ORGANIC
LETTERS

2012
Vol. 14, No. 24
6262–6265

Chemoselective Activities of Fe(III) Catalysts in the Hydrofunctionalization of Allenes

Min Seok Jung, Won Sun Kim, Ye Ho Shin, Ha Jeong Jin, Young Sam Kim, and Eun Joo Kang*

Department of Applied Chemistry, Kyung Hee University, Yongin 446-701, Korea

ejkang24@khu.ac.kr

Received November 3, 2012

ABSTRACT

A range of tetrahydropyrans and piperidines were produced by Fe(III)-catalyzed intramolecular hydroalkoxylation and hydroamination reactions of allenes. Various Fe catalysts with different counterions were tested. Their activities toward allene and alkene activation depended sensitively on their counterion and reaction conditions. Mechanistic study of the reaction intermediates found a new reaction pattern involving the Fe catalysts and diene substrates.

Iron salts can efficiently catalyze organic reactions as alternatives to traditional transition metal catalysts, showing advantages of being more sustainably produced and nontoxic. Iron–oxo complexes have been developed for oxidation, and the chemistry of iron–porphyrins has been broadly explored for catalysis.[1] Iron halides have been extensively used as Lewis acid catalysts in various addition, substitution, cycloaddition and rearrangement reactions of carbonyl and alcohol functional groups.[2] In recent years, iron complexes have been found to be potential catalysts in the following organic reactions. The formation of new carbon–carbon bonds by cross-coupling reactions can involve the use of Fe(II) or Fe(III) precatalysts with the assistance of Grignard reagents to offer broad utility even with alkyl halides.[3] Iron salts catalyze various hydrofunctionalization reactions by activating unsaturated carbon–carbon bonds to nucleophilic attack and allowing new carbon–nitrogen, oxygen and phosphorus bonds to form.[4,5]

Iron-catalyzed carbon–heteroatom bond-forming reactions of unsaturated carbon–carbon bonds were first reported by Rosenblum in 1981: alkynes were hydroalkoxylized to vinyl ethers using $CpFe(CO)_2$(*iso*-butylene)BF_4.[6] The exchange reaction of a cationic η^2-olefin iron complex to an η^2-acetylene iron complex, yielding a competitive vinylidene isomer, was provided as the mechanistic view of iron catalyst. Iron trichloride has been used in hydroamination[7]

---

[1] (a) Barton, D. H. R. *Chem. Soc. Rev.* **1996**, *25*, 237. (b) Goldstein, S.; Meyerstein, D. *Acc. Chem. Res.* **1999**, *32*, 547. (c) Costas, M.; Mehn, M. P.; Jensen, M. P.; Que, L., Jr. *Chem. Rev.* **2004**, *104*, 939. (d) Tshuva, E. Y.; Lippard, S. J. *Chem. Rev.* **2004**, *104*, 987. (e) *The Porphyrin Handbook*; Kadish, K. M., Smith, K. M., Guilard, R., Eds.; Academic Press: San Diego, 2000.

[2] Bolm, C.; Legros, J.; Le Paih, J.; Zani, L. *Chem. Rev.* **2004**, *104*, 6217 and references cited therein.

[3] For review articles of iron-catalyzed cross coupling reactions, see: (a) Czaplik, W. M.; Mayer, M.; Cvengroš, J.; Wangelin, A. J. *ChemSusChem* **2009**, *2*, 396. (b) Sherry, B. D.; Fürstner, A. *Acc. Chem. Res.* **2008**, *41*, 1500.

[4] Correa, A.; Mancheño, O. G.; Bolm., C. *Chem. Soc. Rev.* **2008**, *37*, 1108.

[5] For iron-catalyzed allylic functionalization reactions, see: (a) Guérinot, A.; Serra-Muns, A.; Gnamm, C.; Bensoussan, C.; Reymond, S.; Cossy, J. *Org. Lett.* **2010**, *12*, 1808. (b) Wang, Z.; Li, S.; Yu, B.; Wang, Y.; Sun, X. *J. Org. Chem.* **2012**, *77*, 8615.

[6] Bates, D. J.; Rosenblum, M.; Samuels, S. B. *J. Organomet. Chem.* **1981**, *209*, C55.

[7] (a) Komeyama, K.; Morimoto, T.; Takaki, K. *Angew. Chem., Int. Ed.* **2006**, *45*, 2938. (b) Michaux, J.; Terrasson, V.; Marque, S.; Wehbe, J.; Prim, D.; Campagne, J.-M. *Eur. J. Org. Chem.* **2007**, 2601. (c) Zotto, C. D.; Michaux, J.; Zarate-Ruiz, A.; Gayon, E.; Virieux, D.; Campagne, J.-M.; Terrasson, V.; Pieters, G.; Prim, D. *J. Organomet. Chem.* **2011**, *696*, 296.

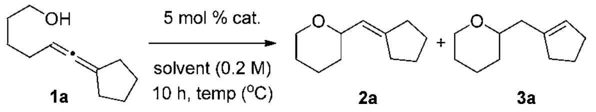
[8] Alcaide, B.; Almendros, P.; del Campo, T. M. *Chem.—Eur. J.* **2008**, *14*, 7756.

10.1021/ol303021d

and hydroalkoxylation[8] of alkenes, intermolecular hydroaryloxylation of alkynes,[9] and tandem annulation reactions of ketones and alkynes.[10] Other iron salts, such as iron toluenesulfonate and iron trifluoromethylsulfonate, have also been reported as effective catalysts for the intramolecular hydroalkoxylation of unactivated alkenes,[11] the intermolecular hydroalkoxylation of styrene[12] and the hydrocarboxylation and hydroalkynylation of norbornene.[13] Electrogenerated Fe^{3+} with a strong base can catalyze heterocycle formation from electron-deficient alkynes and alcohols.[14] Regioselective double hydrophosphination of arylacetylenes was catalyzed by $CpFe(CO)_2Me$.[15] Despite much research into such reactions of alkynes and alkenes, reactivities of Fe catalysts toward allenes remain less well studied.[16] This work reports the delicate reactivities of various iron salts in the hydrofunctionalization of allenes, which have been interesting substrates to control stereo- and regioselectivities.[17]

To examine the possibility of Fe-catalyzed reactions of allenes, various Fe(III) catalysts were tested using cyclopentyl substituted allenyl alcohol (**1a**) in hydroalkoxylation reactions. Iron trichloride and its hydrate catalysts smoothly promoted cyclization to afford the oxacyclic product (Table 1, entries 1 and 2). Using allenyl alcohol **1a** treated with iron tribromide led to an unexpected mixture of products isolated with a 1:2 ratio (entry 3). Time-dependent TLC analysis showed that the reaction first underwent a pathway for the formation of **2a**, which then disappeared with the concurrent appearance of **3a**. The Fe(III) catalyst was therefore presumed to activate the allene moiety in starting material **1a** as well as the alkene moiety in cyclized product **2a**. Double bond isomerization to form the more thermodynamically favored product **3a** was driven at elevated temperature over longer reaction durations.[18] Activities toward specific C–C multiple bonds, such as allenes and alkenes, could be achieved by varying the solvent and reaction temperature. Reaction in chlorobenzene at 60 °C afforded the cyclized product **3a** with high yield (entry 7); lower temperature (−40 °C) suppressed isomerization, resulting a sole product **2a** after 48 h (entry 9). However, the use of low temperature for long reaction times was inefficient, and further examination of the effects of counterions was carried out. Iron(III) trifluoroacetate catalyzed a mild reaction, which was optimized at 30 °C to yield **2a** as sole product within 10 h (entry 11). Iron(III) toluenesulfonate catalyzed the formation of **3a** as sole product at low temperatures and at q80 °C (entry 14). Iron(III) trifluoromethylsulfonate led to poor yields and decomposition of the reaction mixture (entry 15). These propensities of iron salts depended on their counterion; the weaker a basicity of anion is, the stronger a Lewis acidity of iron catalyst is. Additional ligands such as TMEDA and dppp depleted the activity of $FeCl_3\cdot6H_2O$ catalyst, resulting in no reaction even after 3 days. The activity of acid catalysts, particularly trifluoroacetic acid and toluenesulfonic acid,[19] which may be unintentionally generated from the iron salts, was also checked (entries 16 and 17): low conversion was observed under corresponding conditions, suggesting that a simple acid-catalyzed pathway did not greatly contribute to the reaction.

Table 1. Optimization of Hydroalkoxylation for Tetrahydropyran Synthesis[a]



entry	cat.	solvent	temp (°C)	yield (%)[b]	**2a:3a**
1	$FeCl_3$	DCE	60	60	0:1
2	$FeCl_3\cdot6H_2O$	DCE	60	75	0:1
3	$FeBr_3$	DCE	60	45	1:2
4	$FeCl_3\cdot6H_2O$	THF	60	14	1:0
5	$FeCl_3\cdot6H_2O$	MeCN	60	54	2:1
6	$FeCl_3\cdot6H_2O$	Benzene	60	63	1:1
7	$FeCl_3\cdot6H_2O$	PhCl	60	80	0:1
8	$FeCl_3\cdot6H_2O$	DCE	25	68	8:1
9[c]	$\mathbf{FeCl_3\cdot6H_2O}$	**DCE**	**−40**	**95**	**1:0**
10	$Fe(TFA)_3$	DCE	0	60	1:0
11	$\mathbf{Fe(TFA)_3}$	**DCE**	**30**	**91**	**1:0**
12	$Fe(TFA)_3$	DCE	40	93	5:1
13	$Fe(OTs)_3$	DCE	0	58	0:1
14	$\mathbf{Fe(OTs)_3}$	**DCE**	**80**	**89**	**0:1**
15[d]	$Fe(OTs)_3$	DCE	80	73	0:1
16	$Fe(OTf)_3$	DCE	60	38	1:5
17[e]	TFA[d]	DCE	30	31	1:0
18[e]	TsOH[d]	DCE	80	58	0:1

[a] Reactions and conditions: allenyl alcohol (0.25 mmol), catalyst (5 mol %), solvent (0.2 M) for 10 h under N_2, unless otherwise specified. [b] Isolated yield after chromatographic purification. [c] Reaction for 48 h. [d] 3 mol % of catalyst was used. [e] 15 mol % of acid catalyst was used.

A range of substrates was evaluated in two standard cyclizations using $Fe(TFA)_3$ and $Fe(OTs)_3$ catalysts in

---

(9) Xu, X.; Liu, J.; Liang, L.; Li, H.; Li, Y. *Adv. Synth. Catal.* **2009**, *351*, 2599.

(10) Wang, Z.-Q.; Lei, Y.; Zhou, M.-B.; Chen, G.-X.; Song, R.-J.; Xie, Y.-X.; Li, J.-H. *Org. Lett.* **2011**, *13*, 14.

(11) Komeyama, K.; Morimoto, T.; Nakayama, Y.; Takaki, K. *Tetrahedron Lett.* **2007**, *48*, 3259.

(12) Ke, F.; Li, Z.; Xiang, H.; Zhou, X. *Tetrahedron Lett.* **2011**, *52*, 318.

(13) (a) Choi, J.-C.; Kohno, K.; Masuda, D.; Yasuda, H.; Sakakura, T. *Chem. Commun.* **2008**, 777. (b) Kohno, K.; Nakagawa, K.; Yahagi, T.; Choi, J.-C.; Yasuda, H.; Sakakura, T. *J. Am. Chem. Soc.* **2009**, *131*, 2784.

(14) Li, C.-H.; Yuan, G.-Q.; Zheng, J.-H.; He, Z.-J.; Qi, C.-R.; Jiang, H.-F. *Tetrahedron* **2011**, *67*, 4202.

(15) Kamitani, M.; Itazaki, M.; Tamiya, C.; Nakazawa, H. *J. Am. Chem. Soc.* **2012**, *134*, 11932.

(16) For $Fe(CO)_n$-catalyzed reactions of allenes, see: (a) Lennon, P.; Rosan, A. M.; Rosenblum, M. *J. Am. Chem. Soc.* **1977**, *99*, 8426. (b) Sigman, M. S.; Eaton, B. E. *J. Org. Chem.* **1994**, *59*, 7488. (c) Oulié, P.; Altes, L.; Milosevic, S.; Bouteille, R.; Muller-Bunz, H.; McGlinchey, M. J. *Organometallics* **2010**, *29*, 676.

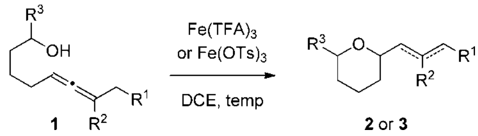
(17) For selected reviews on hydrofunctionalization of allenes, see: (a) Bates, R. W.; Satcharoen, V. *Chem. Soc. Rev.* **2002**, *31*, 12. (b) Ma, S. *Aldrichimica Acta* **2007**, *40*, 91. (c) Alcaide, B.; Almendros, P. *Adv. Synth. Catal.* **2011**, *353*, 2561. (d) Krause, N.; Winter, C. *Chem. Rev.* **2011**, *111*, 1994.

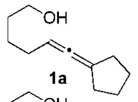
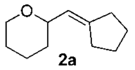
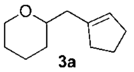
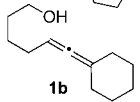
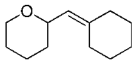
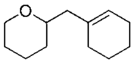
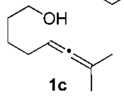
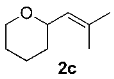
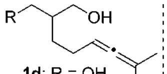
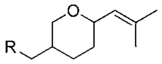
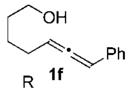
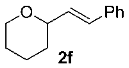
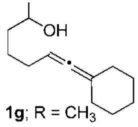
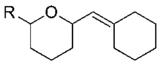
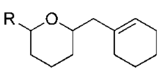
(18) For $Fe(CO)_n$-catalyzed isomerization of alkenes, see: (a) Whetton, R. L.; Fu, K.-J.; Grant, E. R. *J. Am. Chem. Soc.* **1982**, *104*, 4270. (b) Long, G. T.; Weitz, E. *J. Am. Chem. Soc.* **2000**, *122*, 1431.

(19) (a) Li, Z.; Zhang, J.; Brouwer, C.; Yang, C.-G.; Reich, N. W.; He, C. *Org. Lett.* **2006**, *8*, 4175. (b) Rosenfeld, D. C.; Shekhar, S.; Takemiya, A.; Utsunomiya, M.; Hartwig, J. F. *Org. Lett.* **2006**, *8*, 4179.

dichloroethane (DCE) (Table 2). The required allenyl alcohols were prepared by allene formation reactions using tetrahydropyranyloxy alkynols and lithium aluminum hydride. Trialkyl substituted allenes **1a**,**b** were hydroalkoxylated to afford the corresponding tetrahydropyrans **2a**, **b** and their isomers **3a**,**b** in high yields. Dimethyl substituted allene **1c** was transformed to **2c** in 92% yield; double-bond isomerization to generate a terminal olefin did not occur, even at high temperature. The presence of alcohol (**1d**) and benzoate (**1e**) was permitted in the reaction, but these oxygen functional groups led to longer reaction time (20 h). The reaction of allenol **1f**, which has aryl and alkyl substituents, resulted in the formation of only (*E*)-styryl tetrahydropyran **2f** in 85% yield.

Table 2. Selected Hydroalkoxylation Reactions[a]



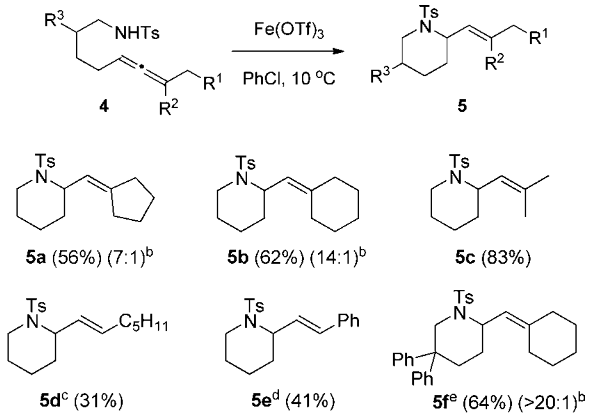
	Fe(TFA)$_3$, 30 °C		Fe(OTs)$_3$, 80 °C	
substrate	product	yield (%)^b	product	yield (%)^b
 1a	 2a	91	 3a	89
 1b	 2b	86	 3b	96
 1c	 2c	92		
 1d; R = OH 1e; R = OBz	 2d 2e	50 (14)^c 74^c		
 1f	 2f	85		
 1g; R = CH$_3$ 1h; R = Ph 1i; R = CH$_2$CHCH$_2$ 1j; R = CCH	 2g 2h 2i 2j	59 (23)^d 21 (39)^d 40 (27)^d 62 (30)^d	 3g 3h 3i 3j	79^d 79^d 93^d 96^d

[a] Reactions and conditions: allenyl alcohol (0.25 mmol), catalyst (5 mol %), DCE (0.2 M) for 10 h under N_2, unless otherwise specified. [b] Isolated yield after chromatographic purification (s.m. recovered yield in parentheses). [c] Reaction with Fe(OTs)$_3$ for 20 h. [d] Reaction with 10 mol % of catalyst.

In comparison, dialkylated or monoalkylated allenol did not undergo cyclization.[20] Secondary alcohols **1g**–**j** also underwent hydroalkoxylation resulting in moderate to good yields. ^{1}H NMR analysis of the isolated tetrahydropyrans showed the exclusive formation of *cis*-disubstituted products, except **2j**, which led to a 1:1 diastereomeric ratio. Sterically unhindered allenols **1g** and **1j** were converted more effectively into the corresponding tetrahydropyrans rather than **1h** and **1i**. Allenols were recovered from the reactions of **1h** and **1i** and were found to be contaminated with small amounts of the corresponding dienes, indicating that the lower susceptibilities to cyclization may have promoted isomerization of the allenes to dienes with *endo*-methylene. The reactions of **1g**–**j** catalyzed by Fe(OTs)$_3$ provided **3g**–**j** in high yields (79–96%).

These hydroalkoxylation results prompted assessment of allenes' Fe(III)-catalyzed hydroamination (Scheme 1). Using Fe(OTf)$_3$ in chlorobenzene at 10 °C afforded piperidine **5** in the best selectivity and yield.[21] Unlike the mixture of **2** and **3**, in which each isomer's slightly different polarity made them distinguishable in TLC analysis, **5** and its isomer were not separately identifiable by TLC analysis. Trialkyl substituted allenes **4a**–**c** reacted smoothly under the tested conditions; dialkyl or alkyl aryl substituted allenes **4d**,**e** required elevated temperatures to afford the corresponding piperidines at slow rates. Diphenyl substituted allene **4f** reacted more quickly and with greater selectivity in DCE over 12 h, possibly due to the Thorpe–Ingold effect.[22]

Scheme 1. Fe(OTf)$_3$-Catalyzed Hydroamination[a]



[a] Reactions and conditions: allenyl amide (0.25 mmol), catalyst (5 mol %), PhCl (0.2 M) for 48 h under N_2, unless otherwise specified. Isolated yield. [b] Ratio of *exo* and *endo* double bond. [c] Reaction at 130 °C for 72 h, resulting with recovered **4d** (38%). [d] Reaction at 80 °C for 72 h, resulting with decomposed products. [e] Reaction in DCE at 25 °C for 12 h.

Overall, the observed results show that Fe(III) catalysts were important in the activation of the allene functional group for cyclization and the alkene functional group for isomerization. Isomerization pathways in the presence of Fe catalysts were further tested by reacting isolated **2b** and

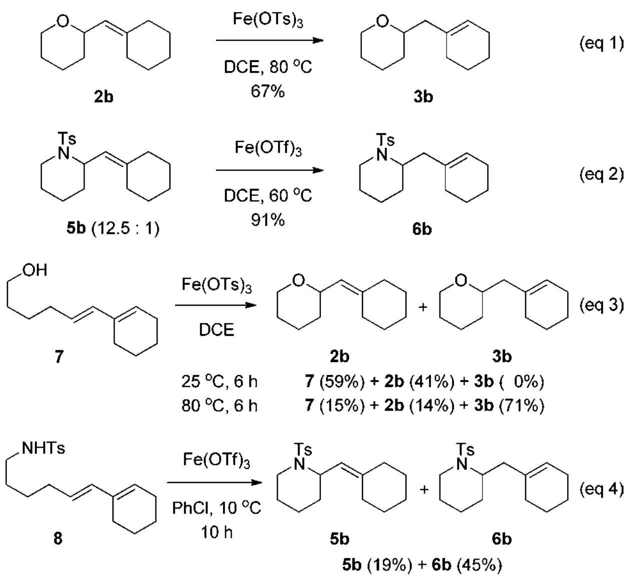
---

(20) The structures of unsuccessful allene substrates are given in the Supporting Information.

(21) Modifying other protecting groups (Ph, Bn, and Boc) proved unsuccessful, except the reaction with ethyl carbamate derivatives. See Tables S1 and S2 in the Supporting Information.

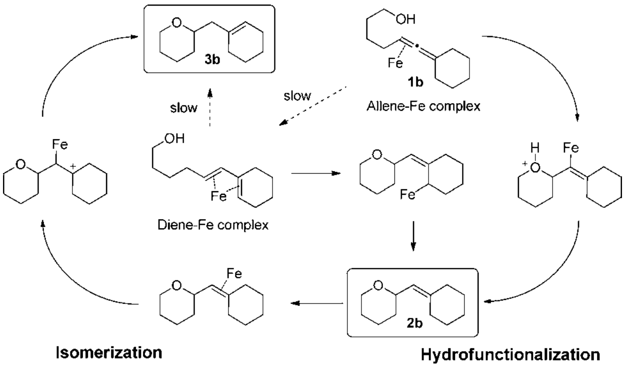
(22) Liu, G.-Q.; Li, W.; Wang, Y.-M.; Ding, Z.-Y.; Li, Y.-M. *Tetrahedron Lett.* **2012**, *53*, 4393.

Scheme 2. Double Bond Isomerization and Hydrofunctionalization of Dienes



5b separately in the presence of Fe(OTs)$_3$ or Fe(OTf)$_3$ (5 mol %) in DCE (Scheme 2, eq 1 and 2); double bond isomerization from *exo*-methylene to *endo*-methylene occurred in high yield. However, an alternative route for the direct transformation of **1b** to **3b** is also possible: isomerization of allenes to dienes followed by the hydrofunctionalization of corresponding dienes.[23,24] Therefore, the hydroalkoxylation of diene **7** was examined in the presence of the Fe(OTs)$_3$ in DCE at room temperature (eq 3). After 6 h, a mixture of unreacted diene **7** (59%) and *exo*-methylene product **2b** (41%) was observed, whereas the reaction at 80 °C afforded **3b** as a major product with a small amount of **7** and **2b**. The hydroamination of diene **8** also afforded a mixture of *exo*-methylene product **5b** (19%) and *endo*-methylene product **6b** (45%). If diene **7** or **8** hydrofunctionalized through alkene activation by the Fe catalyst without any function of conjugated diene system, **3b** or **6b** would be expected as sole products. However, the initial rate of formation of **2b** was faster than that of **3b**, and **2b** underwent olefin isomerization to afford **3b** during a longer reaction.

Scheme 3. Mechanism for Fe-Catalyzed Reactions of Allenes



Overall, these results suggest the mechanism for the Fe-catalyzed reactions of allenes shown in Scheme 3. Hydrofunctionalization involved traditional coordination, nucleophilic addition and proto-demetalation, similar to previous observations of allenes in reactions. The cyclized product can then undergo isomerization depending on the Fe(III) catalyst and reaction conditions. For the cyclization reactions of dienes, diene–iron complexes may lead to cycloisomerization products.[25]

In conclusion, a highly efficient catalytic system is presented for the hydrofunctionalization of allenyl alcohols and amides. Fe(III) salts, FeCl$_3$, Fe(TFA)$_3$, Fe(OTs)$_3$ and Fe(OTf)$_3$, allowed efficient cycloisomerization reactions under mild conditions. They are inexpensive and naturally abundant, which lends to their wide industrial applicability for such reactions. Further study of Fe-catalyzed cycloisomerization using various accumulated multiple bond systems is underway.

Acknowledgment. This study was supported by the National Research Foundation Grant funded by the Ministry of Education, Science and Technology (2011-0003298 and 2011-0004015).

Supporting Information Available. Detailed experimental procedures and characterization of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

---

[23] For iron-catalyzed reactions of dienes, see: (a) Wu, J. Y.; Moreau, B.; Ritter, T. *J. Am. Chem. Soc.* **2009**, *131*, 12915. (b) Moreau, B.; Wu, J. Y.; Ritter, T. *Org. Lett.* **2009**, *11*, 337. (c) Dénès, F.; Pérez-Luna, A.; Chemla, F. *Chem. Rev.* **2010**, *110*, 2366.

[24] For hydrofunctionalization reactions of dienyl alcohols, see: (a) Kanno, O.; Kuriyama, W.; Wang, Z. J.; Toste, F. D. *Angew. Chem., Int. Ed.* **2011**, *50*, 9919. (b) Chandrasekhar, B.; Ryu, J.-S. *Tetrahedron* **2012**, *68*, 4805. (c) Yamamoto, H.; Sasaki, I.; Shiomi, S.; Yamasaki, N.; Imagawa, H. *Org. Lett.* **2012**, *14*, 2266.

[25] Trace amounts of dienes were observed after longer and hotter reactions, suggesting that the isomerization of allenes to dienes proceeded slowly.

The authors declare no competing financial interest.