Angewandte Chemie

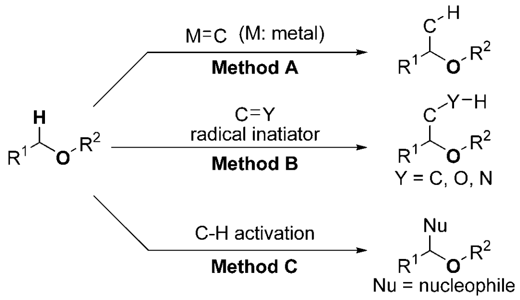
DOI: 10.1002/anie.200802215

Synthetic Methods

Iron-Catalyzed C−C Bond Formation by Direct Functionalization of C−H Bonds Adjacent to Heteroatoms**

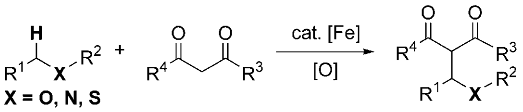
Zhiping Li, Rong Yu, and Haijun Li*

Transition-metal-catalyzed C−H functionalization for the atom- and step-economical synthesis of functional molecules has attracted tremendous efforts in both academia and industry. The advantages of this method are the high efficiency, low cost, and minimal environmental impact.[1,2] Heteroatom-containing molecules are abundant in natural products, pharmaceuticals, and materials. It is highly desirable to synthesize these molecules and their derivatives by direct C−H functionalization. Metal carbene insertion into a C−H bond adjacent to an oxygen atom presents an efficient synthetic approach to ether derivatives (Scheme 1, Method A).[3] The addition of carbon radicals to C(sp^2)=X bonds is another useful synthetic tool for the formation of C−C bonds in organic synthesis (Scheme 1, Method B).[4] The groups of Li[5] and Sames[6] reported C−C bond formation by C−H bond activation adjacent to an oxygen atom (Scheme 1, Method C). Furthermore, our group[7] and others[8] reported direct functionalization of C−H bonds adjacent to either a sulfur or nitrogen atom. Although these methods are efficient for C−H functionalization, a practical and efficient method toward such a transformation is still a challenge in synthetic chemistry.



Scheme 1. Various methods of functionalization of C−H bonds in ethers.

Transition-metal catalysts are widely used in organic synthesis and exhibit high efficiency and selectivity in chemical bond transformation. The numerous advantages of iron catalysts make them highly attractive for chemical synthesis from environmental and economic points of view.[9] Iron catalysts are well-known catalysts for C−H bond oxidation[10] and Friedel–Crafts reactions.[11] Recently, there have been efforts to develop the redox processes involving iron catalysts for C−C bond-forming reactions. Various iron-catalyzed cross-coupling reactions,[12,13] carbometalations,[14] cycloaddition reactions,[15] and substitution reactions[16] have been successfully developed. However, utilization of the redox properties of iron catalysts in C−H bond functionalization, especially in C−C bond formation, is still a challenge.[17] Herein we report direct functionalization of C−H bonds adjacent to heteroatoms, featuring C−H activation with an inexpensive and environmentally benign Fe catalyst (Scheme 2). This method can generate various functionalized molecules and is expected to have broad applications in synthesis.



Scheme 2. Iron-catalyzed functionalization of C−H bonds.

We began our explorations with THF (**1a**) and ethyl benzoylacetate (**2a**) as model substrates to identify suitable reaction conditions (Table 1). Moderate yields of desired product **3a** were obtained when $FeCl_2$ and $FeBr_2$ were used as catalysts (Table 1, entries 1 and 2). $FeCl_3$ was much less effective for this transformation (Table 1, entry 3) and the desired product was not observed when [Fe(acac)$_2$] (acac = acetylacetonate), [Fe(acac)$_3$], or [Fe(dbm)$_3$] (dbm = 1,3-diphenyl-1,3-propanedione) were used (Table 1, entries 4–6). Comparable yields of **3a** were obtained when either $Fe(OAc)_2$ or [$Fe_2(CO)_9$] were used as catalysts (Table 1, entries 7 and 8). The best result was achieved when 3 equivalents of *tert*-butyl peroxide and 10 mol% of [$Fe_2(CO)_9$] were employed (Table 1, entry 9). Other metals with CO ligands, such as W and Cr, were much less effective catalysts (Table 1, entries 10 and 11). Reagents such as *tert*-butyl hydroperoxide and cumyl hydroperoxide were also effective oxidants (Table 1, entries 12 and 13). However, the desired product was not obtained when *tert*-butyl peroxybenzoate or hydrogen peroxide were used (Table 1, entries 14 and 15). Moreover, the desired product was not observed at room temperature or in the absence of an iron catalyst (Table 1, entries 16

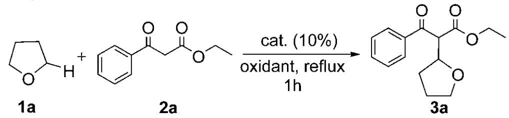
---

[*] Prof. Dr. Z. Li, R. Yu, H. Li
Department of Chemistry, Renmin University of China
Beijing 100872 (P.R. China)
Fax: (+86) 10-6251-6444
E-mail: zhipingli@ruc.edu.cn

[**] We are grateful to the program for New Century Excellent Talents in University, the Scientific Research Starting Foundation of RUC (to Z.L.), and the NSFC (No. 20602038). We also thank Prof. Zhenfeng Xi, Peking University, for helpful discussions and the supply of chemicals and instruments.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.200802215.

Table 1: Optimization of reaction conditions.[a]



Entry	Catalyst	Oxidant (equiv)	Yield [%][b]
1	$FeCl_2$	*t*BuOO*t*Bu (2)	52
2	$FeBr_2$	*t*BuOO*t*Bu (2)	64
3	$FeCl_3$	*t*BuOO*t*Bu (2)	5
4	$[Fe(acac)_2]$	*t*BuOO*t*Bu (2)	n.d.[c]
5	$[Fe(acac)_3]$	*t*BuOO*t*Bu (2)	n.d.
6	$[Fe(dbm)_3]$	*t*BuOO*t*Bu (2)	n.d.
7	$Fe(OAc)_2$	*t*BuOO*t*Bu (2)	70
8	$[Fe_2(CO)_9]$	*t*BuOO*t*Bu (2)	69
9	$[Fe_2(CO)_9]$	*t*BuOO*t*Bu (3)	82
10	$[W(CO)_6]$	*t*BuOO*t*Bu (3)	trace
11	$[Cr(CO)_6]$	*t*BuOO*t*Bu (3)	trace
12	$[Fe_2(CO)_9]$	*t*BuOOH (3)	72
13	$[Fe_2(CO)_9]$	$PhMe_2COOH$ (3)	75
14	$[Fe_2(CO)_9]$	PhCOOO*t*Bu (3)	n.d.
15	$[Fe_2(CO)_9]$	H_2O_2 (3)	n.d.
16[d]	$[Fe_2(CO)_9]$	*t*BuOO*t*Bu (3)	n.d.
17	–	*t*BuOO*t*Bu (3)	trace
18[e]	$[Fe_2(CO)_9]$	*t*BuOO*t*Bu (3)	68

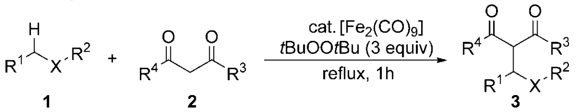
[a] **1a** (1 mL), **2a** (0.25 mmol), catalyst (0.025 mmol, 10 mol%), reflux, 1 h, unless otherwise noted. [b] Yield of isolated product. [c] Not detected by ^{1}H NMR methods. [d] Room temperature for 24 h. [e] **1a** (10 mL), **2a** (10 mmol), catalyst (0.5 mmol, 5 mol%). n.d. = not determined.

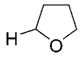
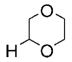
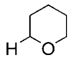
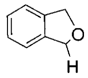
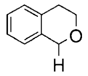
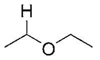
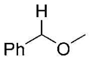
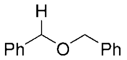
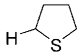
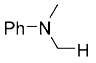
and 17). Notably, **3a** was still isolated in 68% yield when 10 mmol of **2a** was used in 10 mL THF in the presence of 5 mol% of an iron catalyst (Table 1, entry 18).

Subsequently, the scope of this C–H transformation was investigated, and some representative results are listed in Table 2. Both cyclic ether derivatives **1a**–**1e** and linear ether derivatives **1f**–**1h** reacted smoothly with various dicarbonyl substrates (**2**) to give the corresponding products (**3**) (Table 2, entries 1–16). The results show that not only β-ketone esters, but also 1,3-diketones and β-ketone amides reacted with ether derivatives to give the desired products in good yields under the standard reaction conditions. Although the reaction of diethyl ether (**1f**) and **2a** gave desired product **3n** in 73% yield, 30 mol% of the iron catalyst was needed to completely consume substrate **2a** (Table 2, entry 13). We postulated that the low reaction temperature was the main reason for the required higher iron catalyst loading. Notably, sulfide and amine groups could also be used in this novel iron-catalyzed C–H transformation under the standard reaction conditions. The reaction of tetrahydothiophene (**1i**) or *N*,*N*-dimethylaniline (**1j**) with **2** gave the desired products in good to excellent yields (Table 2, entries 17–21). The various types of substrates that can be used make the present transformation attractive for future applications.

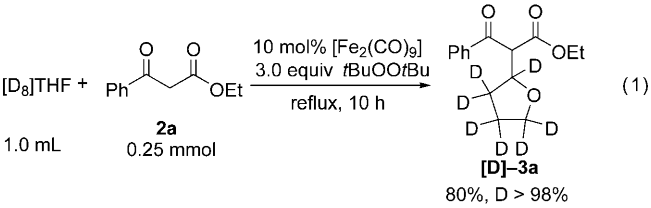
In addition, deuterated product **[D]-3a** was isolated in 80% yield when $[D_8]$THF was used instead of THF [Eq. (1)]. The scrambling of deuterium into the other possible products was not observed. Therefore, the formation of an iron–carbene species was ruled out from this result.[18] Subsequent kinetic isotopic effect (KIE) experiments were carried out by

Table 2: Representative results.[a]



Entry	1	2	Cat. [mol%]	3	Yield [%][b]
1	 **1a**	**2b**: R^3 = Ph, R^4 = Ph	10	**3b**	78
2	**1a**	**2c**: R^3 = Ph, R^4 = Me	10	**3c**	81(1:1)
3	**1a**	**2d**: R^3 = Ph, R^4 = NHPh	10	**3d**	77(1:1)
4	**1a**	**2e**: R^3 = Me, R^4 = OEt	10	**3e**	56(2:1)
5	**1a**	**2f**: R^3 = Me, R^4 = O*t*Bu	10	**3f**	53(2:1)
6	**1a**	**2g**: R^3 = Me, R^4 = Oallyl	20	**3g**	72(1:1)
7	 **1b**	**2a**	5	**3h**	83(1:1)
8	**1b**	**2b**	5	**3i**	54
9	**1b**	**2e**	10	**3j**	56(2:1)
10[c]	 **1c**	**2a**	20	**3k**	83(1:1)
11[d]	 **1d**	**2a**	10	**3l**	90(1:1)
12[d]	 **1e**	**2a**	10	**3m**	88(1:1)
13[c]	 **1f**	**2a**	30	**3n**	73(2:1)
14[c]	**1f**	**2b**	20	**3o**	52
15[d]	 **1g**	**2a**	10	**3p**	75(2:1)
16[e]	 **1h**	**2a**	10	**3q**	82(1:1)
17	 **1i**	**2a**	10	**3r**	98(1:1)
18	**1i**	**2b**	10	**3s**	71
19	**1i**	**2c**	10	**3t**	68(1:1)
20	**1i**	**2e**	10	**3u**	74(1:1)
21[e]	 **1j**	**2a**	10	**3v**	53

[a] **1** (1 mL), **2** (0.25 mmol), *t*BuOO*t*Bu (0.75 mmol), reflux, 1 h, unless otherwise noted. [b] Yield of isolated product reported; the ratios of two diasteromers are reported in the parentheses. [c] Reaction time is 10 h. [d] 100°C. [e] 80°C.



competition experiments [Eq. (2)]. The reaction has a k_H/k_D value of 5.4 ± 0.1;[19] this significant isotopic effect indicated that C–H bond cleavage is the rate-determining step of this transformation.

$$\underset{0.5\text{ mL}}{\text{THF}} + \underset{0.5\text{ mL}}{[D_8]\text{THF}} + \underset{0.25\text{ mmol}}{\mathbf{2a}} \xrightarrow[\text{reflux, 10 h}]{\substack{10\text{ mol\% }[Fe_2(CO)_9]\\ 3.0\text{ equiv }t\text{BuOO}t\text{Bu}}} \underbrace{\underset{5.4}{\mathbf{3a}} \;\underset{:}{+}\; \underset{1}{\mathbf{[D]\text{–}3a}}}_{80\%\text{ combined yield}} \qquad (2)$$

In summary, we have demonstrated that iron is an effective catalyst for the selective activation of C–H bonds adjacent to heteroatoms for subsequent C–C bond formation. Additional investigations (experimental and theorhetical) into the reaction mechanism and synthetic applications of this reaction are in progress.

Experimental Section

General procedure for **3**: Ethyl benzoylacetate (**2a**; 0.25 mmol) was added to a mixture of THF (**1a**; 1 mL) and $[Fe_2(CO)_9]$ (9.2 mg, 0.025 mmol) under a nitrogen atmosphere at room temperature, and then *tert*-butyl peroxide (0.139 mL, 0.75 mmol) was added dropwise to the mixture. The resulting mixture was heated to reflux and stirred for 1 h unless noted otherwise in the text. The resulting reaction mixture was mixed with a small amount of silica gel and concentrated, and then purified by flash column chromatography (ethyl acetate/petroleum ether = 1:20). The fraction having an $R_f = 0.3$ (ethyl acetate/petroleum ether = 1:6) was collected to give desired product **3a**. The ratio of the two diasteromers was 1:1. ^{1}H NMR: $\delta = 8.05$–8.01 (m, 4H), 7.62–7.55 (m, 2H), 7.50–7.44 (m, 4H), 4.74–4.64 (m, 2H), 4.46 (d, $J = 9.0$ Hz, 1H), 4.41 (d, $J = 9.0$ Hz, 1H), 4.17 (q, $J = 7.2$ Hz, 2×2H), 3.92–3.69 (m, 4H), 2.28–2.15 (m, 2H), 1.99–1.84 (m, 4H), 1.57–1.45 (m, 2H), 1.18 (t, $J = 6.9$ Hz, 3H), 1.17 ppm (t, $J = 6.9$ Hz, 3H); ^{13}C NMR: $\delta = 193.5$, 193.2, 167.8, 167.4, 136.7, 136.2, 133.7, 133.3, 128.7, 128.6, 128.5, 78.0, 77.6, 68.1, 68.0, 61.5, 61.3, 60.1, 59.2, 30.1, 29.9, 25.4, 25.3, 13.9, 13.8 ppm.

Received: May 12, 2008
Revised: July 10, 2008
Published online: August 13, 2008

Keywords: C–H activation · cross-coupling · heterocycles · iron · peroxides

---

[1] *Handbook of C–H Transformations* (Ed.: G. Dyker), Wiley-VCH, Weinheim, **2005**.

[2] a) R. G. Bergman, *Nature* **2007**, *446*, 391–393; b) K. Godula, D. Sames, *Science* **2006**, *312*, 67–72; c) V. Ritleng, C. Sirlin, M. Pfeffer, *Chem. Rev.* **2002**, *102*, 1731–1769; d) G. Dyker, *Angew. Chem.* **1999**, *111*, 1808–1822; *Angew. Chem. Int. Ed.* **1999**, *38*, 1698–1712; e) A. E. Shilov, G. B. Shul'pin, *Chem. Rev.* **1997**, *97*, 2879–2932.

[3] a) H. M. L. Davies, R. E. J. Beckwith, *Chem. Rev.* **2003**, *103*, 2861–2903; b) M. M. Diaz-Requejo, T. R. Belderrain, M. C. Nicasio, S. Trofimenko, P. J. Perez, *J. Am. Chem. Soc.* **2002**, *124*, 896–897.

[4] a) T. Akindele, Y. Yamamoto, M. Maekawa, H. Umeki, K.-I. Yamada, K. Tomioka, *Org. Lett.* **2006**, *8*, 5729–5732; b) A. Clerici, R. Cannella, N. Pastori, W. Panzeri, O. Porta, *Tetrahedron* **2006**, *62*, 5986–5994; c) T. Yoshimitsu, Y. Arano, H. Nagaoka, *J. Org. Chem.* **2005**, *70*, 2342–2345; d) K.-I. Yamada, Y. Yamamoto, K. Tomioka, *Org. Lett.* **2003**, *5*, 1797–1799; e) J. Chen, R. L. Kirchmeier, J. M. Shreeve, *Inorg. Chem.* **1996**, *35*, 6676–6681.

[5] a) Y. Zhang, C.-J. Li, *Angew. Chem.* **2006**, *118*, 1983–1986; *Angew. Chem. Int. Ed.* **2006**, *45*, 1949–1952; b) Y. Zhang, C.-J. Li, *J. Am. Chem. Soc.* **2006**, *128*, 4242–4243.

[6] a) S. J. Pastine, K. M. McQuaid, D. Sames, *J. Am. Chem. Soc.* **2005**, *127*, 12180–12181; b) S. J. Pastine, D. Sames, *Org. Lett.* **2005**, *7*, 5429–5431.

[7] a) Z. Li, H. Li, X. Guo, L. Cao, R. Yu, H. Li, S. Pan, *Org. Lett.* **2008**, *10*, 803–805; b) Z. Li, D. S. Bohle, C.-J. Li, *Proc. Natl. Acad. Sci. USA* **2006**, *103*, 8928–8933.

[8] a) J.-Q. Yu, R. Giri, X. Chen, *Org. Biomol. Chem.* **2006**, *4*, 4041–4047; b) A. R. Dick, M. S. Sanford, *Tetrahedron* **2006**, *62*, 2439–2463; c) M. Tobisu, N. Chatani, *Angew. Chem.* **2006**, *118*, 1713–1715; *Angew. Chem. Int. Ed.* **2006**, *45*, 1683–1684; d) D.-H. Wang, X.-S. Hao, D.-F. Wu, J.-Q. Yu, *Org. Lett.* **2006**, *8*, 3387–3390; e) X. Wan, D. Xing, Z. Fang, B. Li, F. Zhao, K. Zhang, L. Yang, Z. Shi, *J. Am. Chem. Soc.* **2006**, *128*, 12046–12047; f) L. Shi, Y.-Q. Tu, M. Wang, F.-M. Zhang, C.-A. Fan, Y.-M. Zhao, W.-J. Xia, *J. Am. Chem. Soc.* **2005**, *127*, 10836–10837; g) L. V. Desai, K. L. Hull, M. S. Sanford, *J. Am. Chem. Soc.* **2004**, *126*, 9542–9543; h) N. Chatani, T. Asaumi, S. Yorimitsu, T. Ikeda, F. Kakiuchi, S. Murai, *J. Am. Chem. Soc.* **2001**, *123*, 10935–10941.

[9] a) C. Bolm, J. Legros, J. Le Paih, L. Zani, *Chem. Rev.* **2004**, *104*, 6217–6254; b) A. Fürstner, K. Majima, R. Martin, H. Krause, E. Kattnig, R. Goddard, C. W. Lehmann, *J. Am. Chem. Soc.* **2008**, *130*, 1992–2004.

[10] a) D. H. R. Barton, D. Doller, *Acc. Chem. Res.* **1992**, *25*, 504–512; b) M. Christmann, *Angew. Chem.* **2008**, *120*, 2780–2783; *Angew. Chem. Int. Ed.* **2008**, *47*, 2740–2742; c) M. S. Chen, M. C. White, *Science* **2007**, *318*, 783–787; d) M. P. Sibi, M. Hasegawa, *J. Am. Chem. Soc.* **2007**, *129*, 4124–4125.

[11] *Lewis Acids in Organic Synthesis*, *Vols. 1–2* (Ed.: H. Yamamoto), Wiley-VCH, Weinheim, **2000**.

[12] Carbon–carbon bond formation: a) A. Fürstner, R. Martin, *Chem. Lett.* **2005**, *34*, 624–629; b) T. Hatakeyama, M. Nakamura, *J. Am. Chem. Soc.* **2007**, *129*, 9844–9845; c) A. Guérinot, S. Reymond, J. Cossy, *Angew. Chem.* **2007**, *119*, 6641–6644; *Angew. Chem. Int. Ed.* **2007**, *46*, 6521–6524; d) J. Kischel, K. Mertins, D. Michalik, A. Zapf, M. Beller, *Adv. Synth. Catal.* **2007**, *349*, 865–870; e) L. K. Ottesen, F. Ek, R. Olsson, *Org. Lett.* **2006**, *8*, 1771–1773; f) K. Bica, P. Gaertner, *Org. Lett.* **2006**, *8*, 733–735; g) I. Sapountzis, W. Lin, C. C. Kofink, C. Despotopoulou, P. Knochel, *Angew. Chem.* **2005**, *117*, 1682–1685; *Angew. Chem. Int. Ed.* **2005**, *44*, 1654–1658; h) K. Itami, S. Higashi, M. Mineno, J. Yoshida, *Org. Lett.* **2005**, *7*, 1219–1222; i) M. Nakamura, K. Matsuo, S. Ito, E. Nakamura, *J. Am. Chem. Soc.* **2004**, *126*, 3686–3687; j) A. Fürstner, A. Leitner, M. Mendez, H. Krause, *J. Am. Chem. Soc.* **2002**, *124*, 13856–13863.

[13] Carbon–heteroatom bond formation: a) A. Correa, O. G. Mancheno, C. Bolm, *Chem. Soc. Rev.* **2008**, *37*, 1108–1117; b) A. Correa, M. Carril, C. Bolm, *Angew. Chem.* **2008**, *120*, 2922–2925; *Angew. Chem. Int. Ed.* **2008**, *47*, 2880–2883; c) O. Bistri, A. Correa, C. Bolm, *Angew. Chem.* **2008**, *120*, 596–598; *Angew.*

Chem. Int. Ed. **2008**, *47*, 586–588; d) Z. Wang, Y. Zhang, H. Fu, Y. Jiang, Y. Zhao, *Org. Lett.* **2008**, *10*, 1863–1866; e) A. Correa, C. Bolm, *Angew. Chem.* **2007**, *119*, 9018–9021; *Angew. Chem. Int. Ed.* **2007**, *46*, 8862–8865.

[14] a) Z. Lu, G. Chai, S. Ma, *J. Am. Chem. Soc.* **2007**, *129*, 14546–14547; b) D. Zhang, J. M. Ready, *J. Am. Chem. Soc.* **2006**, *128*, 15050–15051; c) E. Shirakawa, T. Yamagami, T. Kimura, S. Yamaguchi, T. Hayashi, *J. Am. Chem. Soc.* **2005**, *127*, 17164–17165.

[15] a) Reference [3b]; b) G. Hilt, P. Bolze, K. Harms, *Chem. Eur. J.* **2007**, *13*, 4312–4325; c) D. Necas, P. Drabina, M. Sedlak, M. Kotora, *Tetrahedron Lett.* **2007**, *48*, 4539–4541; d) A. Fürstner, R. Martin, K. Majima, *J. Am. Chem. Soc.* **2005**, *127*, 12236–12237; e) W. Imhof, E. Anders, *Chem. Eur. J.* **2004**, *10*, 5717–5729; f) B. E. Eaton, B. Rollman, J. A. Kaduk, *J. Am. Chem. Soc.* **1992**, *114*, 6245–6246.

[16] a) B. Plietker, A. Dieskau, K. Mows, A. Jatsch, *Angew. Chem.* **2008**, *120*, 204–207; *Angew. Chem. Int. Ed.* **2008**, *47*, 198–201; b) B. Åkermark, M. P. T. Sjogren, *Adv. Synth. Catal.* **2007**, *349*, 2641–2646; c) G. S. Silverman, S. Strickland, K. M. Nicholas, *Organometallics* **1986**, *5*, 2117–2124.

[17] a) J. Norinder, A. Matsumoto, N. Yoshikai, E. Nakamura, *J. Am. Chem. Soc.* **2008**, *130*, 5858–5859; b) Z. Li, L. Cao, C.-J. Li, *Angew. Chem.* **2007**, *119*, 6625–6627; *Angew. Chem. Int. Ed.* **2007**, *46*, 6505–6507; c) Y. Zhang, C.-J. Li, *Eur. J. Org. Chem.* **2007**, 4654–4657.

[18] a) H. M. Mbuvi, L. K. Woo, *Organometallics* **2008**, *27*, 637–645; b) Y. Li, J.-S. Huang, Z.-Y. Zhou, C.-M. Che, X.-Z. You, *J. Am. Chem. Soc.* **2002**, *124*, 13185–13193.

[19] The KIE value was determined by analyzing the ratio of **3a** to **[D]-3a**; see details in the Supporting Information.