ORGANIC
LETTERS

2011
Vol. 13, No. 23
6272–6275

Iron-Catalyzed Oxidation of Tertiary Amines: Synthesis of β-1,3-Dicarbonyl Aldehydes by Three-Component C–C Couplings

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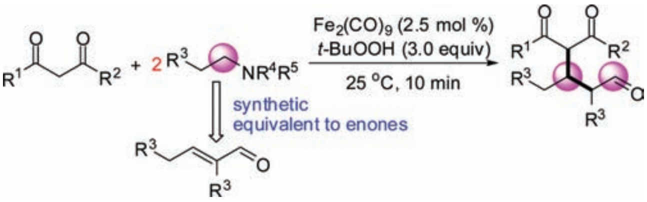
Received October 13, 2011

ABSTRACT



β-1,3-Dicarbonyl aldehydes were synthesized by iron-catalyzed oxidative reactions between 1,3-dicarbonyl compounds and two molecules of tertiary amines in the presence of *tert*-butyl hydroperoxide (TBHP). α,β-Unsaturated aldehydes generated by tertiary amine oxidation in situ act as key intermediates under mild reaction conditions.

Catalytic dehydrogenative oxidation of a C–H bond presents one of the most important and useful strategies for achieving a variety of C–H functionalizations.[1,2] The oxidation of tertiary amines has attracted much interest from the viewpoints of both biochemistry and chemistry.[3,4] Imines or iminium ions, selectively generated by oxidation of the C–H bond adjacent to a nitrogen atom, are key intermediates toward various nucleophiles,[5] leading to oxidatively coupled products, which presents an excellent alternative protocol for the Mannich-type reactions (Scheme 1, path a).[6,7] Recently, we[8] have developed an efficient double alkylation of *N*-methyl amines, in which two molecules of nucleophiles were involved in the final

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(1) Dobereiner, G. E.; Crabtree, R. H. *Chem. Rev.* **2010**, *110*, 681.

(2) (a) Bergman, R. G. *Nature* **2007**, *446*, 391. (b) Godula, K.; Sames, D. *Science* **2006**, *312*, 67. (c) Dyker, D., Ed. *Handbook of C–H Transformations*: Wiley-VCH: Weinheim, 2005. (d) Special issue on selective functionalization of C–H bonds: *Chem. Rev.* 2010, *110*, 575–1211.

(3) (a) *Cytochrome P-450, Structure, Mechanism, and Biochemistry*, 2nd ed.; Ortiz de Montellano, P. R., Ed.; Plenum Press: New York, 1995. (b) Gorrod, J. W. *Biological Oxidation of Nitrogen*; Elsevier/North Holland Biomedical Press: New York, 1978.

(4) (a) Murahashi, S.-I.; Zhang, D. *Chem. Soc. Rev.* **2008**, *37*, 1490. (b) Murahashi, S.-I. *Angew. Chem., Int. Ed.*. **1995**, *34*, 2443.

(5) For representative reviews, see: (a) Campos, K. R. *Chem. Soc. Rev.* **2007**, *36*, 1069. (b) Godula, K.; Sames, D. *Science* **2006**, *312*, 67. (c) Tobisu, M.; Chatani, N. *Angew. Chem., Int. Ed.* **2006**, *45*, 1683.

(6) For representative reviews, see: (a) Li, C.-J. *Acc. Chem. Res.* **2009**, *42*, 335. (b) Li, C.-J.; Li., Z. *Pure Appl. Chem.* **2006**, *78*, 935. (c) Murahashi, S.-I.; Takaya, H. *Acc. Chem. Res.* **2000**, *33*, 225. (d) Murahashi, S.-I. *Pure Appl. Chem.* **1992**, *64*, 403.

(7) For selected examples: (a) Li, S.; Wu, J. *Org. Lett.* **2011**, *13*, 712. (b) Xu, X.; Ge, Z.; Cheng, D.; Ma, L.; Lu, C.; Zhang, Q.; Yao, N.; Li, X. *Org. Lett.* **2010**, *12*, 897. (c) Xia, X.-F.; Shu, X.-Z.; Ji, K.-G.; Yang, Y.-F.; Shaukat, A.; Liu, X.-Y.; Liang, Y.-M. *J. Org. Chem.* **2010**, *75*, 2893. (d) Tian, J.-S.; Loh, T.-P. *Angew. Chem., Int. Ed.* **2010**, *49*, 8417. (e) Shu, X.-Z.; Xia, X.-F.; Yang, Y.-F.; Ji, K.- G.; Liu, X.-Y.; Liang, Y.-M. *J. Org. Chem.* **2009**, *74*, 7464. (f) Tsang, A. S. K.; Todd, M. H. *Tetrahedron Lett.* **2009**, *50*, 1199. (g) Huang, L.; Zhang, X.; Zhang, Y. *Org. Lett.* **2009**, *11*, 3730. (h) Xu, X.; Li, X. *Org. Lett.* **2009**, *11*, 1027. (i) Xu, X.; Li, X.; Ma, L.; Ye, N.; Weng, B. *J. Am. Chem. Soc.* **2008**, *130*, 14048. (j) Niu, M.; Yin, Z.; Fu, H.; Jiang, Y.; Zhao, Y. *J. Org. Chem.* **2008**, *73*, 3961. (k) Zhang, Y.; Fu, H.; Jiang, Y.; Zhao, Y. *Org. Lett.* **2007**, *9*, 3813. (l) Li, Z.; Li, C.-J. *J. Am. Chem. Soc.* **2005**, *127*, 3672. (m) Li, Z.; Li, C.-J. *Eur. J. Org. Chem.* **2005**, 3173. (n) Li, Z.; Li, C.-J. *J. Am. Chem. Soc.* **2004**, *126*, 11810. (o) Murahashi, S.-I.; Komiya, N.; Terai, H.; Nakae, T. *J. Am. Chem. Soc.* **2003**, *125*, 15312. (p) Hwang, D.-R.; Uang, B.-J. *Org. Lett.* **2002**, *4*, 463.

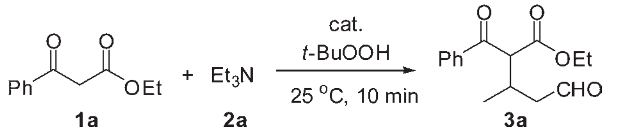
(8) Li, H.; He, Z.; Guo, X.; Li, W.; Zhao, X.; Li, Z. *Org. Lett.* **2009**, *11*, 4176.

10.1021/ol202749x

Scheme 1. Applications of Amine Oxidation in Synthetic Organic Chemistry

product via a C−N bond cleavage.[9] We were curious to know whether *N*-ethyl amines can also give the same type of products. But we found that β-substituted aldehydes were obtained through the dimerization of two alkyl-substituted amines (path b). Herein, we report this novel reaction route, which provides an efficient and easy way to synthesize useful β-substituted aldehydes using a cheap iron catalyst[10] and the widely found tertiary amines.[11]

Table 1. Optimization of the Reaction Conditions[a]



entry	2a (equiv)	cat. (mol %)	*t*-BuOOH (equiv)	3a (%)[b]
1	20	$Fe_2(CO)_9$ (10)	2	45
2	20	$FeBr_2$ (10)	2	40
3	20	$FeCl_2$ (10)	2	trace
4	20	$Fe(OAc)_2$ (10)	2	trace
5	20	$FeCl_3$ (10)	2	N.D.
6	20	$Fe(acac)_2$ (10)	2	N.D.
7	20	$CoCl_2$ (10)	2	N.D.
8	20	CuCl (10)	2	N.D.
9	20	$CuBr_2$ (10)	2	N.D.
10	20	$Mn(OAc)_2$ (10)	2	N.D.
11	20	$Fe_2(CO)_9$ (10)	3	69
12	20	$Fe_2(CO)_9$ (2.5)	3	76
13	10	$Fe_2(CO)_9$ (2.5)	3	73
14	8	$Fe_2(CO)_9$ (2.5)	3	70
15	8	$FeBr_2$ (2.5)	3	trace
16	8	–	3	N.D.

[a] Conditions: **1a** (0.5 mmol); *t*-BuOOH was added over 30 s under N_2 at 25 °C. [b] Isolated yields based on **1a**; N.D. = not detected by TLC.

The reaction of ethyl 3-oxo-3-phenylpropanoate (**1a**) and triethylamine (**2a**) was chosen as a model reaction to investigate the suitable reaction conditions (Table 1). Ethyl 2-benzoyl-3-methyl-5-oxopentanoate (**3a**) were obtained in 45% and 40% yields, respectively, when $Fe_2(CO)_9$ and $FeBr_2$ were used as the catalyst (entries 1 and 2). $FeCl_2$ and $Fe(OAc)_2$ led to a trace amount of **3a** at room temperature in 10 min (entries 3 and 4). Other examined metal salts, including $FeCl_3$, $Fe(acac)_2$, $CoCl_2$, CuCl, $CuBr_2$, and $Mn(OAc)_2$, were ineffective for the generation of **3a** (entries 5−10). The yield of the desired product **3a** was improved to 69% when 3 equiv of *tert*-butyl hydroperoxide (TBHP) were applied (entry 11). Gratifyingly, the yield of **3a** was improved up to 76% when the loading of $Fe_2(CO)_9$ was reduced to 2.5 mol % (entry 12). Comparable yields were obtained even in the cases of reducing the amount of **2a** (entries 13 and 14). Surprisingly, only a trace amount of **3a** was generated under the present conditions when $FeBr_2$ was used (entry 15), indicating that $FeBr_2$ is a less effective catalyst compared to $Fe_2(CO)_9$. Importantly, **3a** was not observed in the absence of the iron catalyst (entry 16). Although the exact roles of $Fe_2(CO)_9$ are still not clear, we have previously reported that the binuclear iron complex shows great versatility for the oxidation of a C−H bond adjacent to a heteroatom.[9]

Subsequently, a scope of the present transformation was examined using triethylamine (**2a**) as a model substrate to react with various β-keto esters **1** under the optimized reaction conditions (Scheme 2). In all cases, the desired β-1,3-dicarbonyl aldehydes **3** were obtained with two diastereomers in a ratio of 1:1. Although the aryl groups with electron-donating substituents gave the corresponding products in moderate yields, an electron-withdrawing substituent, such as NO_2, led to a lower yield of the desired product **3f**. Importantly, the alkyl substituents can be tolerated in the reactions, as demonstrated by the formation of the desired aldehydes **3j**−**3m**.

When 1,3-diphenylpropane-1,3-dione (**4**) was applied, 3-methyl-5-oxo-5-phenylpentanal (**6**) was obtained via decarbonylation of the expected product **5** (eq 1). In contrast, the reaction of dimethyl malonate (**7**) with **2a** afforded tetramethyl 2-methylpropane-1,1,3,3-tetracarboxylate (**8**) instead of the expected aldehyde under the standard reaction conditions (eq 2). It is worthy to note that ethyl 2-methyl-3-oxobutanoate and 1*H*-indene-1,3(2*H*)-dione did not react with **2a**. We postulated that this is attributed to a steric bulkiness of the substrate, which weakens the coordination of the substrate to the catalyst.

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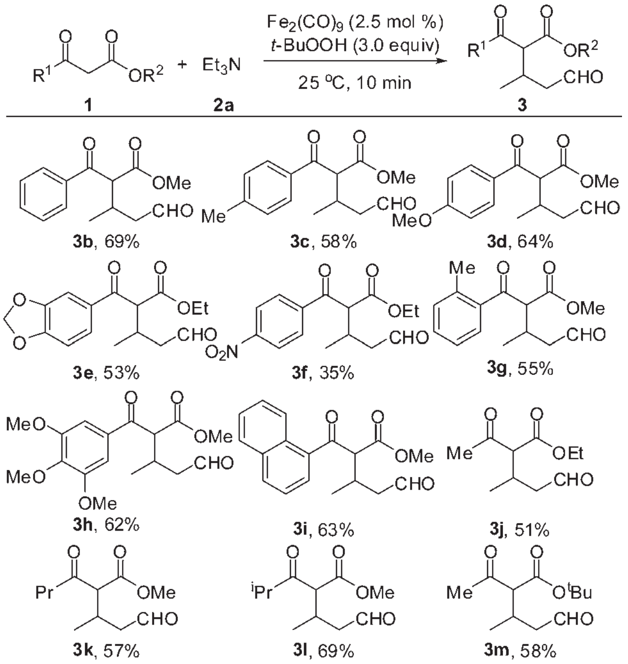
(9) Iron-catalyzed C−N bond cleavage: (a) Liu, C.-R.; Yang, F.-L.; Jin, Y.-Z.; Ma, X.-T.; Cheng, D.-J.; Li, N.; Tian, S.-K. *Org. Lett.* **2010**, *12*, 3832. (b) Kuninobu, Y.; Nishi, M.; Takai, K. *Chem. Commun.* **2010**, *46*, 8860.

(10) For representative reviews on iron-catalyzed reactions: (a) Sun, C.-L.; Li, B.-J.; Shi, Z.-J. *Chem. Rev.* **2011**, *111*, 1293. (b) Nakamura, E.; Yoshikai, N. *J. Org. Chem.* **2010**, *75*, 6061. (c) Sarhan, A. A. O.; Bolm, C. *Chem. Soc. Rev.* **2009**, *38*, 2730. (d) Sherry, B. D.; Fürstner, A. *Acc. Chem. Res.* **2008**, *41*, 1500. (e) Correa, A.; Mancheño, O. G.; Bolm, C. *Chem. Soc. Rev.* **2008**, *37*, 1108. (f) Enthaler, S.; Junge, K.; Beller, M. *Angew. Chem., Int. Ed.* **2008**, *47*, 3317. (g) Bolm, C.; Legros, J.; Le Paih, J.; Zani, L. *Chem. Rev.* **2004**, *104*, 6217.

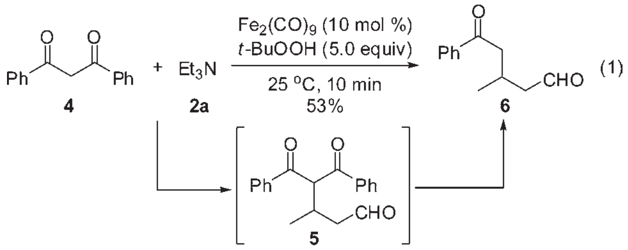
(11) For selected iron-catalyzed oxidation of tertiary amines: (a) Shirakawa, E.; Uchiyama, N.; Hayashi, T. *J. Org. Chem.* **2011**, *76*, 25. (b) Ghobrial, M.; Harhammer, K.; Mihovilovic, M. D.; Schnurch, M. *Chem. Commun.* **2010**, *46*, 8836. (c) Liu, P.; Zhou, C.-Y.; Xiang, S.; Che, C.-M. *Chem. Commun.* **2010**, *46*, 2739. (d) Volla, C. M. R.; Vogel, P. *Org. Lett.* **2009**, *11*, 1701. (e) Wang, S.; Wang, Z.; Zheng, X. *Chem. Commun.* **2009**, 7372. (f) Han, W.; Ofial, A. R. *Chem. Commun.* **2009**, 6023. (g) Han, W.; Ofial, A. R. *Chem. Commun.* **2009**, 5024. (h) Ohta, M.; Quick, M. P.; Yamaguchi, J.; Wunsch, B.; Itami, K. *Chem.—Asian J.* **2009**, *4*, 1416. (i) Murata, S.; Miura, M.; Nomura, M. *J. Chem. Soc., Chem. Commun.* **1989**, 116.

(12) Li, Z.; Yu, R.; Li, H. *Angew. Chem., Int. Ed.* **2008**, *47*, 7497.

Scheme 2. Reaction of β-Keto Esters with Triethylamine (**2a**)[a]



[a] Conditions: **1** (0.5 mmol), **2a** (4.0 mmol); 25 °C, 10 min; *t*-BuOOH was added over 30 s under N_2. Isolated yields based on **1**; two diastereomers were obtained in a ratio of 1:1.



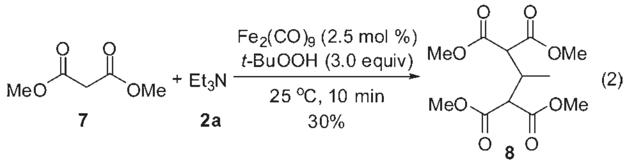
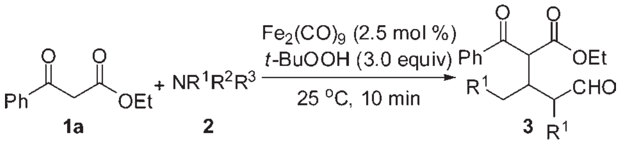
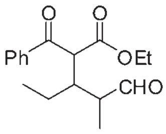
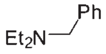
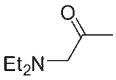
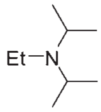


Table 2. Reactions of Amines **2** with **1a**[a]



entry	2		3 (%)[b]
1	Pr$_3$N	**2b**	 **3n**, 40%
2[c]	Et$_2$N−Me	**2c**	**3a**, 12%
3		**2d**	**3a**, 51%
4		**2e**	**3a**, 56%
5[d]		**2f**	**3a**, 20%
6[e]		**2g**	**3a**, 63%

[a] Conditions: **1a** (0.5 mmol), **2** (4.0 mmol). [b] Isolated yields based on **1a**. [c] Diethyl 2,4-dibenzoylpentanedioate (**9**) was obtained in 30% yield. [d] Ethyl 2-benzoyl-4-oxopentanoate (**10**) was obtained in 14% yield. [e] **2g** (7.5 mmol), *t*-BuOOH (5.0 equiv), and MeCN (1.0 mL).

Other tertiary amines were also investigated, as shown in Table 2. Tripropylamine (**2b**) led to the desired product **3n**, albeit in a low yield due to the steric effect (entry 1). In the case of *N*-ethyl-*N*-methylethanamine (**2c**), methylene-bridged bis-1,3-dicarbonyl product **9** was obtained as a major product,[8] along with a 12% yield of **3a** (entry 2). This result indicated that the oxidation of a *N*-methyl group is faster than that of an *N*-ethyl group, consistent with the steric effect of oxidation.[13] Moderate yields of **3a** were selectively obtained when **2d** and **2e** were used (entries 3 and 4). Interestingly, the reaction of 1-(diethylamino)propan-2-one (**2f**) with **1a** gave **3a** and **10**, which was derived via a C−N bond cleavage (entry 5). Importantly, *N*-ethyl-*N*-isopropylpropan-2-amine (**2g**) reacted with **1a** to give **3a** (entry 6). This result suggests that intramolecular migration is unlikely to be involved in this transformation.

In order to investigate the reaction mechanism, the iron-catalyzed reaction of **1a**, acetaldehyde (**11**), and diethylamine (**12**) was carried out in the absence of peroxide (eq 3). To our delight, a comparable yield of desired product **3a** was obtained. We speculated that this reaction starts with the condensation reaction of two molecules of **11** in the presence of **12** to generate but-2-enal (**13**),[14] which then undergoes Michael addition to give **3a**.[15] This mechanism was further supported by the control experiment: when (*E*/*Z*)-ethyl 2-benzoylbut-2-enoate (**14**) was subjected to the iron catalysis with **11** and **12**. In this reaction, the expected product **3a** was generated. Interestingly, a new product **15** was also generated as a byproduct in this reaction. The formation of **15** indicated that **1a** had to be generated from **14**. Accordingly, we rationalized that **1a** was generated through the C−C bond cleavage of **16**, which was obtained by the addition of **12** to **14** (Scheme 3). These results

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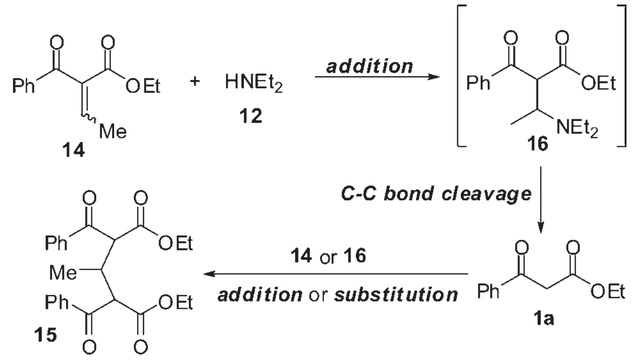
(13) The selectivity of tertiary amine oxidation is attributed to both steric and kinetic acidity effects on the deprotonation step: Lewis, F. D.; Ho, T.-I. *J. Am. Chem. Soc.* **1980**, *102*, 1751.

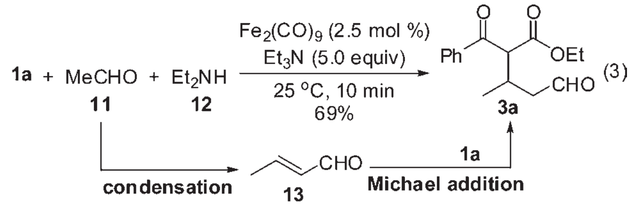
(14) Ye, J.-H.; Ling, K.-Q.; Zhang, Y.; Li, N.; Xu, J.-H. *J. Chem. Soc., Perkin Trans. 1* **1999**, 2017.

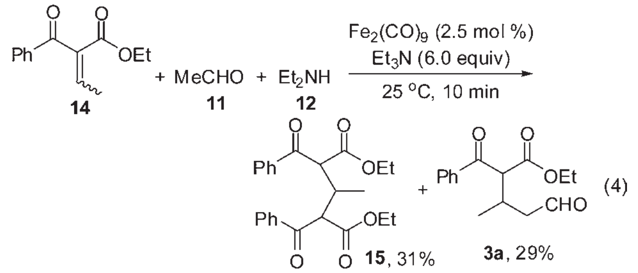
(15) Bensa, D.; Brunel, J.-M.; Buono, G.; Rodriguez, J. *Synlett* **2001**, 715.

Scheme 3. A Proposed Mechanism for the Formation of **15**

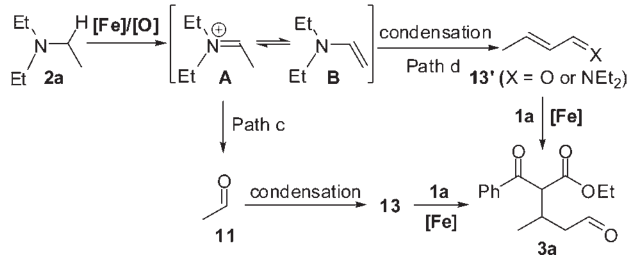


indicate that **13** rather than **14** or **16** acts as a key intermediate for the formation of **3a**.





Scheme 4. Tenative Pathways for the Formation of **3**



Based on our results and the commonly accepted mechanism from the literature, a plausible mechanism for the present transformation is depicted by the reaction of **1a** and **2a** as an illustrative case (Scheme 4). Iminium ion **A** is first generated in this reaction system via the general accepted mechanism: one-electron oxidation of nitrogen, deprotonation of C–H adjacent to a nitrogen atom, and second one-electron oxidation.[16] Then hydrolysis of **A** leads to acetaldehyde (**11**), which further undergoes aldol condensation to give unsaturated aldehyde. Finally Michael addition of nucleophile **1a** to **13** assisted by an iron catalyst gives the target product (path c).[17] However, an alternative pathway, which involves a direct aldol-type condensation of **A** and **B**, followed by Michael addition with iron catalysis, could also explain the formation of the final product **3** (path d).[18]

In summary, we reported three-component C–C coupling reactions of 1,3-dicarbonyl compounds and two molecules of tertiary amines using a cheap and commercially available iron catalyst to give β-1,3-dicarbonyl aldehydes. This reaction could start from amine oxidation to give aldehyde, which undergoes condensation to generate unsaturated aldehyde. Then Micheal addition of the nuceophile to the in situ generated unsaturated aldehyde gave the final product.

Acknowledgment. Financial support by the National Science Foundation of China (20832002 and 21072223), the Fundamental Research Funds for the Central Universities, and the Research Funds of Renmin University of China (10XNL017). We thank Profs. Zhenfeng Xi and Zhi-Xiang Yu at Peking University for helpful discussions.

Supporting Information Available. Representative experimental procedure, characterization of all new compounds, and ^{1}H and ^{13}C NMR data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(16) (a) McCamley, K.; Ripper, J. A.; Singer, R. D.; Scammells, P. J. *J. Org. Chem.* **2003**, *68*, 9847. (b) Minisci, F.; Fontana, F.; Araneo, S.; Recupero, F.; Zhao, L. *Synlett* **1996**, 119.

(17) Wang, G.-W.; Chen, X.-P.; Cheng, X. *Chem.—Eur. J.* **2006**, *12*, 7246.

(18) (a) Anguille, S.; Brunet, J.-J.; Chu, N. C.; Diallo, O.; Pages, C.; Vincendeau, S. *Organometallics* **2006**, *25*, 2943. (b) Kharasch, M. S.; Richlin, I.; Mayo, F. R. *J. Am. Chem. Soc.* **1940**, *62*, 494.