

Iron-Catalyzed Oxidative C–H/C–H Cross-Coupling: An Efficient Route to α -Quaternary α -Amino Acid Derivatives**

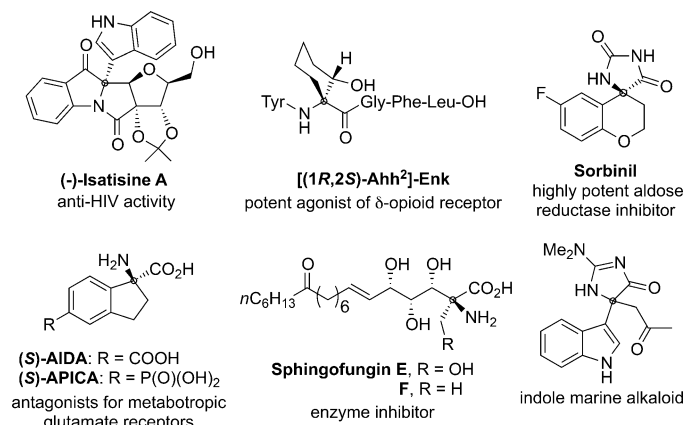
Kaizhi Li, Guangying Tan, Jingsheng Huang, Feijie Song, and Jingsong You*

α,α -Disubstituted α -amino acids are the prominent structural units of many natural products, pharmaceuticals, bioactive compounds, and organocatalysts (Scheme 1). They are also

has remained a challenging issue because of the inherent steric hindrance in the formation of the C–C bond.^[5]

Over the past few years the transition-metal-catalyzed oxidative cross-coupling reactions between two C–H centers have been recognized as efficient, atom-economical, and environmentally friendly synthetic methods for the formation of a C–C bond which avoids the tedious and time-consuming prefunctionalization of both substrates.^[6] Among these reactions, the coupling of α -C(sp³)–H centers of α -amino acid derivatives with various nucleophiles has been used to prepare α -substituted α -amino acids (Scheme 2A).^[7] An α -aldimine intermediate is usually proposed in these reactions. However, this strategy has put constraints on the synthesis of α -tertiary α -amino acids because amino acid substrates are restricted to glycine derivatives. To our knowledge, the transition-metal-catalyzed oxidative cross-coupling reactions of α -tertiary α -amino acids to give α -quaternary derivatives are unprecedented.

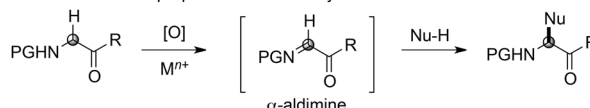
Although glycine derivatives form an aldimine intermediate, we rationalized that α -tertiary amino acid derivatives may involve a ketimine intermediate (Scheme 2). In general,



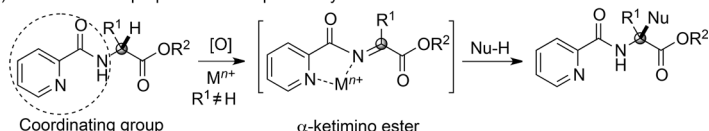
Scheme 1. Selected medicinal and natural molecules containing α,α -disubstituted α -amino acids and their derivatives.

versatile building blocks for the synthesis of various biologically active and structurally complex molecules.^[1,2] In addition, these α -quaternary amino acids are of great importance in the design of biologically active peptides with enhanced properties.^[3] Incorporation of α,α -disubstituted α -amino acids into peptides can alter their stabilization toward proteolysis as well as the conformation of the secondary structure of the corresponding proteins, which may give valuable information on enzymatic mechanisms.^[4] Thus, the synthesis of α -quaternary α -amino acids has attracted great interest from organic chemists. Despite significant efforts over the past decades, the rapid and efficient construction of the quaternary center through transition-metal catalysis

A) Previous work: The preparation of α -tertiary α -amino acids



B) This work: The preparation of α -quaternary α -amino acids



Scheme 2. Transition-metal-catalyzed oxidative cross-coupling of α -C(sp³)–H centers of α -amino acid derivatives.

a ketimine double bond is more difficult to form and less reactive than an aldimine double bond because of steric repulsion, and this constitutes a challenge for α -tertiary amino acid substrates.^[8] Inspired by the concept of chelation-assisted C–H bond activation,^[9] we hypothesized that these substantial hurdles could be overcome by tethering a suitable coordinating group at the nitrogen atom. The coordination of a metal center with the nearby N–H moiety and the coordinating group could promote the formation of an α -ketimine and further activate the resulting intermediate for nucleophilic attack.^[7a,k] Herein, we report the generation of fully substituted carbon centers from α -tertiary amino acid

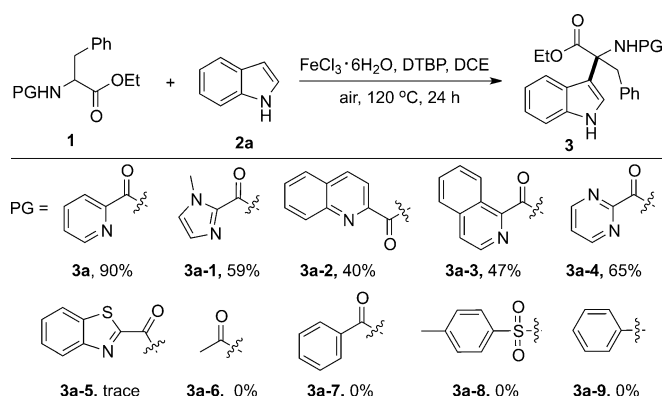
[*] K. Li, G. Tan, J. Huang, Dr. F. Song, Prof. Dr. J. You
Key Laboratory of Green Chemistry and Technology of Ministry of Education, College of Chemistry
and State Key Laboratory of Biotherapy
West China Medical School, Sichuan University
29 Wangjiang Road, Chengdu 610064 (PR China)
E-mail: jsyou@scu.edu.cn

[**] This work was supported by grants from the National Basic Research Program of China (973 Program, 2011CB808600) and the National NSF of China (Nos 21025205, 21272160, 21021001, and J1103315J0104).

Supporting information for this article is available on the WWW under <http://dx.doi.org/10.1002/ange.201306181>.

esters through an oxidative C–H/C–H cross-coupling reaction (Scheme 2B).

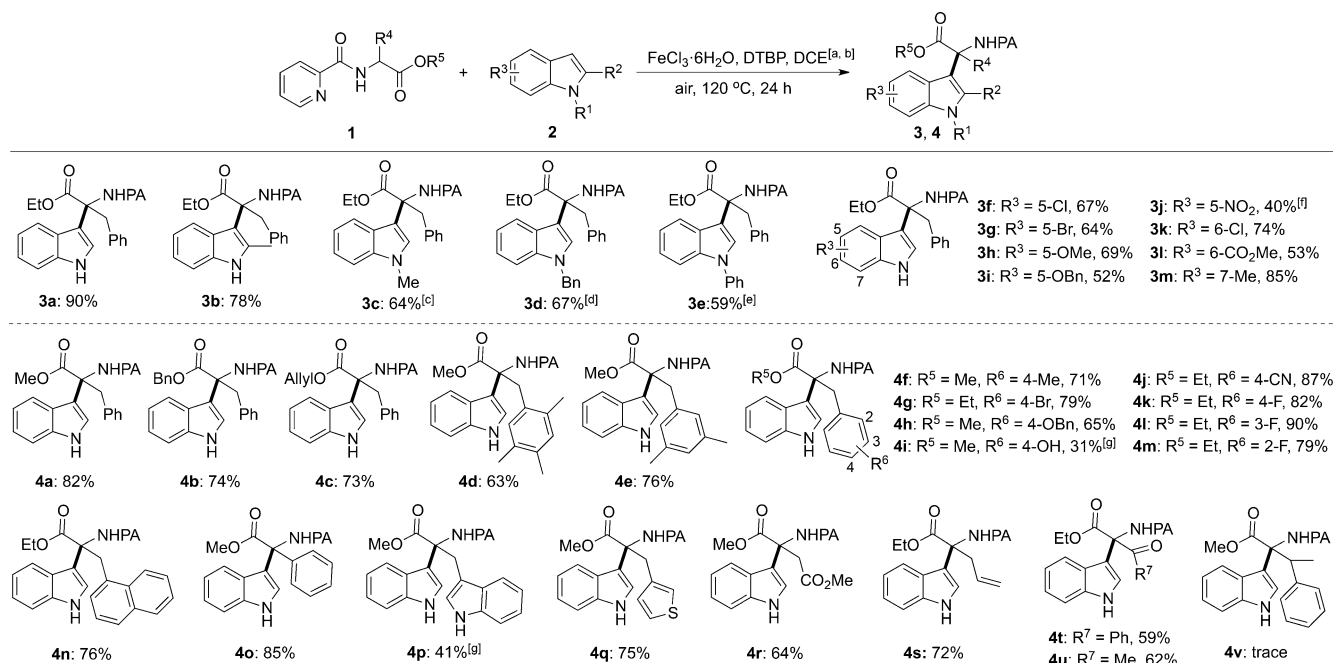
Indole is a popular heteroaromatic ring found in many biologically active molecules, natural products, agrochemicals, pharmaceuticals, and materials. Indolylglycines are also versatile intermediates for natural product synthesis and drug discovery. Therefore, the unsubstituted indole (**2a**) was initially employed as the coupling partner. To test our hypothesis, a set of N-protecting groups (PGs) on phenylalanine ethyl ester **1** were examined in the presence of $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$ by using di-*tert*-butyl peroxide (DTBP) as the oxidant in 1,2-dichloroethane (DCE) and an air atmosphere (Scheme 3). It was found that a variety of (*N*-heteroarene)-carbonyl groups such as 2-pyridine-, 2-imidazole-, 2-quinoline-, 1-isoquinoline-, and 2-pyrimidinecarbonyl groups were effective auxiliaries to promote the oxidative coupling reaction, with the 2-pyridinecarbonyl group (**3a**) giving the



Scheme 3. The effect of N-protecting groups on the oxidative cross-coupling of the N-substituted phenylalanine ethyl ester with indole.

best result (90% yield, Scheme 3). However, other N-protecting groups such as 2-benzo[*d*]thiazole carbonyl, acetyl, benzoyl, tosyl, and phenyl were incapable of promoting the coupling reactions. As the 2-pyridinecarbonyl group can be readily removed, it was an ideal candidate for illuminating the coordinating activation strategy. Various parameters, such as metal sources, solvents, oxidants, and reaction temperature, were then explored (see Table S1 in the Supporting Information). The coupling reaction between **2a** and **1a** gave the desired product **3a** in the highest yield of 90% when 20 mol % $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$ was employed in combination with DTBP (2.0 equiv) in DCE at 120 °C under air for 24 h (see Table S1, entry 7). $\text{Fe}(\text{NO}_3)_3 \cdot 9\text{H}_2\text{O}$ afforded a trace amount of **3a**, but an extra addition of 60 mol % LiCl significantly improved the yield of the reaction to 72% yield, which indicated that the chloro anion played a critical role in the reaction (Table S1, entries 4, 7, and 30). X-ray analysis of single crystals of **3a** confirmed that the oxidative cross-coupling reaction occurred at the $\alpha\text{-C}(\text{sp}^3)\text{-H}$ position of the α -amino acid ester (Figure S1).^[10]

With the optimal system now in hand, we next examined the scope of the indole substrates (**3a–3m**, Scheme 4). To our delight, a broad range of indoles could couple with ethyl 3-phenyl-2-(picolinamido)propanoate (**1a**). For example, the sterically hindered 2-substituted indole reacted to give **3b** in 78% yield (Scheme 4). Besides the free-NH indoles, indoles with N-protecting groups such as methyl, benzyl, or phenyl gave the corresponding indolyl α -quaternary α -amino acids **3c–3e**. More importantly, this method was highly tolerant of synthetically valuable functional groups on the phenyl moiety of the indoles (e.g., chloro, bromo, nitro, ester, and alkoxy groups, etc.; **3f–3l**); these functional groups could afford an opportunity for further transformation (Scheme 4).

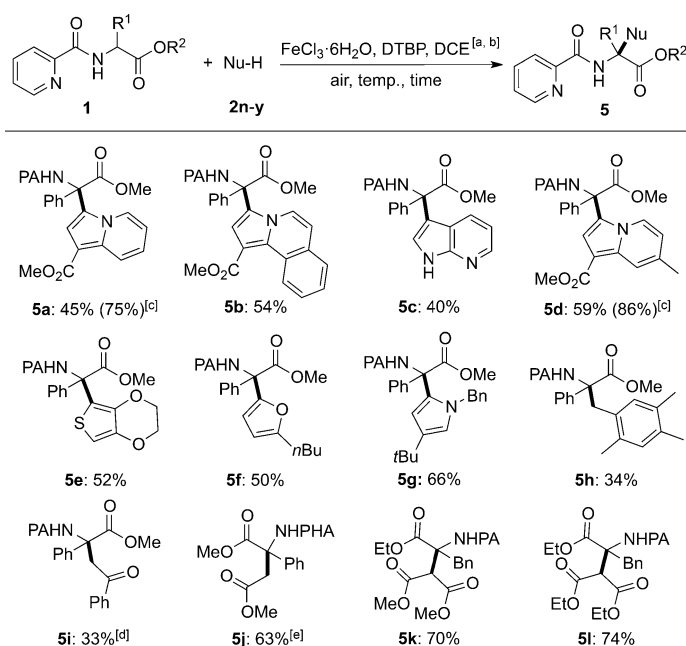


Scheme 4. Substrate scope of the oxidative cross-coupling reactions of various α -substituted α -amino acid esters with indoles. [a] Reaction conditions: **1** (0.25 mmol), **2** (0.50 mmol), $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$ (20 mol %), DTBP (2.0 equiv), and DCE (1.0 mL) at 120 °C under air for 24 h. [b] Yields of isolated products. [c] 1.5 equiv of DTBP. [d] 18 h. [e] 1.5 equiv of DTBP and 36 h. [f] 130 °C for 18 h. [g] 36 h. PA = picolinamido group, Bn = benzyl.

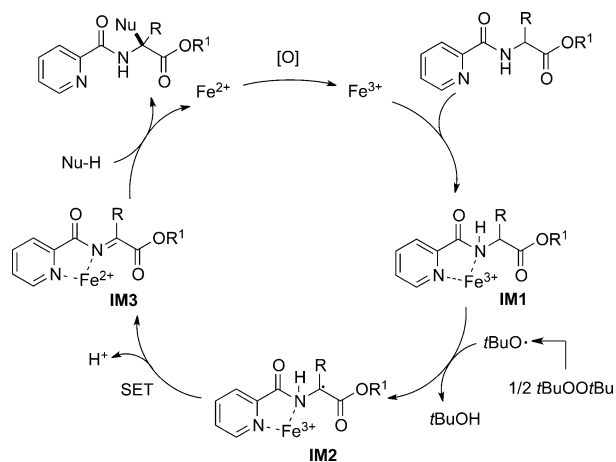
Encouraged by the promising results achieved above, we then tested the scope of α -tertiary α -amino acids by using 1*H*-indole (**2a**) as the nucleophile (Scheme 4). We were pleased to find that a wide range of α -substituted α -amino acids underwent a smooth oxidative coupling. For example, the reactions of methyl, ethyl, benzyl, and allyl phenylalanine esters afforded the coupled products in good yields (Scheme 4, **3a** and **4a–4c**). When the phenyl ring of the phenylalanine ester substrates was functionalized with electron-donating, electron-withdrawing, sterically hindered, or multiple groups, all of them gave the desired products (**4d–4m**) in moderate to good yields (Scheme 4). The catalytic system was highly compatible with various functional groups on the phenyl ring (e.g. halide, nitrile, alkoxy, and even hydroxy groups). We subsequently applied this procedure to other natural and non-natural α -amino acid derivatives for the synthesis of α,α -disubstituted α -amino acids (**4n–4u**; Scheme 4). It is worth noting that a variety of natural α -amino acid substrates (e.g. phenylalanine, tyrosine, tryptophane, and aspartic acid) and non-natural α -amino acid substrates (e.g. naphthylalanine, phenylglycine, thienylalanine, allylglycine, benzoylglycine, and acetylglycine) could undergo the oxidative cross-coupling reactions with 1*H*-indole in satisfactory yields. Notably, the reaction of the β,β -disubstituted alanine substrate failed to produce the targeted compound (**4v**; Scheme 4) under the standard reaction conditions.

To further highlight the synthetic usefulness of our strategy we turned our attention to the scope of nucleophiles (Scheme 5). A series of electron-rich N-heterocycles was first investigated because of their central place in synthetic, medicinal, and material chemistry. Besides indoles, other types of electron-rich heteroarenes such as indolizines, 7-aza-1*H*-indoles, thiophenes, furans, and *N*-alkyl pyrroles also coupled smoothly with the 2-pyridinecarbonyl phenylglycine ester to afford α,α -disubstituted α -amino acids in synthetically useful yields (**5a–5g**; Scheme 5). Malonates were also suitable nucleophilic substrates. The oxidative cross-coupling of the phenylalanine derivative with dimethyl and diethyl malonates afforded **5k** and **5l** in 70% and 74% yields, respectively (Scheme 5). Interestingly, the phenylglycine derivative underwent a tandem reaction involving the oxidative C–H/C–H cross-coupling and decarboxylation to give **5j** in 63% yield. To our surprise, 1,2,4,5-tetramethylbenzene could couple with the phenylglycine substrate to give **5h** in 34% yield. The present method also allowed for the use of trimethyl(1-phenylvinyl)oxy)silane as the nucleophile to prepare the benzoyl-substituted α -quaternary α -amino acid **5i**.

Although the detailed mechanism of this transformation is not clear at this stage, the possible pathway was proposed to involve a single-electron transfer (SET), which was demonstrated by the addition of radical inhibitors. When treated with 2,2,6,6-tetramethylpiperidine oxide (TEMPO) or 2,6-di-*tert*-butyl-4-methylphenol (BHT), the coupling reaction of ethyl 3-phenyl-2-(picolinamido)propanoate (**1a**) with 1*H*-indole (**2a**) could be suppressed (see Part V in the Supporting Information). The plausible catalytic route is illustrated in Scheme 6. First, 2-picolinamido α -tertiary amino acid ester coordinates with Fe^{III} to yield the intermediate **IM1**. Next, the *tert*-butoxyl radical (*t*BuO $\cdot$) generated from DTBP abstracts



Scheme 5. Scope of nucleophiles. [a] Reaction conditions: **1** (0.25 mmol), **2** (2.0 equiv), $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$ (20 mol%), DTBP (2.0 equiv), and DCE (1.0 mL) at 120°C under air for 24 h. See the Supporting Information for details. [b] Yield of isolated products. [c] $\text{Cu}(\text{OAc})_2$ (20 mol%) and dioxane (1.0 mL) at 110°C. [d] Trimethyl(1-phenylvinyl)oxy)silane (4.0 equiv) was used as the nucleophile. [e] Dimethyl malonate (4.0 equiv) and DTBP (3.0 equiv) for 24 h.



Scheme 6. Possible mechanism of the α -C(sp^3)–H functionalization of α -substituted α -amino acid esters.

the α -hydrogen atom of **IM1** to form the radical **IM2**.^[7k] Subsequently, the radical species **IM2** undergoes an intramolecular single-electron transfer (SET) to give the α -ketimine intermediate **IM3**. The coordination of Fe^{III} with the picolinamido group activates the α -ketimine and facilitates the addition of nucleophile to **IM3** to afford the desired α -quaternary α -amino acid ester. Given the fact that **3a** was obtained in 39% yield in a N_2 atmosphere (Table S1, entry 28), we assumed that the released Fe^{II} is reoxidized to Fe^{III} by air^[11] as well as DTBP^[7j, 12] to fulfill the catalytic cycle.

In summary, we have developed a coordinating activation strategy to furnish α -quaternary α -amino acids through the iron(III)-catalyzed oxidative functionalization of α -C(sp³)-H bonds of α -tertiary α -amino acid esters. The oxidative C-H/C-H cross-coupling has exhibited a broad substrate scope for both α -amino acids and nucleophiles as well as good functional-group tolerance. The findings have suggested that the oxidative C-H/C-H cross-coupling reactions would be an ideal pathway to create fully substituted carbon centers from tertiary stereogenic centers. Extending this procedure to other reactions and enantioselective versions is underway.

Received: July 16, 2013

Published online: September 25, 2013

Keywords: coordinating activation · cross-coupling · homogeneous catalysis · iron · α -quaternary α -amino acids

- [1] a) B. W. Cue, Jr., B. S. Moore, US 4435578, Mar. 6, 1984; b) R. Pellicciari, R. Luneia, G. Costantino, M. Marinozzi, B. Natalini, P. Jakobsen, A. Kanstrup, G. Lombardi, F. Moroni, C. Thomsen, *J. Med. Chem.* **1995**, 38, 3717–3719; c) A. Loukaci, M. Guyot, A. Chiaroni, C. Riche, *J. Nat. Prod.* **1998**, 61, 519–522; d) D. D. Schoepp, D. E. Jane, J. A. Monn, *Neuropharmacology* **1999**, 38, 1431–1476; e) D. Ma, *Bioorg. Chem.* **1999**, 27, 20–34; f) S. J. Miller, *Acc. Chem. Res.* **2004**, 37, 601–610; g) J.-F. Liu, Z.-Y. Jiang, R.-R. Wang, Y.-T. Zheng, J.-J. Chen, X.-M. Zhang, Y.-B. Ma, *Org. Lett.* **2007**, 9, 4127–4129.
- [2] a) Y. Ohfuné, T. Shinada, *Eur. J. Org. Chem.* **2005**, 5127–5143; b) C. D. Hupp, J. J. Tepe, *Org. Lett.* **2008**, 10, 3737–3739.
- [3] a) P. Balaram, *Curr. Opin. Struct. Biol.* **1992**, 2, 845–851; b) E. Benedetti, E. Gavuzzo, A. Santini, D. R. Kent, Y.-F. Zhu, Q. Zhu, C. Mahr, M. Goodman, *J. Pept. Sci.* **1995**, 1, 349–359; c) O. Déry, H. Josien, J. Grassi, G. Chassaing, J. Y. Couraud, S. Lavielle, *Biopolymers* **1996**, 39, 67–74; d) B. Bellier, I. McCort-Tranchepain, B. Ducos, S. Danascimento, H. Meudal, F. Noble, C. Garbay, B. P. Roques, *J. Med. Chem.* **1997**, 40, 3947–3956; e) H. Bräuner-Osborne, J. Egebjerg, E. Ø. Nielsen, U. Madsen, P. Krogsgaard-Larsen, *J. Med. Chem.* **2000**, 43, 2609–2645.
- [4] a) P. K. C. Paul, M. Sukumar, R. Bardi, A. M. Piazzesi, G. Valle, C. Toniolo, P. Balaram, *J. Am. Chem. Soc.* **1986**, 108, 6363–6370; b) P. W. Schiller, G. Weltrowska, T. M.-D. Nguyen, C. Lemieux, N. N. Chung, B. J. Marsden, B. C. Wilkes, *J. Med. Chem.* **1991**, 34, 3125–3132; c) A. W. Burgess, *Proc. Natl. Acad. Sci. USA* **1994**, 91, 2649–2653; d) T. Knöpfel, R. Kuhn, H. Allgeier, *J. Med. Chem.* **1995**, 38, 1417–1426; e) I. L. Karle, R. Kaul, R. B. Rao, S. Raghothama, P. Balaram, *J. Am. Chem. Soc.* **1997**, 119, 12048–12054.
- [5] For selected reviews on the synthesis of quaternary carbon centers, see a) E. A. Peterson, L. E. Overman, *Proc. Natl. Acad. Sci. USA* **2004**, 101, 11943–11948; b) J. P. Das, I. Marek, *Chem. Commun.* **2011**, 47, 4593–4623; for selected examples, see c) J. C. Ruble, G. C. Fu, *J. Am. Chem. Soc.* **1998**, 120, 11532–11533; d) B. M. Trost, X. Ariza, *J. Am. Chem. Soc.* **1999**, 121, 10727–10737; e) J. S. Dickstein, M. W. Fennie, A. L. Norman, B. J. Paulose, M. C. Kozlowski, *J. Am. Chem. Soc.* **2008**, 130, 15794–15795; f) S. Hata, H. Koyama, M. Shimizu, *J. Org. Chem.* **2011**, 76, 9670–9677; g) P. Fang, M. R. Chaulagain, Z. D. Aron, *Org. Lett.* **2012**, 14, 2130–2133.
- [6] For selected reviews, see a) C.-J. Li, *Acc. Chem. Res.* **2009**, 42, 335–344; b) C. J. Scheuermann, *Chem. Asian J.* **2010**, 5, 436–451; c) J. A. Ashenurst, *Chem. Soc. Rev.* **2010**, 39, 540–548; d) S. H. Cho, J. Y. Kim, J. Kwak, S. Chang, *Chem. Soc. Rev.* **2011**, 40, 5068–5083; e) J. Le Bras, J. Muzart, *Chem. Rev.* **2011**, 111, 1170–1214; f) C. S. Yeung, V. M. Dong, *Chem. Rev.* **2011**, 111, 1215–1292; g) C. Liu, H. Zhang, W. Shi, A. Lei, *Chem. Rev.* **2011**, 111, 1780–1824; h) C. Zhang, C. Tang, N. Jiao, *Chem. Soc. Rev.* **2012**, 41, 3464–3484.
- [7] a) L. Zhao, C.-J. Li, *Angew. Chem.* **2008**, 120, 7183–7186; *Angew. Chem. Int. Ed.* **2008**, 47, 7075–7078; b) L. Zhao, O. Baslé, C.-J. Li, *Proc. Natl. Acad. Sci. USA* **2009**, 106, 4106–4111; c) J. Xie, Z.-Z. Huang, *Angew. Chem.* **2010**, 122, 10379–10383; *Angew. Chem. Int. Ed.* **2010**, 49, 10181–10185; d) G. Zhang, Y. Zhang, R. Wang, *Angew. Chem.* **2011**, 123, 10613–10616; *Angew. Chem. Int. Ed.* **2011**, 50, 10429–10432; e) H. Richter, O. G. Mancheño, *Org. Lett.* **2011**, 13, 6066–6069; f) J.-C. Wu, R.-J. Song, Z.-Q. Wang, X.-C. Huang, Y.-X. Xie, J.-H. Li, *Angew. Chem.* **2012**, 124, 3509–3513; *Angew. Chem. Int. Ed.* **2012**, 51, 3453–3457; g) Z.-Q. Wang, M. Hu, X.-C. Huang, L.-B. Gong, Y.-X. Xie, J.-H. Li, *J. Org. Chem.* **2012**, 77, 8705–8711; h) Z. Xu, X. Yu, X. Feng, M. Bao, *J. Org. Chem.* **2012**, 77, 7114–7118; i) X. Jia, F. Peng, C. Qing, C. Huo, X. Wang, *Org. Lett.* **2012**, 14, 4030–4033; j) P. Liu, Z. Wang, J. Lin, X. Hu, *Eur. J. Org. Chem.* **2012**, 1583–1589; k) T. Sonobe, K. Oisaki, M. Kanai, *Chem. Sci.* **2012**, 3, 3249–3255.
- [8] a) S. Saaby, K. Nakama, M. A. Lie, R. G. Hazell, K. A. Jørgensen, *Chem. Eur. J.* **2003**, 9, 6145–6154; b) C. J. Pierce, M. Nguyen, C. H. Larsen, *Angew. Chem.* **2012**, 124, 12455–12458; *Angew. Chem. Int. Ed.* **2012**, 51, 12289–12292.
- [9] For selected examples, see a) V. G. Zaitsev, D. Shabashov, O. Daugulis, *J. Am. Chem. Soc.* **2005**, 127, 13154–13155; b) F.-R. Gou, X.-C. Wang, P.-F. Huo, H.-P. Bi, Z.-H. Guan, Y.-M. Liang, *Org. Lett.* **2009**, 11, 5726–5729; c) G. He, G. Chen, *Angew. Chem.* **2011**, 123, 5298–5302; *Angew. Chem. Int. Ed.* **2011**, 50, 5192–5196; d) Y. Ano, M. Tobisu, N. Chatani, *J. Am. Chem. Soc.* **2011**, 133, 12984–12986; e) H. Shiota, Y. Ano, Y. Aihara, Y. Fukumoto, N. Chatani, *J. Am. Chem. Soc.* **2011**, 133, 14952–14955; f) G. He, Y. Zhao, S. Zhang, C. Lu, G. Chen, *J. Am. Chem. Soc.* **2012**, 134, 3–6; g) E. T. Nadres, O. Daugulis, *J. Am. Chem. Soc.* **2012**, 134, 7–10; h) S.-Y. Zhang, G. He, Y. Zhao, K. Wright, W. A. Nack, G. Chen, *J. Am. Chem. Soc.* **2012**, 134, 7313–7316; i) Y. Xie, Y. Yang, L. Huang, X. Zhang, Y. Zhang, *Org. Lett.* **2012**, 14, 1238–1241; j) S.-Y. Zhang, G. He, W. A. Nack, Y. Zhao, Q. Li, G. Chen, *J. Am. Chem. Soc.* **2013**, 135, 2124–2127; k) X. Cong, J. You, G. Gao, J. Lan, *Chem. Commun.* **2013**, 49, 662–664; l) N. Rodríguez, J. A. Romero-Revilla, M. Á. Fernández-Ibáñez, J. C. Carretero, *Chem. Sci.* **2013**, 4, 175–179; m) X. Ye, Z. He, T. Ahmed, K. Weise, N. G. Akhmedov, J. L. Petersen, X. Shi, *Chem. Sci.* **2013**, 4, 3712–3716; n) Y. Aihara, N. Chatani, *J. Am. Chem. Soc.* **2013**, 135, 5308–5311; o) Y. Aihara, N. Chatani, *Chem. Sci.* **2013**, 4, 664–670; p) G. Rouquet, N. Chatani, *Chem. Sci.* **2013**, 4, 2201–2208.
- [10] CCDC 934501 (**3a**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
- [11] M. O. Ratnikov, X. Xu, M. P. Doyle, *J. Am. Chem. Soc.* **2013**, 135, 9475–9479.
- [12] a) E. Shirakawa, N. Uchiyama, T. Hayashi, *J. Org. Chem.* **2011**, 76, 25–34; b) Q. Xia, W. Chen, H. Qiu, *J. Org. Chem.* **2011**, 76, 7577–7582; c) Q. Xia, W. Chen, *J. Org. Chem.* **2012**, 77, 9366–9373; d) N. Takasu, K. Oisaki, M. Kanai, *Org. Lett.* **2013**, 15, 1918–1921.