varied potassium alkynyltrifluoroborates in high efficiency (**3a** and **3d**–**k**; Scheme 1). The desired product was not detected when either the boronic acid **2b** or boronate ester **2c** was used, and might be ascribed to their reduced nucleophilicity compared with **2a** or the incompatibility towards the reaction conditions.[2d,9] Alkenyl trifluoroborate salts (**2l** and **2m**) are suitable coupling partners to deliver the desired vinyl THFs in good yields with olefin geometry highly conserved. The arylation of **1a** also proceeded smoothly when Ph_3CClO_4 was used as the oxidant. The reaction is efficient not only for the π-rich aryl (**3n** and **3o**) and heteroaryl borates (**3r**), but also for π-neutral (**3p**) and π-deficient (**3q**) arylboranes, though electron-poor 2-pyridinyl borate (**3s**) failed to give any desired product. The mild reaction possesses excellent functional-group compatibility, with halogens (**3d** and **3e**) and benzyl ether (**3k**) well-tolerated for further manipulations.



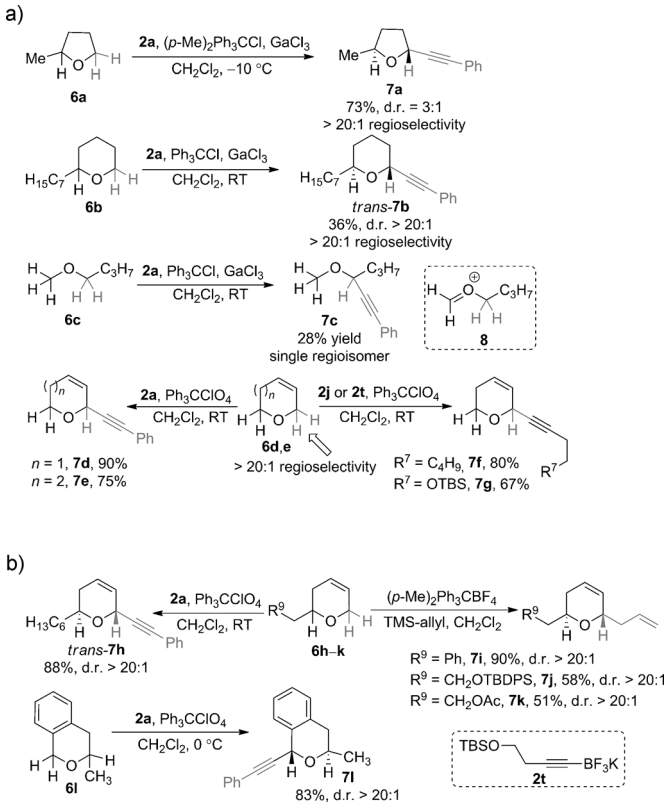
Scheme 1. Scope of organoboranes. Reaction conditions: **1a** (4 mmol), **2** (0.2 mmol), Ph_3CCl (0.1 mmol), and $GaCl_3$ (0.1 mmol) in CH_2Cl_2 (1.0 mL) at RT in 2 h. [a] (Phenylethynyl)boronic acid used. [b] Diethyl (phenylethynyl)boronate used. [c] (*p*-MeO)Ph_3CCl and $GaCl_3$ used. [d] Ph_3CClO_4 in CH_3CN at 60 °C. [e] Ph_3CClO_4 in CH_3CN at 80 °C. [f] Ph_3CClO_4 without solvent at 100 °C.



Scheme 2. Scope of heteroatom-containing components. Reaction conditions: **4** (0.1 mmol), **2** (0.2 mmol), Ph_3CCl (0.1 mmol), and $GaCl_3$ (0.1 mmol) in CH_2Cl_2 (1.0 mL) at 0 °C or RT in 1 h. [a] 5–20 equiv of ether employed. [b] Ph_3CClO_4 as oxidant. [c] Ph_3CBF_4 as oxidant. [d] $(m\text{-F})_2Ph_3CCl$ and $GaCl_3$ as oxidant.

With the expansive scope of organoboranes in hand, we next explored the scope with respect to the ether (Scheme 2). Besides THF, commonly encountered saturated cyclic ethers including tetrahydrothiophene (**5b**), THP (**5c**), oxepane (**5d**), and 2,2-disubstituted THF (**5e**) were well compatible with the reaction. Cyclic benzyl ethers like isochroman (**5f**), phthalan (**5g**), and benzoxathiole (**5h**) reacted smoothly with **2a**. The reaction of cyclic allyl ether 2*H*-chromene (**5i**) was highly regioselective, thus delivering predominantly the C2-addition products, and no C4 addition or double addition was observed. Acyclic ethers also proved to be competent substrates, with Et_2O (**5j**) and $n Bu_2O$ (**5k**) well tolerated. Alkoxy aryl ethers, the core scaffold of a large number of synthetic drugs like Duloxetine and Atomoxetine,[1c] were also explored. While anisole failed to yield **5l**, ethoxybenzene delivered **5m** in modest yield. Acyclic benzyl ether (**5n**) was not compatible with the reaction. Besides the ether candidates, the scope was expanded to amines (**5o**–**q**) and saturated carbamates (**5r**–**s**).

Selective functionalization of non-equivalent C–H bonds in saturated ethers with high regio- and diastereoselectivity by bimolecular C–C bond formation has not been well established probably because of the harsh reaction conditions.[10]

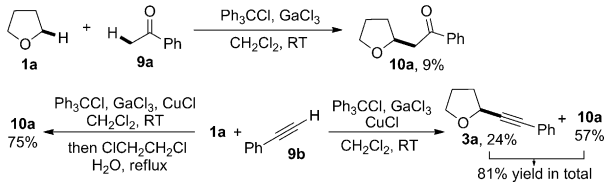


Scheme 3. Studies on the regio- and diastereoselectivity. Reaction conditions: ether **6d–l** (0.1 mmol), nucleophile (0.2 mmol), and oxidant (0.1 mmol) in CH_2Cl_2 (1.0 mL) in 1 h. **6a–c** (20 equiv). TBS = *tert*-butyldimethylsilyl.

The mild reaction conditions prompted us to evaluate the regio- and diastereoselectivity for unsymmetric ethers (Scheme 3). 2-Methyl THF (**6a**) reacted smoothly with **2a** to yield **7a** in 73% yield with overwhelming selectivity at the less sterically hindered secondary C–H bond. With (*p*-Me)$_2$Ph$_3$CCl as the trityl ion source the best diastereocontrol (3:1) was obtained. The similar site selectivity was also observed for the 2-alkyl THP **6b**, thus affording *trans*-**7b** as the single diastereomer. The chemoselectivity advantages for secondary C–H bond oxidation might be ascribed to the increased steric accessibility compared to tertiary C–H bonds. The site-selectivity between primary and secondary C–H bonds was also evaluated, as demonstrated by the reaction of methyl butyl ether (**6c**), and **7c** was isolated as a single regioisomer. Such selectivity for the secondary C–H bond oxidation might arise from the greater electron-rich character compared to primary C–H bonds. Another possibility which cannot be excluded is that the carbocation **8** formed by primary C–H bond oxidation might collapse before the addition of **2a**.

The electronic effect on the site-selectivity is also obvious, with excellent selectivity at the electron-rich allyl methylene site (Scheme 3). 3,6-dihydropyran (3,6-DHP; **6d**) and 2,3,4,7-tetrahydrooxepine (**6e**) participated in the coupling efficiently, thus yielding the corresponding products **7d–g** as a single regioisomer. The reaction of **6h** displayed excellent yields, thus affording the *trans*-2,6-disubstituted DHP **7h** as a single diastereomer. Such structure was routinely accessed through Ferrier reaction employing an allylic acetate or tosylate as the nucleofuge, whose synthesis usually suffered from extra steps.[11] Considering that *trans*-2,6-disubstituted THP or DHP is the core unit within a multitude of biologically active natural products, DHPs bearing commonly encountered functional groups like the aryl ring **6i**, acid-sensitive silyl ether **6j**, and electrophilic acetate **6k** were studied to demonstrate the synthetic potential of the practical method. Notably, allyl trimethylsilane proved to be compatible with the system to give the *trans*-DHPs **7i–k** as the single diastereomer, thus highlighting the capacity of the protocol in creating unique and useful chemoselectivity patterns in highly functionalized molecules. Indeed **7j** is the real synthetic intermediate leading to the synthesis of natural products swinholide A.[11b] The efficiency dropped for the substrates bearing electron-withdrawing moieties, probably because of the inductive deactivation effect on the cation intermediates. Such excellent *trans* selectivity was also observed for 3-methyl isochroman (**6l**) when Ph_3CClO_4 was employed.[5l] While no single set of trityl ion was applicable to all of the substrates studied, an optimal set could be identified for each substrate according to an understanding of the reactivities of substrates and trityl ions. Equivalents of unsaturated substrates sufficed for the reaction, but excess of saturated ones were always required. While the origin of the difference has not been elucidated, the volatility and reactivity of the substrate together with the stability of the formed carbocation intermediate might contribute to the observation.[12f,13c]

Trityl ion mediated cross-dehydrogenative coupling (CDC) with C–H reagents was next explored (Scheme 4).



Scheme 4. The CDC reaction of THF and phenylacetylene.

While acetophenone (**9a**) only afforded trace amounts of the desired **10a**, the alkyne **9b** proved to be a good partner, thus giving desired **3a** and hydrated **10a** in a total yield of 81%. Accordingly, **10a** was uniquely achieved in 75% yield through CDC and a simple hydration process in one pot.

The trityl ion is typically recognized to act as a hydride acceptor or one-electron oxidant in the C–H oxidation process (Figure 2).[12] Given the different oxidation potentials, the mechanisms for saturated and unsaturated ethers will be discussed independently. With respect to the saturated ether, THF showed an intermolecular KIE of 2.9, thus suggesting the C–H cleavage involved in the rate-determining step. Judging from the oxidation potential of THF ($E^{\circ}_{ox} > 2.5$ V vs SCE)[13] and the reduction potential of Ph_3C^+ ($E^{\circ}_{red} = 0.19$ V vs SCE),[14] single-electron transfer (SET) from THF to Ph_3C^+ is highly endergonic, with a minimum barrier of 222 kJ mol^{-1} at 25 °C, and a maximum second-order rate constant of $5.3\times$

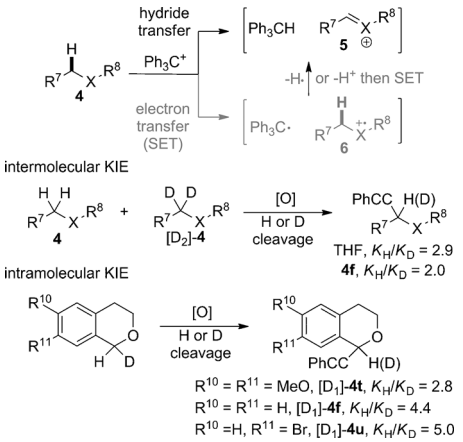


Figure 2. Mechanistic studies for Ph_3C^+-mediated ether oxidation.

$10^{-27}\,M^{-1}s^{-1}$.[15] Such a number is much smaller than the experimentally determined second-order rate constant for the oxidation of THF by Ph_3C^+ ($6.3\times10^{-3}\,M^{-1}s^{-1}$),[12d] and therefore the SET pathway might be ruled out for THF and other saturated ethers having a relatively high oxidation potential. With respect to unsaturated ethers with lower oxidation potential, several KIE experiments were conducted for evidence. Firstly, the intermolecular KIE (2.0) for isochroman **4f** is lower than that for the intramolecular one (4.4), thus implying that a reactive intermediate is formed prior to C–H cleavage, and its formation is not rapidly reversible.[16,17] Secondly, the more reactive substrate displays a lower intramolecular KIE than the less reactive one (2.8 for **4t** versus 4.4 for **4f** versus 5.0 for **4u**). This trend implies that bond cleavage is easier for ethers reacting more quickly, and is opposite to DDQ-induced C–H cleavage initiated by an SET process.[16c,18] However, the phenomenon could be well explained by a direct hydride abstraction process.[16] Therefore SET pathway might also be ruled out for **4f** and other unsaturated ethers with a relatively low oxidation potential. The coupling of either THF or **4f** was not affected by 1 equivalent of either the radical-trapping reagent TEMPO or BHT, thus indicating that the radical intermediate might not be involved in the reaction.[6a,c,7b–e] Therefore, we envision that the reaction proceeds through an irreversible hydride abstraction to afford the cation **5** for subsequent nucleophilic addition.[8e]

In conclusion, a method to achieve the direct construction of diverse α-functionalized ethers using readily available trityl ion has been developed. The reaction proceeds under ambient temperature with excellent chemoselectivity, and exhibits a broad scope with respect to both the ether and nucleophile components with high functional-group tolerance. The ability to tune reactivity of the trityl ion in a rational manner endows the protocol with excellent regio- and diastereoselectivity for the unsymmetric ethers, thus stereoselectively yielding highly functionalized disubstituted 2,5-*trans* THF, 2,6-*trans* THP and DHP, and 1,3-*trans* isochroman moieties. The practical and selective protocol outlined herein will not only provide a straightforward approach to synthesize complex molecules of biological relevance, but also allow facile and rapid access to series of multiple compounds by a structural-core diversification strategy to discover novel biologically interesting agents.

Received: July 10, 2014
Revised: August 31, 2014
Published online: October 24, 2014

Keywords: boron · C–H functionalization · ethers · Lewis acid · regioselectivity

[1] a) E. J. Kang, E. Lee, *Chem. Rev.* **2005**, *105*, 4348; b) T. Nakata, *Chem. Rev.* **2005**, *105*, 4314; c) S. D. Roughley, A. M. Jordan, *J. Med. Chem.* **2011**, *54*, 3451.

[2] a) A. W. Williamson, *J. Chem. Soc.* **1852**, *4*, 229; b) J. P. Wolfe, M. B. Hay, *Tetrahedron* **2007**, *63*, 261; c) I. Larrosa, P. Romea, F. Urpí, *Tetrahedron* **2008**, *64*, 2683; d) C.-V. T. Vo, T. A. Mitchell, J. W. Bode, *J. Am. Chem. Soc.* **2011**, *133*, 14082; e) S. E. Reisman, A. G. Doyle, E. N. Jacobsen, *J. Am. Chem. Soc.* **2008**, *130*, 7198; f) P. N. Moquist, T. Kodama, S. E. Schaus, *Angew. Chem. Int. Ed.* **2010**, *49*, 7096; *Angew. Chem.* **2010**, *122*, 7250.

[3] a) B. M. Trost, *Acc. Chem. Res.* **2002**, *35*, 695; b) P. A. Wender, V. A. Verma, T. J. Paxton, T. H. Pillow, *Acc. Chem. Res.* **2008**, *41*, 40.

[4] a) K. Godula, D. Sames, *Science* **2006**, *312*, 67; b) C. J. Li, *Acc. Chem. Res.* **2009**, *42*, 335; c) S. A. Girard, T. Knauber, C. J. Li, *Angew. Chem. Int. Ed.* **2014**, *53*, 74; *Angew. Chem.* **2014**, *126*, 76; d) C. Liu, H. Zhang, W. Shi, A. Lei, *Chem. Rev.* **2011**, *111*, 1780; e) S. Y. Zhang, F. M. Zhang, Y. Q. Tu, *Chem. Soc. Rev.* **2011**, *40*, 1937; f) C. L. Sun, B. J. Li, Z. J. Shi, *Chem. Rev.* **2011**, *111*, 1293.

[5] a) Y. Zhang, C. J. Li, *J. Am. Chem. Soc.* **2006**, *128*, 4242; b) W. Muramatsu, K. Nakano, C. J. Li, *Org. Lett.* **2013**, *15*, 3650; c) Y. Zhang, C. J. Li, *Angew. Chem. Int. Ed.* **2006**, *45*, 1949; *Angew. Chem.* **2006**, *118*, 1983; d) C. A. Correia, C. J. Li, *Heterocycles* **2010**, *82*, 555; e) M. Ghobrial, K. Harhammer, M. D. Mihovilovic, M. Schnürch, *Chem. Commun.* **2010**, *46*, 8836; f) H. Richter, R. Rohlmann, O. G. Mancheño, *Chem. Eur. J.* **2011**, *17*, 11622; g) B. Zhang, Y. Cui, N. Jiao, *Chem. Commun.* **2012**, *48*, 4498; h) Á. Pintér, A. Sud, D. Sureshkumar, M. Klussmann, *Angew. Chem. Int. Ed.* **2010**, *49*, 5004; *Angew. Chem.* **2010**, *122*, 5124; i) B. Schweitzer-Chaput, A. Sud, Á. Pintér, S. Dehn, P. Schulze, M. Klussmann, *Angew. Chem. Int. Ed.* **2013**, *52*, 13228; *Angew. Chem.* **2013**, *125*, 13470; j) Z. Li, H. Li, X. Guo, L. Cao, R. Yu, H. Li, S. Pan, *Org. Lett.* **2008**, *10*, 803; k) D. J. Clausen, P. E. Floreancig, *J. Org. Chem.* **2012**, *77*, 6574; l) Y. Xu, D. T. Kohlman, S. X. Liang, C. Erikkson, *Org. Lett.* **1999**, *1*, 1599; m) X. Liu, B. Sun, Z. Xie, X. Qin, L. Liu, H. Lou, *J. Org. Chem.* **2013**, *78*, 3104; n) X. Pan, Q. Hu, W. Chen, X. Liu, B. Sun, Z. Huang, Z. Zeng, L. Wang, D. Zhao, M. Ji, L. Liu, H. Lou, *Tetrahedron* **2014**, *70*, 3447; o) Z. Meng, S. Sun, H. Yuan, H. Lou, L. Liu, *Angew. Chem. Int. Ed.* **2014**, *53*, 543; *Angew. Chem.* **2014**, *126*, 553.

[6] C–O bond formation: a) L. Chen, E. Shi, Z. Liu, S. Chen, W. Wei, H. Li, K. Xu, X. Wan, *Chem. Eur. J.* **2011**, *17*, 4085; b) G. S. Kumar, B. Pieber, K. R. Reddy, C. O. Kappe, *Chem. Eur. J.* **2012**, *18*, 6124; c) S. Pan, J. Liu, H. Li, Z. Wang, X. Guo, Z. Li, *Org. Lett.* **2010**, *12*, 1932.

[7] C–C bond formation: a) Z. Li, R. Yu, H. Li, *Angew. Chem. Int. Ed.* **2008**, *47*, 7497; *Angew. Chem.* **2008**, *120*, 7607; b) D. Liu, C. Liu, H. Li, A. Lei, *Angew. Chem. Int. Ed.* **2013**, *52*, 4453; *Angew. Chem.* **2013**, *125*, 4549; c) D. Liu, C. Liu, H. Li, A. Lei, *Chem. Commun.* **2014**, *50*, 3623; d) T. He, L. Yu, L. Zhang, L. Wang, M. Wang, *Org. Lett.* **2011**, *13*, 5016; e) X. F. Huang, Z. Q. Zhu, Z. Z. Huang, *Tetrahedron* **2013**, *69*, 8579; f) X. Guo, S. Pan, J. Liu, Z. Li, *J. Org. Chem.* **2009**, *74*, 8848; g) P. P. Singh, S. Gudup, H.

Aruri, U. Singh, S. Ambala, M. Yadav, S. D. Sawant, R. A. Vishwakarma, *Org. Biomol. Chem.* **2012**, *10*, 1587; h) S. Kamijo, T. Hoshikawa, M. Inoue, *Org. Lett.* **2011**, *13*, 5928; i) T. Hoshikawa, S. Kamijo, M. Inoue, *Org. Biomol. Chem.* **2013**, *11*, 164; j) J. Gong, P. L. Fuchs, *J. Am. Chem. Soc.* **1996**, *118*, 4486; k) Y. Zhang, C. J. Li, *Tetrahedron Lett.* **2004**, *45*, 7581; l) Z. Xie, Y. Cai, H. Hu, C. Lin, J. Jiang, Z. Chen, L. Wang, Y. Pan, *Org. Lett.* **2013**, *15*, 4600.

[8] a) T. R. Hoye, A. J. Caruso, J. F. Dellaria, Jr., M. J. Kurth, *J. Am. Chem. Soc.* **1982**, *104*, 6704; b) M. E. Jung, L. M. Speltz, *J. Am. Chem. Soc.* **1976**, *98*, 7882; c) T. Mukaiyama, Y. Hayashi, Y. Hashimoto, *Chem. Lett.* **1986**, 1627; d) Y. Hayashi, K. Wariishi, T. Mukaiyama, *Chem. Lett.* **1987**, 1243; e) R. Damico, C. Broaddus, *J. Org. Chem.* **1966**, *31*, 1607; f) D. H. R. Barton, P. D. Magnus, G. Smith, G. Streckert, D. Zurr, *J. Chem. Soc. Perkin Trans. 1* **1972**, 542.

[9] a) H. Kim, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2008**, *130*, 398; b) D. K. Nielsen, A. G. Doyle, *Angew. Chem. Int. Ed.* **2011**, *50*, 6056; *Angew. Chem.* **2011**, *123*, 6180; c) Y. Fujiwara, V. Domingo, I. B. Seiple, R. Gianatassio, M. Del Bel, P. S. Baran, *J. Am. Chem. Soc.* **2011**, *133*, 3292; d) Z. Xie, L. Liu, W. Chen, H. Zheng, Q. Xu, H. Yuan, H. Lou, *Angew. Chem. Int. Ed.* **2014**, *53*, 3904; *Angew. Chem.* **2014**, *126*, 3985.

[10] P. A. Wender, M. K. Hilinski, A. V. W. Mayweg, *Org. Lett.* **2005**, *7*, 79.

[11] a) R. J. Ferrier, *Top. Curr. Chem.* **2001**, *215*, 153; b) R. Kartika, J. D. Frein, R. E. Taylor, *J. Org. Chem.* **2008**, *73*, 5592 and references therein.

[12] a) N. G. Connelly, W. E. Geiger, *Chem. Rev.* **1996**, *96*, 877; b) S. Fukuzumi, T. Kitano, M. Ishikawa, *J. Am. Chem. Soc.* **1990**, *112*, 5631; c) H. Mayr, N. Basso, G. Hagen, *J. Am. Chem. Soc.* **1992**, *114*, 3060; d) M. Horn, L. H. Schappele, G. Lang-Wittkowski, H. Mayr, A. R. Ofial, *Chem. Eur. J.* **2013**, *19*, 249; e) J. M. Allen, T. H. Lambert, *J. Am. Chem. Soc.* **2011**, *133*, 1260; f) H. Meerwein, V. Hederich, H. Morschel, K. Wunderlich, *Justus Liebigs Ann. Chem.* **1960**, *635*, 1 and references therein.

[13] a) J. Yoshida, K. Nishiwaki, *J. Chem. Soc. Dalton Trans.* **1998**, 2589; b) X. Zhang, J. K. Pugh, P. N. Ross, *J. Electrochem. Soc.* **2001**, *148*, 183–188; c) S. A. Campbell, C. Bowes, R. S. McMillan, *J. Electroanal. Chem.* **1990**, *284*, 195–204.

[14] a) H. Volz, W. Lotsch, *Tetrahedron Lett.* **1969**, *27*, 2275; b) M. R. Wasielewski, R. Breslow, *J. Am. Chem. Soc.* **1976**, *98*, 4222.

[15] A. R. Ofial, K. Ohkubo, S. Fukuzumi, R. Lucius, H. Mayr, *J. Am. Chem. Soc.* **2003**, *125*, 10906.

[16] a) D. R. Anderson, N. C. Faibish, P. Beak, *J. Am. Chem. Soc.* **1999**, *121*, 7553; b) J. Shearer, C. X. Zhang, L. Q. Hatcher, K. D. Karlin, *J. Am. Chem. Soc.* **2003**, *125*, 12670; c) H. H. Jung, P. E. Floreancig, *Tetrahedron* **2009**, *65*, 10830.

[17] S. Słomkowski, S. Penczek, *J. Chem. Soc. Perkin Trans. 2* **1974**, 1718.

[18] a) R. J. Sundberg, P. J. Hunt, P. Desos, K. G. Gadamasetti, *J. Org. Chem.* **1991**, *56*, 1689; b) D. Buckley, S. Dunstan, H. B. Henbest, *J. Chem. Soc.* **1957**, 4880.

