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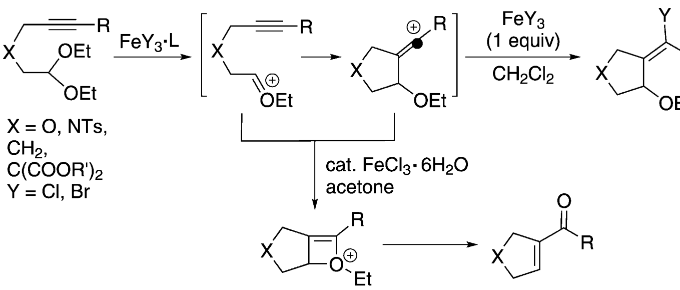
Substituent-Dependent, Iron-Mediated Tandem Cyclization of Diynes with Benzaldehyde Acetals to Form Highly Functionalized Indene Derivatives

Tongyu Xu,[a] Qin Yang,[a] Wenjing Ye,[a] Quanbin Jiang,[a] Zhaoqing Xu,[a]
Jiping Chen,[a] and Zhengkun Yu*[a, b]

Dedicated to Professor Christian Bruneau on the occasion of his 60th birthday

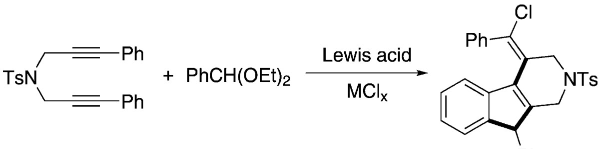
The construction of functionalized carbo- and heterocycles from relatively simple and readily available starting materials in a convergent manner is always desired in organic synthesis.[1] Diynes have been used as versatile building blocks for the preparation of carbo- and heterocycles through transition-metal catalyzed carbocyclization, cycloaddition, and cycloisomerization reactions.[2] The indene backbone is frequently found in natural products,[3] pharmaceuticals,[4] functional materials,[5] and metallocene complexes,[6] and a variety of synthetic methods have been developed for their construction.[7] Although enediynes have been documented for the synthesis of indenes,[8] diynes have seldom been applied for this purpose.[9] Recently, iron catalysis has emerged as a promising, environmentally benign alternative to traditional transition-metal catalysis due to the many advantages of utilizing iron-catalyst precursors, such as low cost, nontoxicity, good stability, and straightforward methods of handling.[10–12] Very recently, we discovered that $FeCl_3$ and $FeCl_3{\cdot}6H_2O$ can efficiently promote the intramolecular cyclization of monoalkynyl aldehyde acetals to generate solvent-dependent Prins-type products[13a] and α,β-unsaturated cyclic ketones,[13b] respectively (Scheme 1). Herein, we report the $FeCl_3$- and $FeBr_3$-mediated tandem cyclization of simple diynes with benzaldehyde acetals for the synthesis of highly functionalized indenes.

In our initial studies, the reaction of diyne **1a** with diethyl benzaldehyde acetal **2a** was investigated to screen the reaction conditions (Table 1). Under a nitrogen atmosphere, compound **1a** was reacted with an equimolar amount of **2a** in the presence of $FeCl_3$ (1.0 equiv) in CH_2Cl_2 at ambient temperature, to give 3-chlorovinyl-2,3-trisubstituted 1*H*-indene **3a** in 55 % isolated yield (Table 1, entry 1). Although several other products could be seen in the TLC analysis of the reaction mixture, no isomers of **3a** or other potential products were successfully isolated. At −10 °C, **3a** was formed in a better yield (63 %), although formation of **3a** (66 %) was further improved by performing the reaction at 0 °C (Table 1, entries 2 and 3). The reaction was less efficient



Scheme 1. The iron-mediated intramolecular cyclization of monoalkynyl aldehyde acetals (Ts = tosyl).[13]

Table 1. The screening of reaction conditions for the cyclization of diyne **1a** with diethyl benzaldehyde acetal (**2a**).[a]



1a **2a** **3a**

	Lewis acid ([equiv])	Solvent	*T* [°C]	*t* [h]	Yield[b] [%]
1	$FeCl_3$ (1.0)	CH_2Cl_2	RT	1	55
2	$FeCl_3$ (1.0)	CH_2Cl_2	−10	1	63
3	$FeCl_3$ (1.0)	CH_2Cl_2	0	0.5	66
4	$FeCl_3$ (1.2)	CH_2Cl_2	0	0.5	61
5	$FeCl_3$ (1.0)	DCE	0	1	36
6	$FeCl_3$ (1.0)	DCE	RT	1	34
7	$FeCl_3$ (1.0)	toluene	RT	1	40
8	$FeCl_3/CH_3COCl$ (0.1:2.0)	CH_2Cl_2	RT	10	24
9	$FeCl_3/Me_3SiCl$ (0.1:2.0)	CH_2Cl_2	RT	4	37
10	$FeCl_3{\cdot}6H_2O$ (1.0)	CH_2Cl_2	0	4	n.r.
11	$SnCl_4$ (1.0)	CH_2Cl_2	0	0.5	70
12	$TiCl_4$ (1.0)	CH_2Cl_2	0	0.5	48

[a] Reaction conditions: **1a** (0.5 mmol), **2a** (0.5 mmol), solvent (5 mL), N_2 atmosphere. [b] Isolated yields of **3a**. DCE = 1,2-dichloroethane.

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[a] T. Y. Xu, Q. Yang, W. J. Ye, Q. B. Jiang, Dr. Z. Q. Xu,
Prof. Dr. J. P. Chen, Prof. Dr. Z. K. Yu
Dalian Institute of Chemical Physics, Chinese Academy of Sciences
457 Zhongshan Road, Dalian, Liaoning 116023 (P.R. China)
Fax: (+86) 411-8437-9227
E-mail: zkyu@dicp.ac.cn

[b] Prof. Dr. Z. K. Yu
State Key Laboratory of Organometallic Chemistry
Shanghai Institute of Organic Chemistry (CAS)
354 Fenglin Road, Shanghai 200032 (P. R. China)

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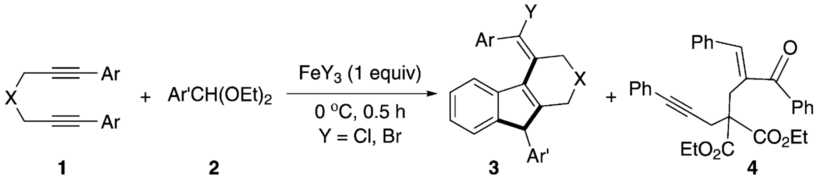
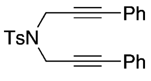
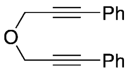
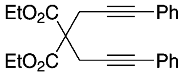
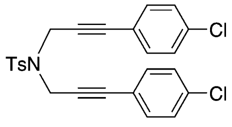
if it was carried out in DCE or toluene, whereas dichloromethane seems to be the most suitable solvent for the reaction (Table 1, entries 1–7). The use of an excess of FeCl$_3$ or catalytic amounts of FeCl$_3$ with a chloride source, such as CH$_3$COCl or Me$_3$SiCl, led to a lower reaction efficiency (Table 1, entries 4, 8, and 9). Unexpectedly, iron(III) trichloride hydrate (FeCl$_3$•6H$_2$O) exhibited no activity in this reaction (Table 1, entry 10). However, Lewis acids SnCl$_4$ and TiCl$_4$ showed moderate to good activity (Table 1, entries 11 and 12). Due to the easier manipulation of FeCl$_3$ than SnCl$_4$, the former was chosen as the mediator/chloride source for the tandem cyclization/halogenation of **1a** with benzaldehyde acetals. The reactions of **1a** with PhCH(OMe)$_2$ (**2ab**), PhCH(OCH$_2$CH$_2$O) (**2ac**), and their parent aldehyde, PhCHO (**2ad**), were also carried out under the same conditions, producing **3a** in 48, 41 and 0% yields, respectively, and revealing that diethyl benzaldehyde acetal **2a** exhibits much higher reactivity than its analogues (Scheme 2).

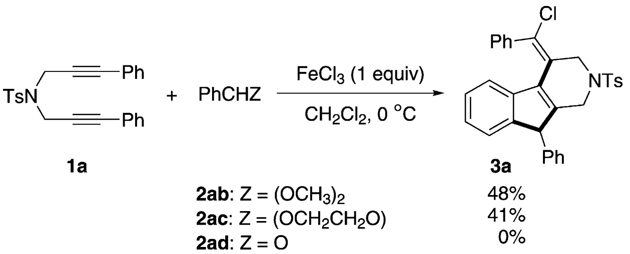
Under the optimized conditions, a variety of reactions of compounds **1** with compounds **2** were explored (Table 2). Ts*N*-linked diyne **1a** reacted with diethyl benzaldehyde acetals **2a**–**e** to form the desired products **3a**–**e** in 46–66% yields (Table 2, entries 1–5). By using FeBr$_3$ instead of FeCl$_3$ as the Lewis acid mediator/halogen source, the reactions of **1a** with **2a** and **2f** gave the same type of products, that is, **3f** (70%) and **3g** (50%), respectively, which have incorporated a bromovinyl moiety (Table 2, entries 6 and 7). *O*-Tethered diyne **1b** reacted with acetal **2b** and FeCl$_3$ to generate **3h** in 41% yield (Table 2, entry 8). Unexpectedly, the reaction of *C*-tethered diyne **1c** with acetal **2a** in the presence of FeCl$_3$ formed the desired product **3i** (25%) as only the minor product, while alkynyl enone **4** (60%) was the major product (Table 2, entry 9), which suggests that one of the alkynyl moieties underwent intramolecular cyclization with **2a**.[13b] These results suggest that the tethering heteroatoms may stabilize a cationic intermediate during the reaction.[14] It is noteable that the reaction of functionalized diyne **1d** with **2a** also formed the desired product **3j** in the presence of either FeCl$_3$ or SnCl$_4$ (Table 2, entry 10).

Table 2. The FeCl$_3$-mediated cyclization of diynes **1a**–**d** with acetals **2**.[a]



	diyne (1)		Ar′ (2)	Product (Y; yield[b] [%])
1	**1a**	 **1a**	Ph (**2a**)	**3a** (Cl; 66)
2[c]	**1a**		4-MeOC$_6$H$_4$ (**2b**)	**3b** (Cl; 52)
3[c]	**1a**		3-MeOC$_6$H$_4$ (**2c**)	**3c** (Cl; 51)
4	**1a**		3-CF$_3$C$_6$H$_4$ (**2d**)	**3d** (Cl; 49)
5	**1a**		3-BrC$_6$H$_4$ (**2e**)	**3e** (Cl; 46)
6[d]	**1a**		Ph (**2a**)	**3f** (Br; 70)
7[d]	**1a**		4-ClC$_6$H$_4$ (**2f**)	**3g** (Br; 50)
8	**1b**	 **1b**	4-MeOC$_6$H$_4$ (**2b**)	**3h** (Cl; 41)
9	**1c**	 **1c**	Ph (**2a**)	**3i** (Cl; 25) + **4** (60)
10	**1d**	 **1d**	Ph (**2a**)	**3j** (Cl; 62) **3j** (Cl; 67)[e]

[a] Reaction conditions: **1** (0.5 mmol), **2** (0.5 mmol), FeCl$_3$ (0.5 mmol), CH$_2$Cl$_2$ (5 mL), N$_2$ atmosphere, 0°C, 0.5 h. [b] Isolated yields. [c] 25°C. [d] FeBr$_3$ (0.75 mmol) was used instead of FeCl$_3$. [e] SnCl$_4$ (0.5 mmol) was used instead of FeCl$_3$.

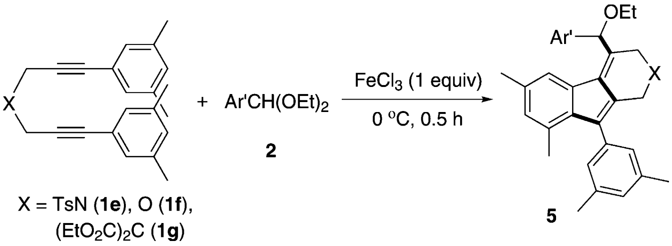


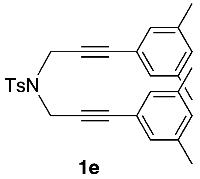
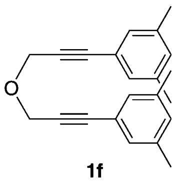
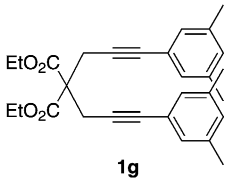
Scheme 2. The reactions of diyne **1a** with acetals **2ab**–**ad**.

The formation of the desired product was clearly affected by the substituents on the aryl moieties and by the tether atom in diyne **1** (Table 2 and the Supporting Information). Moreover, increasing the electron density of the aryl functionalities in diynes **1e**–**g** by introducing two electron-donating methyl groups led to the formation of 1-methylene-2,3-disubstituted 1*H*-indenes **5** (51–72%) as the major product (Table 3). The presence of electron-withdrawing substituents on the aryl moiety of acetals **2** improved the yield of compounds **5** from the reaction of **1e**–**g** with compounds **2** (Table 3). The generation of indenes **3** and **5** was further confirmed by X-ray crystallographic structural analysis of products **3a** and **5i** (Figure 1 and Figure 2, respectively), revealing their fused tricyclic structures and the construction of three new carbon–carbon bonds in the newly formed backbones.

Possible mechanisms for the reaction are proposed in Scheme 3. In pathway *a*, the oxocarbonium cation Ar′CH=OEt$^+$ (**A**) is generated in situ from the interaction of FeCl$_3$ with diethyl benzaldehyde acetal **2**, Ar′CH(OEt)$_2$, by loss of the FeCl$_3$(OEt)$^-$ anion. Diyne **1** then reacts with **A** through a [2+2] cycloaddition reaction to form oxete **B**, which is shown to be preferentially formed by our theoretical study of the reaction.[13b] Ring-opening of **B** gives 4π-cation **C**, which undergoes a Nazarov-type cyclization reaction,[15] yielding oxocarbonium cation **F** via species **D** and **E**. Intra-

Table 3. The $FeCl_3$-mediated cyclization of diynes **1e–g** with acetals **2**.[a]



	Diyne (**1**)		Ar′ (**2**)	Product (yield[b] [%])
1	**1e**	 **1e**	Ph (**2a**)	**5a** (67)
2	**1e**		4-$MeOC_6H_4$ (**2b**)	**5b** (51)
3	**1e**		3-BrC_6H_4 (**2e**)	**5c** (72)
4	**1e**		4-ClC_6H_4 (**2f**)	**5d** (61)
5	**1e**		4-MeC_6H_4 (**2g**)	**5e** (53)
6	**1e**		2-$MeOC_6H_4$ (**2h**)	**5f** (60)
7	**1e**		2-naphthyl (**2i**)	**5g** (60)
8	**1f**	 **1f**	Ph (**2a**)	**5h** (61)
9	**1f**		3-BrC_6H_4 (**2e**)	**5i** (60)
10	**1f**		4-$NO_2C_6H_4$ (**2j**)	**5j** (70)
11	**1g**	 **1g**	Ph (**2a**)	**5k** (70)

[a] Reaction conditions: **1** (0.5 mmol), **2** (0.5 mmol), $FeCl_3$ (0.5 mmol), CH_2Cl_2 (5 mL), N_2 atmosphere, 0 °C, 0.5 h. [b] Isolated yields.

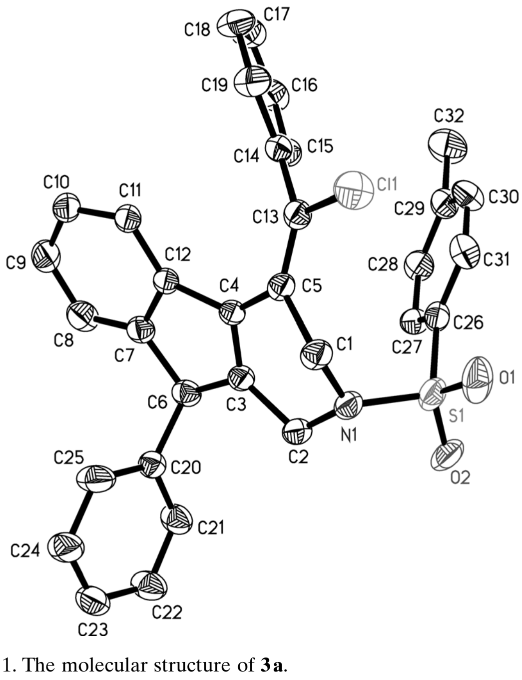


Figure 1. The molecular structure of **3a**.

molecular cyclization occurs in **F** to generate vinyl cation **G**, which is traped by a chloride anion from $FeCl_3(OEt)^-$, forming intermediate **H** and $FeCl_2(OEt)$. The Lewis acid promotes elimination of EtOH from **H** then affords product **3**.

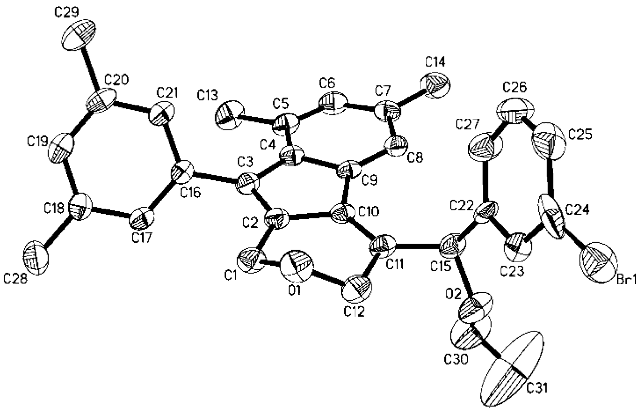


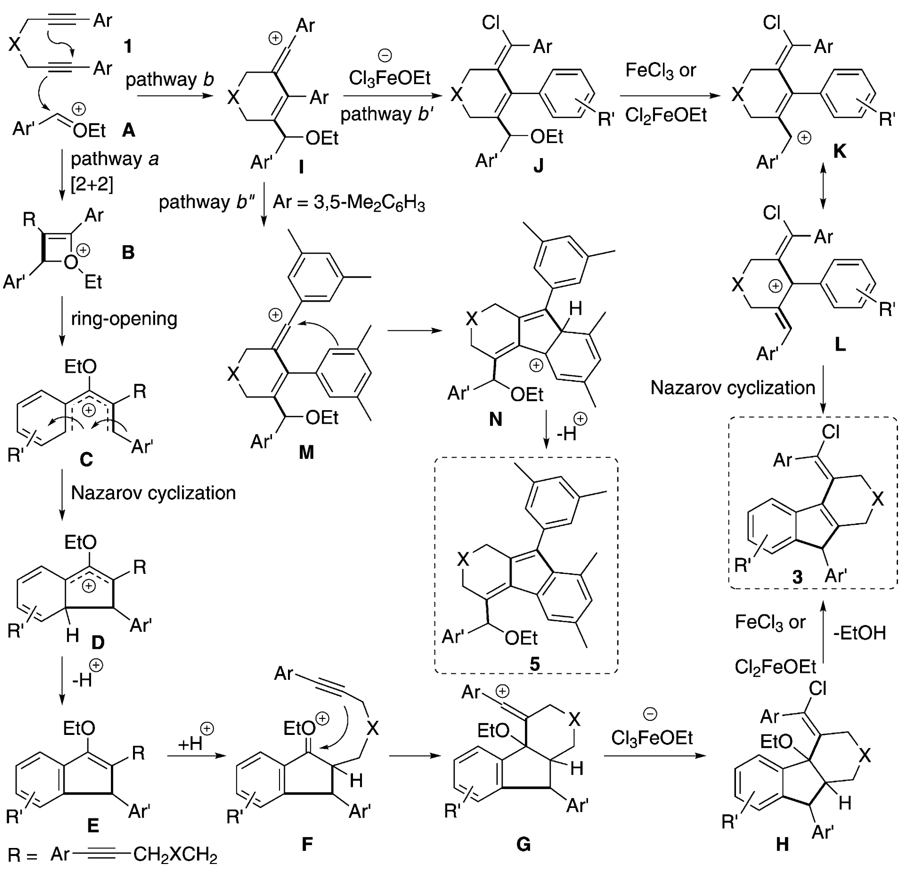
Figure 2. The molecular structure of **5i**.

On the other hand, pathway *b* more plausibly describes the diverging route that allows the formation of products **3** and **5**. Tandem intra- and intermolecular interactions of diyne **1** with oxocarbonium cation **A** produce vinyl cation **I**, which reacts with an external chloride anion to give intermediate **J** if the aryl groups in the diyne substrate are insufficiently electron-rich for the alternative pathway. Lewis acid $FeCl_3$ or Cl_2FeOEt then initiates a Nazarov-type cyclization to form product **3** via cations **K** and **L** (pathway *b*′). However, if the aryl groups in the diyne substrates are electron-rich, for example, 3,4-dimethylphenyl groups, one of these two aryl groups behaves as the nucleophile to capture the developing vinyl cation in **I** and form product **5** (pathway *b*″) via intermediates **M** and **N**.

In summary, the $FeCl_3$- and $FeBr_3$-mediated cyclization of diynes with diethyl benzaldehyde acetals has been realized, producing highly functionalized indene derivatives in which three new carbon–carbon bonds have been formed. The substituents on the aryl moieties of the diyne direct the formation of either 3-halovinyl-2,3-disubstituted or 1-methylene-2,3-disubstituted 1*H*-indenes. This synthetic protocol provides a new route to fused functionalized tricyclic indenes.

Experimental Section

Typical procedure: **The iron-mediated formation of 3a**: Under a nitrogen atmosphere, a suspension of $FeCl_3$ (81 mg, 0.5 mmol) in CH_2Cl_2 (5 mL) was cooled to 0 °C. While this mixture was being stirred, diyne **1a** (200 mg, 0.5 mmol) and then benzaldehyde diethyl acetal **2a** (90 mg, 0.5 mmol) were added. The mixture was stirred at 0 °C for 30 min, and then quenched with water (10 mL). The organic layer was separated off and the aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting residue was purified by silica gel flash column chromatography (eluent: petroleum ether (60–90 °C)/diethyl ether, 20:1, v/v) to give **3a** as a white solid (173 mg, 66 %).



Scheme 3. The proposed reaction mechanisms.

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Keywords: acetals · cyclization · diynes · indenes · iron · Lewis acids

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[1] For selected recent reviews, see: a) S. E. Denmark, J. H.-C. Liu, *Angew. Chem.* **2010**, *122*, 3040–3049; *Angew. Chem. Int. Ed.* **2010**, *49*, 2978–2986; b) B. B. Touré, D. G. Hall, *Chem. Rev.* **2009**, *109*, 4439–4486; c) W. A. L. van Otterlo, C. B. de Koning, *Chem. Rev.* **2009**, *109*, 3743–3782.

[2] For selected recent examples, see: a) S. M. Abu Sohel, R. S. Liu, *Chem. Soc. Rev.* **2009**, *38*, 2269–2281; b) P. A. Wender, J. P. Christy, A. B. Lesser, M. T. Gieseler, *Angew. Chem.* **2009**, *121*, 7823–7826; *Angew. Chem. Int. Ed.* **2009**, *48*, 7687–7690; c) W. X. Zhao, J. L. Zhang, *Chem. Commun.* **2010**, *46*, 4384–4386.

[3] S.-J. Nam, S. P. Gaudêncio, C. A. Kauffman, P. R. Jensen, T. P. Kondratyuk, L. E. Marler, J. M. Pezzuto, W. Fenical, *J. Nat. Prod.* **2010**, *73*, 1080–1086.

[4] N. Mesquida, S. López-Pérez, I. Dinarès, J. Frigola, R. Mercè, J. Holenz, R. Pérez, J. Burgueño, E. Alcalde, *J. Med. Chem.* **2009**, *52*, 6153–6157.

[5] Y. J. He, H.-Y. Chen, J. H. Hou, Y. F. Li, *J. Am. Chem. Soc.* **2010**, *132*, 1377–1382.

[6] S. Y. Ren, E. Igarashi, K. Nakajima, K. Kanno, T. Takahashi, *J. Am. Chem. Soc.* **2009**, *131*, 7492–7493.

[7] For selected recent reports, see: a) L. N. Guo, X. H. Duan, Y. M. Liang, *Acc. Chem. Res.* **2011**, *44*, 111–122; b) Y. X. Zhu, G. W. Yin, D. Hong, P. Lu, Y. G. Wang, *Org. Lett.* **2011**, *13*, 1024–1027; c) P. Nun, S. Gaillard, A. Poater, L. Cavallo, S. P. Nolan, *Org. Biomol. Chem.* **2011**, *9*, 101–104; d) F. Zhou, X. L. Han, X. Y. Lu, *J. Org. Chem.* **2011**, *76*, 1491–1494; e) S. Q. Ye, H. Ren, J. Wu, *J. Comb. Chem.* **2010**, *12*, 670–675; f) A. Martínez, P. García-García, M. A. Fernández-Rodríguez, F. Rodríguez, R. Sanz, *Angew. Chem.* **2010**, *122*, 4737–4741; *Angew. Chem. Int. Ed.* **2010**, *49*, 4633–4637; g) H. Kurouchi, H. Sugimoto, Y. Otani, T. Ohwada, *J. Am. Chem. Soc.* **2010**, *132*, 807–815; h) S. D. Yang, Z. G. Li, X. Jian, C. He, *Angew. Chem.* **2009**, *121*, 4059–4061; *Angew. Chem. Int. Ed.* **2009**, *48*, 3999–4001; i) X. Z. Zhu, C. Mitsui, H. Tsuji, E. Nakamura, *J. Am. Chem. Soc.* **2009**, *131*, 13596–13597.

[8] a) H. W. Chi, Y. C. Chien, C. Y. Liu, C. J. Tseng, Y. J. Lee, J. L. Chan, Y. R. Chu, D. H. Chin, *Chem. Eur. J.* **2011**, *17*, 1493–1506; b) S. Bonazzi, M. Binaghi, C. Fellay, J.-Y. Wach, K. Gademann, *Synthesis* **2010**, 631–642; c) K. C. Nicolaou, Y. F. Tang, J. H. Wang, *Angew. Chem.* **2009**, *121*, 3501–3505; *Angew. Chem. Int. Ed.* **2009**, *48*, 3449–3453; d) C. Vavilala, N. Byrne, C. M. Kraml, D. M. Ho, R. A. Pascal, *J. Am. Chem. Soc.* **2008**, *130*, 13549–13551; e) S. W. Peabody, B. Breiner, S. V. Kovalenko, S. Patil, I. V. Alabugin, *Org. Biomol. Chem.* **2005**, *3*, 218–221.

[9] a) W. X. Zhao, J. L. Zhang, *Org. Lett.* **2011**, *13*, 688–691; b) J.-J. Lian, P.-C. Chen, Y.-P. Lin, H.-C. Ting, R.-S. Liu, *J. Am. Chem. Soc.* **2006**, *128*, 11372–11373; c) H.-J. Wu, C.-F. Lin, J.-L. Lee, W.-D. Lu, C.-Y. Lee, C.-C. Chen, M.-J. Wu, *Tetrahedron* **2004**, *60*, 3927–3934; d) R. F. C. Brown, F. W. Eastwood, N. R. Wong, *Tetrahedron Lett.* **1993**, *34*, 3607–3608.

[10] For selected recent reviews, see: a) C. J. R. Bataille, T. J. Donohoe, *Chem. Soc. Rev.* **2011**, *40*, 114–128; b) B. D. Sherry, A. Fürstner, *Acc. Chem. Res.* **2008**, *41*, 1500–1511; c) A. Correa, O. García Mancheño, C. Bolm, *Chem. Soc. Rev.* **2008**, *37*, 1108–1117; d) S. Enthaler, K. Junge, M. Beller, *Angew. Chem.* **2008**, *120*, 3363–3367; *Angew. Chem. Int. Ed.* **2008**, *47*, 3317–3321.

[11] For selected recent reports, see: a) B. Chen, S. M. Ma, *Chem. Eur. J.* **2011**, *17*, 754–757; b) K. M. Driller, S. Prateeptongkum, R. Jackstell, M. Beller, *Angew. Chem.* **2011**, *123*, 558–562; *Angew. Chem. Int. Ed.* **2011**, *50*, 537–541; c) Y. S. Zhao, S. W. Foo, S. Saito, *Angew. Chem.* **2011**, *123*, 3062–3065; *Angew. Chem. Int. Ed.* **2011**, *50*, 3006–3009; d) R. Langer, G. Leitus, Y. Ben-David, D. Milstein, *Angew. Chem.* **2011**, *123*, 2168–2172; *Angew. Chem. Int. Ed.* **2011**, *50*, 2120–2124; e) S. Enthaler, *ChemCatChem* **2011**, *3*, 666–670; f) J. Bonnamour, C. Bolm, *Org. Lett.* **2011**, *13*, 2012–2014; g) A. K. Steib, T. Thaler, K. Komeyamak, P. Mayer, P. Knochel, *Angew. Chem.* **2011**, *123*, 3361–3365; *Angew. Chem. Int. Ed.* **2011**, *50*, 3303–3307; h) N. Yoshikai, A. Mieczkowski, A. Matsumoto, L. Ilies, E. Nakamura, *J.*

Am. Chem. Soc. **2010**, *132*, 5568–5569; i) K. S. Williamson, T. P. Yoon, *J. Am. Chem. Soc.* **2010**, *132*, 4570–4571; j) F. Vallée, J. J. Mousseau, A. B. Charette, *J. Am. Chem. Soc.* **2010**, *132*, 1514–1516; k) W. Liu, H. Cao, A. W. Lei, *Angew. Chem.* **2010**, *122*, 2048–2052; *Angew. Chem. Int. Ed.* **2010**, *49*, 2004–2008; l) Y.-Z. Li, B.-J. Li, X.-Y. Lu, S. Lin, Z.-J. Shi, *Angew. Chem.* **2009**, *121*, 3875–3878 ; *Angew. Chem. Int. Ed.* **2009**, *48*, 3817–3820; m) K. T. Sylvester, P. J. Chirik, *J. Am. Chem. Soc.* **2009**, *131*, 8772–8774; n) X. W. Guo, R. Yu, H. J. Li, Z. P. Li, *J. Am. Chem. Soc.* **2009**, *131*, 17387–17393.

[12] a) H. R. Li, W. J. Li, W. P. Liu, Z. H. He, Z. P. Li, *Angew. Chem.* **2011**, *123*, 3031–3034; *Angew. Chem. Int. Ed.* **2011**, *50*, 2975–2978; b) W. D. Rao, P. W. H. Chan, *Org. Biomol. Chem.* **2010**, *8*, 4016–4025.

[13] a) T. Y. Xu, Z. K. Yu, L. D. Wang, *Org. Lett.* **2009**, *11*, 2113–2116; b) T. Y. Xu, Q. Yang, D. P. Li, J. H. Dong, Z. K. Yu, Y. X. Li, *Chem. Eur. J.* **2010**, *16*, 9264–9272.

[14] H. J. Li, R. Guillot, V. Gandon, *J. Org. Chem.* **2010**, *75*, 8435.

[15] a) T. Vaidya, G. F. Manbeck, S. Chen, A. J. Frontier, R. Eisenberg, *J. Am. Chem. Soc.* **2011**, *133*, 3300–3303; b) P. Cordier, C. Aubert, M. Malacria, E. Lacôte, V. Gandon, *Angew. Chem.* **2009**, *121*, 8913–8916; *Angew. Chem. Int. Ed.* **2009**, *48*, 8757–8760; c) A. J. Frontier, C. Collison, *Tetrahedron* **2005**, *61*, 7577–7606.

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