DOI: 10.1002/adsc.201100009

Regioselective Addition of Organometallic Reagents to 2-(1-Alkynyl)-2-alken-1-ones for an Efficient Synthesis of Substituted 1,2-Allenyl Ketones

Xiuzhao Yu[a] and Junliang Zhang[a,b,*]

[a] Shanghai Key Laboratory of Green Chemistry and Chemical Processes, Department of Chemistry, East China Normal University, 3663 N. Zhongshan Road, Shanghai 200062, People's Republic of China
Fax: (+86)-021-6223-5039; e-mail: jlzhang@chem.ecnu.edu.cn
[b] State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, Shanghai 200032, People's Republic of China

Received: January 5, 2011; Revised: March 26, 2011; Published online: May 17, 2011

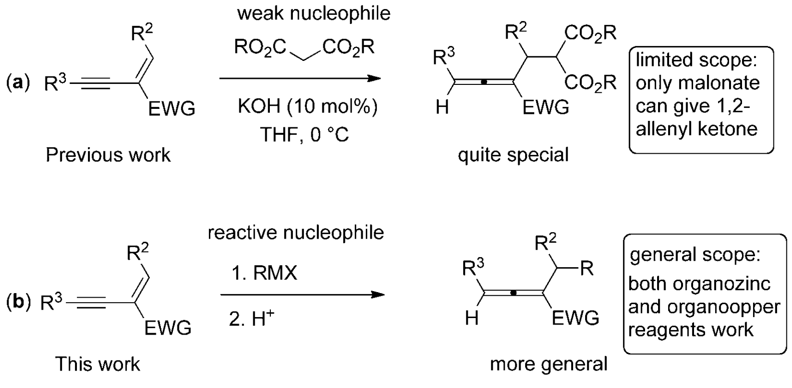
Supporting information for this article is available on the WWW under http://dx.doi.org./10.1002/adsc.201100009.

Abstract: Highly substituted 1,2-allenyl ketones can be easily and efficiently prepared from organometallic reagents and readily available 2-(1-alkynyl)-2-alken-1-ones. The synthetic application of 1,2-allenyl ketone products was also showcased by palladium-catalyzed further transformation.

Keywords: 2-(1-alkynyl)-2-alken-1-ones; 1,2-allenyl ketones; organometallic reagents; regioselectivity

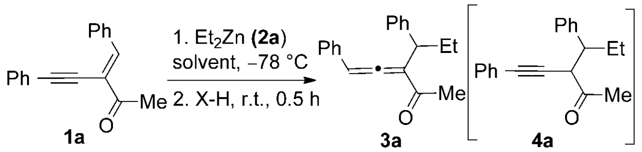
Allenes are important molecules in modern organic chemistry, and their unique chemical structure is found in many bioactive natural products and pharmaceuticals.[1] Since the prediction of allenes by van't Hoff in 1875,[2a] and the first documented synthesis disclosed by Burton and von Pechmann in 1887,[2b] increasing attention has been paid to their interesting reactivities.[3,4] Throughout the past century, many methods based on functionalized alkynes, alkenes and carbonyl compounds have been dedicated to the development of efficient synthesis of allenes.[5,6] However, the search for efficient and practical synthetic methods for highly functionalized allenes from readily available starting materials is still highly desirable. Herein, we wish to report a regio- and chemoselective conjugate addition of organozinc/copper reagents to electron-deficient enynes **1**,[7,8] leading to a facile approach to highly substituted 1,2-allenyl ketones.

We recently developed a simple base-catalyzed nucleophilic addition reaction of weak nucleophilic malonates to electron-deficient 1,3-conjugated enynes, leading to the quite special malonate substituted 1,2-allenyl ketones [Scheme 1, (**a**)].[8a] During this study, we became interested in the nucleophilic addition reaction by using more reactive and commonly used organometallic reagents as nucleophiles which, if it worked, would give a more general type of 1,2-allenyl ketones [Scheme 1, (**b**)].



Scheme 1. The previous work (**a**) and our projected design (**b**).

Table 1. Screening of the reaction conditions for the reaction of **1a** and **2a**.[a]

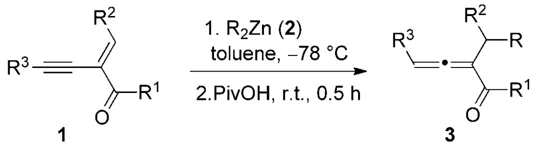


Entry	Solvent	X-H	Yield[b] [%] of **3a** (*dr*)
1[c]	THF	NH_4Cl	33 (1.4:1)
2[c]	Et_2O	NH_4Cl	35 (1.1:1)
3[c]	CH_2Cl_2	NH_4Cl	55 (1:1)
4	toluene	NH_4Cl	97 (1:1)
5	toluene	$PhCO_2H$	88 (2.5:1)
6	toluene	t-$BuCO_2H$	94 (3:1)

[a] The reaction was carried out on a 0.5-mmol scale.
[b] Isolated yield.
[c] A trace amount of **4a** was formed.

Initially, we tested the reaction by using ketone **1a** and Et_2Zn **2a** as the model substrates (Table 1). Substrate **2a** was treated with the solution of **1a** in THF at −78 °C for 2 h and then the solution was slowly warmed to room temperature. Gratifyingly, after the reaction was quenched by the aqueous NH_4Cl solution, the desired allenyl ketone **3a** was obtained in 33% isolated yield (Table 1, entry 1), and a trace amount of **4a** was also detected. The screening of different solvents showed that the solvent has a significant influence on the reaction (Table 1, entries 1–4). Toluene was found to be quite successful for this additon reaction. During the processing, it is interesting to find that the acid, as the quencher, plays an important role in affecting the diastereo- and regioslecticity. Finally, we were pleased to find that **3a** could be isolated in 94% yield with a 3:1 ratio of two diastereomers using PivOH as the quencher (Table 1, entry 6).

Table 2. Synthesis of multifunctionalized allenes **3**.



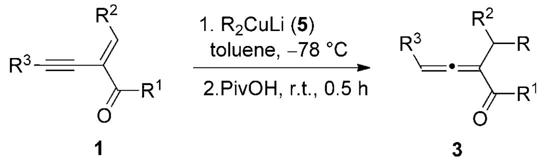
Entry	R (**2**)	$R^1/R^2/R^3$ (**1**)	Yield [%][a] of **3**
1	Et	Me/Ph/Ph	94 (**3a**)
2	Et	Me/Ph/4-$MeOC_6H_4$	79 (**3b**)
3	Et	Me/Ph/1-naphthyl	72 (**3c**)
4	Et	Me/Ph/4-$NO_2C_6H_4$	85 (**3d**)
5	Et	Me/Ph/n-C_4H_9	65 (**3e**)
6	Et	Me/Ph/cyclopropyl	65 (**3f**)
7[b]	Et	Me/4-$MeOC_6H_4$/Ph	65 (**3g**)
8	Et	Me/4-$MeOC_6H_4$/1-naphthyl	72 (**3h**)
9[b]	Et	Me/4-$MeOC_6H_4$/4-$MeOC_6H_4$	64 (**3i**)
10	Et	Me/n-C_4H_9/Ph	90 (**3j**)
11	Et	Ph/Ph/Ph	99 (**3k**)
12	Et	Ph/Ph/4-$MeOC_6H_4$	91 (**3l**)
13	Et	Ph/4-$MeOC_6H_4$/Ph	86 (**3m**)
14	Et	Ph/Ph/n-C_4H_9	67 (**3n**)
15	Et	Ph/Ph/1-cyclohexenyl	93 (**3o**)
16	Et	4-ClC_6H_4/Ph/Ph	93 (**3p**)
17	Et	CO_2Me/Ph/Ph	78 (**3q**)
18	Ph	Me/Ph/Ph	62 (**3r**)

[a] Isolated yield of **3**, and if **4** exists, the yield is less than 5%.
[b] CH_2Cl_2 was used as solvent instead of toluene.

With the optimal conditions in hand, we next examined the scope of this transformation by variation of enynes **1** and the results are summarized in Table 2. Several points are noteworthy: (i) in general, highly substituted 1,2-allenyl ketones can be prepared in good to excellent yields under the standard conditions (Table 2); (ii) various substitutents (R^1) on the ketone such as aliphatic (Table 2, entries 1–10), aromatic (Table 2, entries 11–16) and ester (Table 2, entry 17) are compatible; (ii) the substituent on the alkene moiety (R^2) can be either an aromatic (Table 2, entries 1–9, 11–17) or an aliphatic group (Table 2, entry 10). For example, the reaction of an aliphatic substituted enyne with Et_2Zn affords the desired allene **3j** in 90% yield; (iv) substituents on the alkyne moiety (R^3) with aromatic (Table 2, entries 1–4, 7–13, 16, and 17) or aliphatic groups (Table 2, entries 5, 6, 14, and15) were also tolerated, and the reactions proceed smoothy to afford the disired allenes with good to excellent yields; (v) gratifyingly, the reaction of Ph_2Zn works also well to give the corresponding allenyl ketone product **3r** in 62% yield (Table 2, entry 18); (vi) the regioselectivity is pretty high and only a trace amount of the homo-alkynyl ketone can be detected in a few cases.

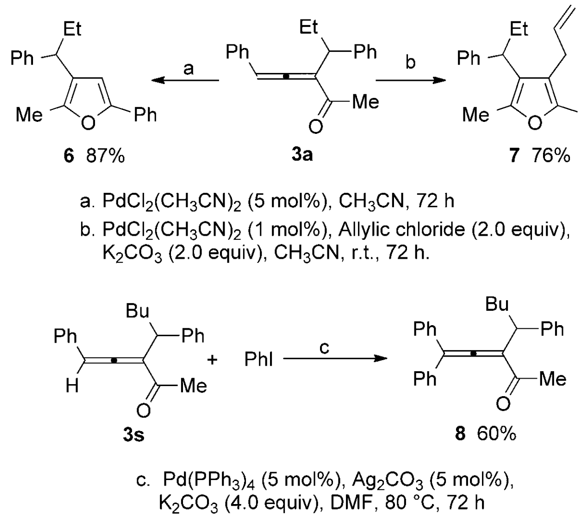
We next turned to investigate the chemistry of the organometallic reagent such as lithium organocuprate (prepared from RLi and CuI).[9] The additions of

Table 3. Substrate scope of **1** and **5** in the reaction.



Entry	$R^1/R^2/R^3$ (**1**)	R (**5**)	Yield [%][a] of **3**
1	Me/Ph/Ph	n-Bu	94 (**3s**)
2	Me/Ph/1-naphthyl	n-Bu	83 (**3t**)
3	Me/4-$MeOC_6H_4$/4-$MeOC_6H_4$	n-Bu	88 (**3u**)
4	Me/Ph/Ph	Me	63 (**3v**)
5	Me/Ph/Ph	i-Pr	75 (**3w**)
6	Me/Ph/Ph	t-Bu	63 (**3x**)
7	Me/Ph/Ph	Ph	64 (**3r**)

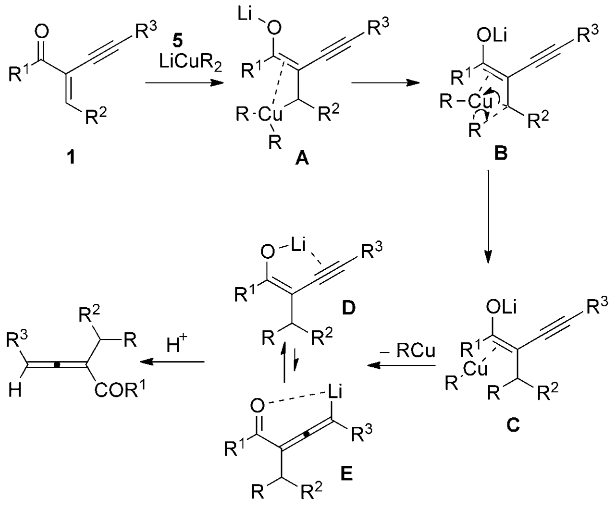
[a] Isolated yield.



a. $PdCl_2(CH_3CN)_2$ (5 mol%), CH_3CN, 72 h
b. $PdCl_2(CH_3CN)_2$ (1 mol%), Allylic chloride (2.0 equiv), K_2CO_3 (2.0 equiv), CH_3CN, r.t., 72 h.

c. $Pd(PPh_3)_4$ (5 mol%), Ag_2CO_3 (5 mol%), K_2CO_3 (4.0 equiv), DMF, 80 °C, 72 h

Scheme 2. Synthetic applications of **3a** and **3s**.



Scheme 3. Plausible mechanism to account for the addition reaction.

R_2CuLi to the ketones **1** proceed smoothly to afford the expected products in good to excellent yields with excellent regioselevity (Table 3, entries 1–7). Gratifyingly, even the bulky (i-Pr)$_2$CuLi and (t-Bu)$_2$CuLi can be used as the organometallic reagents to give the corresponding products in good yields (Table 3, entries 5 and 6). It is noteworthy that the reaction with Ph_2CuLi (Table 3, entry 7) also works well to give the same product as Ph_2Zn (Table 2, entry 18).

The synthetic utilities of the allene product **3** were demonstrated by transformations of two representative 1,2-allenyl ketones **3a** and **3s** (Scheme 2). The cycloisomerization reaction of **3a** in CH_3CN at room temperature under the catalysis of $PdCl_2(CH_3CN)_2$ (5 mol%) for 72 h gives the 2,3,5-trisubstituted furan **6** in 87% isolated yield. The cross-coupling cyclization reaction of **3a** with allyl choride affords the tetrasubstituted furan **7** in 76% isolated yield after 72 h under the catalysis of $PdCl_2(CH_3CN)_2$ (5 mol%).[10] Interstingly, the reaction of **3s** with PhI affords the tetrasubstituted allene **8**[11a,b] *via* the direct cross-coupling reaction at the γ-position rather than the expected tetrasubstituted furan[11c] under the catalysis of $Pd(PPh_3)_4$ (5 mol%) and Ag_2CO_3 (5 mol%).

One plausible mechanism that accounts for this highly regioselective addition reaction is depicted in Scheme 3. The 1,4-addition of nucleophile cuprates to enones **1** would afford intermediates **A**, which would then undergo the cleavage of the copper-carbon bond *via* intermediates **B** to produce enolates **C**. The dissociation of RCu affords two convertible intermediates – lithium enolate **D** and allenic lithium **E** – which in turn upon protonation give the product.[12]

In summary, we have developed a highly regioselective addition of organometallic reagents to readily available 2-(1-alkynyl)-2-alken-1-ones, which provides a rapid and efficient approach to synthetically useful highly substituted 1,2-allenyl ketones. Further studies including synthetic applications, the asymmetric catalysis of this reaction are ongoing in this laboratory.

Experimental Section

Typical Procedure for the Synthesis of 1,2-Allenyl Ketone 3 *via* R_2Zn addition

To a solution of 3-benzylidene-5-phenylpent-4-yn-2-one (**1a**) (0.5 mmol, 123 mg) in 5 mL of anhydrous toluene at −78 °C under N_2 in a Schlenk tube was slowly added Et_2Zn (0.6 mmol, 1 M in THF, 0.6 mL) by a syringe in 1 min. After 2 h, the reaction mixture was then warmed to room temperature. After the enyne **1a** had been consumed completely determined by TLC analysis, PivOH (2.0 equiv.) was slowly added to the reaction mixture. The reaction mixture was then stirred at room temperature for another 0.5 h. After routine work-up, the crude product was purified by column chromatography on silica gel (hexanes:ethyl acetate = 30:1) to give **3a**; yield: 130 mg (94%).

Typical Procedure for the Synthesis of 1,2-Allenyl Ketone 3 *via* R_2CuLi Addition

To a solution of CuI (0.6 mmol, 115 mg) in dried ether (3 mL) at −30 °C in a Schlenk tube under N_2, was added BuLi (1.2 mmol, 2.5 M in hexane, 0.48 mL). After the reaction mixture had been stirred for 30 min, it was transferred to a solution of 3-benzylidene-5-phenylpent-4-yn-2-one **1a** (0.5 mmol, 123 mg) in 5 mL of toluene (dried) at −78 °C under N_2 by a syringe in 1 min. After being stirred for another 2 h, the reaction mixture was then warmed to room temperature. After the enyne **1a** had been consumed completely determined by TLC analysis, PivOH (2.0 equiv.) was slowly added to the reaction mixture. The reaction mixture was then stirred at room temperature for another 0.5 h. After routine work-up, the crude product was purified by column chromatography on silica gel (hexanes:ethyl acetate = 30:1) to give **3s**; yield: 143 mg (94%).

Supporting Information

Experimental details and copies of $^1H/^{13}C$ NMR spectra of all new compounds are available as Supporting Information.

Acknowledgements

Financial supports from National Natural Science Foundation of China (20972054) and 973 program (2011CB808600), Ministry of Education of PRC (NCET, 20090076110007) are greatly appreciated.

References

[1] a) A. Hoffmann-Röder, N. Krause, *Angew. Chem.* **2004**, *116*, 1216; *Angew. Chem. Int. Ed.* **2004**, *43*, 1196; b) Z. Wan, S. G. Nelson, *J. Am. Chem. Soc.* **2000**, *122*, 10470.

[2] a) J. H. van't Hoff, *La Chimie dans l'Espace*, P. M. Bazendijk (publisher), Rotterdam, **1875**; b) B. S. Burton, H. v. Pechman, *Ber. Dtsch. Chem. Ges.* **1887**, *20*, 145.

[3] For reviews see: a) R. Zimmer, C. Dinesh, E. Nandanan, F. Khan, *Chem. Rev.* **2000**, *100*, 3067; b) J. Marshall, *Chem. Rev.* **2000**, *100*, 3163; c) A. S. K. Hashmi, *Angew. Chem.* **2000**, *112*, 3737; *Angew. Chem. Int. Ed.* **2000**, *39*, 3590; d) R. Bates, V. Satcharoen, *Chem. Soc. Rev.* **2002**, *31*, 12; e) L. Sydnes, *Chem. Rev.* **2003**, *103*, 1133; f) S. Ma, *Acc. Chem. Res.* **2003**, *36*, 701; g) *Modern Allene Chemistry*, (Eds.: N. Krause; A. S. K. Hashmi), Wiley-VCH, Weinheim, **200**4; h) S. Ma, *Chem. Rev.* **2005**, *105*, 2829; i) S. Ma, *Aldrichimica Acta* **2007**, *40*, 91; j) M. Brasholz, H.-U. Reissig, R. Zimmer, *Acc. Chem. Res.* **2009**, *42*, 45; k) S. Ma, *Acc. Chem. Res.* **2009**, *42*, 1679.

[4] For selected recent examples using allene as versatile synthons, see: a) H. Wei, H. Zhai, P.-F. Xu, *J. Org. Chem.* **2009**, *74*, 2224; b) V. M. Marx, D. J. Burnell, *Org. Lett.* **2009**, *11*, 1229; c) W. Kong, J. Cui, Y. Yu, G. Chen, C. Fu, S. Ma, *Org. Lett.* **2009**, *11*, 1213; d) A. S. Dudnik, A. W. Sromek, M. Rubina, J. T. Kim, A. V. Kel'in, V. Gevorgyan, *J. Am. Chem. Soc.* **2008**, *130*, 1440; e) Y. Xia, A. S. Dudnik, V. Gevorgyan, Y. Li, *J. Am. Chem. Soc.* **2008**, *130*, 6940; f) A. S. Dudnik, V. Gevorgyan, *Angew. Chem.* **2007**, *119*, 5287; *Angew. Chem. Int. Ed.* **2007**, *46*, 5195; g) D. J. Wallace, R. L. Sidda, R. A. Reamer, *J. Org. Chem.* **2007**, *72*, 1051.

[5] For reviews, please see: a) J. Tsuji, T. Mandai, *Angew. Chem.* **1995**, *107*, 2830; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 2589; b) J. Tsuji, T. Mandai, in: *Metal- Catalyzed Cross-Coupling Reactions*, (Eds.: F. Diedrich, P. J. Stang, Wiley-VCH, New York, **1998**, p 455; c) K. M. Brummond, J. E. DeForrest, *Synthesis* **2007**, 795.

[6] For selected recent examples for allene synthesis, please see: a) X. Zhao, Z. Zhong, L. Peng, W. Zhang, J. Wang, *Chem. Commun.* **2009**, 2535; b) S. Hayashi, K. Hirano, H. Yorimitsu, K. Oshima, *J. Am. Chem. Soc.* **2008**, *130*, 5048; c) V. Lavallo, G. D. Frey, S. Kousar, B. Donnadieu, G. Bertrand, *Proc. Natl. Acad. Sci. U. S. A.* **2007**, *104*, 13569; d) J. Kuang, S. Ma, *J. Org. Chem.* **2009**, *74*, 1763; e) J. Kuang, S. Ma, *J. Am. Chem. Soc.* **2010**, *132*, 1786; f) W. Zhang, H. Xu, W. Tang, *J. Am. Chem. Soc.* **2009**, *131*, 3832; g) H. Jiang, X. Liu, L. Zhou, *Chem. Eur. J.* **2008**, *14*, 11305; h) X.-T. Pu, J. M. Ready, *J. Am. Chem. Soc.* **2008**, *130*, 10874; i) C.-Y. Li, X.-B. Wang, X.-L. Sun, Y. Tang, J. C. Zheng, Z.-H. Xu, Y.-G. Zhou, L.-X. Dai, *J. Am. Chem. Soc.* **2007**, *129*, 1494; j) C.-Y. Li, B.-H. Zhu, L.-W. Ye, Q. Jing, X.-L. Sun; Y. Tang, *Tetrahedron* **2007**, *63*, 8046; k) P. Lee, K. Lee, Y. Kang, *J. Am. Chem. Soc.* **2006**, *128*, 1139; l) D. R. Fandrick, J. T. Reeves, Z. Tan, H. Lee, J. J. Song, N. K. Yee, C. H. Senanayake, *Org. Lett.* **2009**, *11*, 5458; m) H. Zhang, X. Fu, J. Chen, E. Wang, Y. Liu, Y. Li, *J. Org. Chem.* **2009**, *74*, 9351; n) J. Terao, F. Bandob, N. Kambe, *Chem. Commun.* **2009**, 7336; o) Q. Xiao, Y. Xia, H. Li, Y. Zhang, J. Wang, *Angew. Chem.* **2011**, *123*, 1146; *Angew. Chem. Int. Ed.* **2011**, *50*, 1114.

[7] For selected recent examples using electron-dificient 1,3-conjugated enynes as synthons, see: a) T. Yao, X. Zhang, R. C. Larock, *J. Am. Chem. Soc.* **2004**, *126*, 11164; b) T. Yao, X. Zhang, R. C. Larock, *J. Org. Chem.* **2005**, *70*, 7679; c) Y. H. Liu, S. Zhou, *Org. Lett.* **2005**, *7*, 4609; d) N. T. Patil, H. Wu, Y. Yamamoto, *J. Org. Chem.* **2005**, *70*, 4531; e) Y. H. Liu, S. Zhou, *Org. Lett.* **2005**, *7*, 4609; f) C. H. Oh, V. R. Reddy, A. Kim, C. Y. Rhim, *Tetrahedron Lett.* **2006**, *47*, 5307; g) L. Zhao, G. Cheng, Y. Hu, *Tetrahedron Lett.* **2008**, *49*, 7364; h) X. Liu, Z. Pan, X. Shu, X. Duan, Y. Liang, *Synlett*, **2006**, *12*, 1962.

[8] For work from our group, see: a) X. Yu, H. Ren, Y. Xiao, J. Zhang, *Chem. Eur. J.* **2008**, *14*, 8481; b) Y. Xiao, J. Zhang, *Angew. Chem.* **2008**, *120*, 1929; *Angew. Chem. Int. Ed.* **2008**, *47*, 1903; c) Y. Xiao, J. Zhang, *Adv. Synth. Catal.* **2009**, *351*, 617; d) Y. Xiao, J. Zhang, *Chem. Commun.* **2009**, 3594; e) F. Liu, J. Zhang, *Angew. Chem.* **2009**, *121*, 5613; *Angew. Chem. Int. Ed.* **2009**, *48*, 5505; f) W. Li, Y. Xiao, J. Zhang, *Adv. Synth. Catal.* **2009**, *351*, 3083; g) R. Liu, J. Zhang, *Chem. Eur. J.* **2009**, *15*, 9303; h) H. Gao, X. Zhao, Y. Yu, J. Zhang, *Chem. Eur. J.* **2010**, *16*, 456; i) Y. Xiao, J. Zhang, *Chem. Commun.* **2010**, *46*, 752; j) F. Liu, D. Qian, L. Li, X. Zhao, J. Zhang, *Angew. Chem.* **2010**, *122*, 6819; *Angew. Chem. Int. Ed.* **2010**, *49*, 6669; k) X. Yu, B. Du, K. Wang, J. Zhang, *Org. Lett.* **2010**, *12*, 1876.

[9] Method for the preparation of R_2CuLi: H. Gilman, R. G. Jones; L. A. Woods, *J. Org. Chem.* **1952**, *17*, 1630.

[10] S. Ma, L. Li, *Org. Lett.* **2000**, *2*, 941.

[11] a) C. Fu, S. Ma, *Org. Lett.* **2005**, *7*, 1605; b) S. Ma, J. Zhang, L. Lu, *Chem. Eur. J.* **2003**, *9*, 2447; c) S. Ma, J. Zhang, L. Lu, *Chem. Eur. J.* **2003**, *9*, 2447.

[12] N. Yoshikai, T. Yamashita, E. Nakamura *Chem. Asian J.* **2006**, *1*, 322.