DOI: 10.1002/chem.200901685

Application of Asymmetric Ylide Cyclopropanation in the Total Synthesis of Halicholactone

Chun-Yin Zhu,[a] Xiao-Yu Cao,[b] Ben-Hu Zhu,[c] Chao Deng,[a] Xiu-Li Sun,[a] Bi-Qin Wang,[b] Qi Shen,[c] and Yong Tang*[a]

Halicholactone belongs to a family of oxylipins that have important and interesting biological activities, such as inhibiting lipoxygenase and farnesyl protein transferase. These compounds are featured unique molecular structures containing a 1,2-*trans*-substituted cyclopropane subunit with a 6-, 8- or 9-membered lactone (Figure 1).[1] The first total synthesis of halicholactone **1** was accomplished by Wills et al. using (*S*)-malic acid as the starting material.[2a] In their synthesis, the cyclopropane fragment was obtained by the reaction of the unsaturated ester with Corey ylide; the lactone unit was constructed by Yamaguchi's mixed anhydride method. Later, Takemoto, Tanaka,[2c] and their co-workers reported an asymmetric total synthesis of halicholactone **1** from chiral [(diene)Fe(CO)$_3$], in which the cyclopropane fragment was prepared in moderate yields with excellent diastereoselectivity by the modified Simmons–Smith reaction of a chiral allylic alcohol. Kitahara[2d] documented a total synthesis of halicholactone by using (1*S*,5*S*,6*R*)-5-hydroxybicyclo[4.1.0]-heptan-2-one as a chiral building block. Datta's group[2b] described a 12-step synthesis of compound **29** by employing the cyclopropanation of *trans*-cinnamyl alcohol through Charette's protocol, finishing the formal synthesis of halicholactone. Mohapatra et al. also reported the total synthesis of halicholactone with (*R*)-2,3-*O*-isopropylidene glyceraldehyde as a chiral pool building block.[2e] In our studies on ylide chemistry in organic synthesis,[3] we developed an efficient method for the preparation of vinylcyclopropanes from a readily available D-camphor-derived ylide.[3c,e] In this cyclopropanation,[3c,e] excellent diastereoselectivity (*cis*/*trans*) and enantioselectivity can be achieved. Very recently, we found that this cyclopropanation could be applied successfully to the preparation of intermediate **13** in five steps to provide a formal synthesis of halicholactone. In this communication, we wish to report our results as well as the total synthesis of halicholactone in detail.

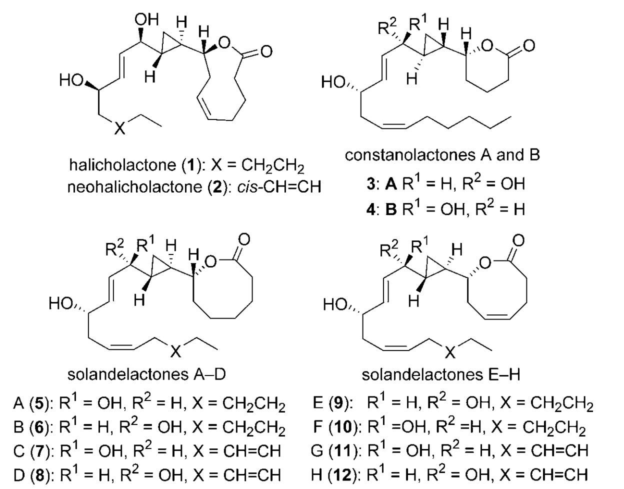


Figure 1. Halicholactone and related compounds (where X = CH_2=CH_2 the double bond has *Z* configuration).

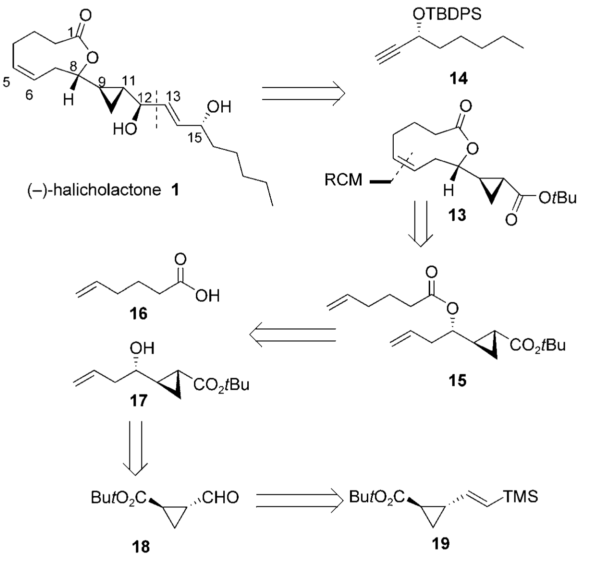
Our retrosynthetic approach is shown in Scheme 1. Disconnecting the C12–C13 bond will afford two fragments **13** and **14**. Compound **14** is accessible from (*R*)-(+)-1-octyn-3-ol.[2a] Fragment **13** can be obtained by the ring-closing metathesis reaction of compound **15**, which would be prepared by the reaction of 5-hexenoic acid **16** with cyclopropane

[a] Dr. C.-Y. Zhu, C. Deng, Dr. X.-L. Sun, Prof. Y. Tang
State Key Laboratory of Organometallic Chemistry
Shanghai Institute of Organic Chemistry
345 Lingling Lu, Shanghai 200032 (PR China)
Fax: (+86) 21-54925078
E-mail: tangy@mail.sioc.ac.cn

[b] X.-Y. Cao, Prof. B.-Q. Wang
College of Chemistry and Material Sciences
Sichuan Normal University, Chengdu
Sichuan 410066 (PR China)

[c] B.-H. Zhu, Prof. Q. Shen
School of Chemistry and Chemical Engineering
Suzhou University, Suzhou 215123 (PR China)

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.200901685.

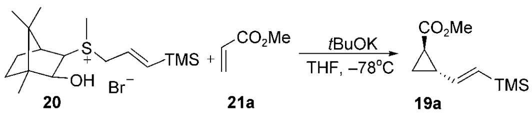


Scheme 1. Retrosynthetic approach to Halicholactone.

piece **17**. The *trans*-disubstituted cyclopropane **19** should be synthesized by an asymmetric ylide cyclopropanation developed by our group.[3c]

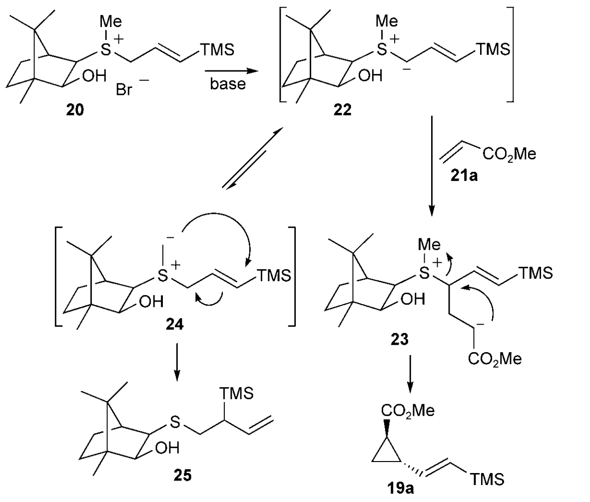
The synthesis of fragment **13**[2a] started with the enantioselective cyclopropanation of acrylate with the ylide derived from sulfonium salt **20**.[3c] Initially, we tried the cyclopropanation of methyl acrylate on a much larger scale at much higher concentration of sulfonium salt than that in our previous reports.[3c,e] As shown in Table 1, unfortunately, only a trace amount of the desired product was obtained (entry 1). In this case, the 2,3-sigma rearrangement of the ylide was obtained as the major product. The probable reason is that the increasing concentration of the sulfonium salt decreased the molar ratio of acrylate **21a** to ylide **22**; this would favor the rearrangement reaction (Scheme 2). On the basis of the aforementioned analysis, we assumed that the addition of base in portions would lower the concentration of the ylide, thus improving the cyclopropanation. As expected, the yield was increased to 63 % when KO*t*Bu was added in 7–10 portions within 2 h. By employing this method, the yield was improved to 72 % when the scale was increased to 4.8 mmol at a concentration of 0.1 M (entry 4, Table 1). Under the optimal conditions, the desired compound **19b** was synthesized in 76 % yield with 97 % *ee* and excellent diastereoselectivity (dr > 99:1) (Scheme 3).

Table 1. Ylide cyclopropanation.[a]

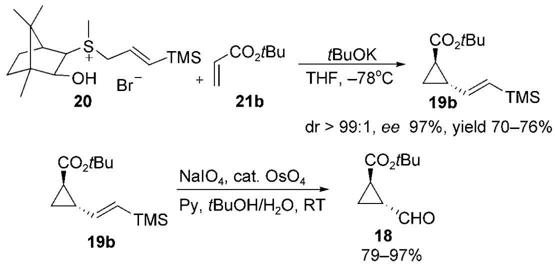


Entry	*c* of **20** [mol L^{-1}] ([mmol])	**21a** [equiv]	Yield [%]
1	0.21 (4.2)	4	trace[b]
2	0.25 (0.5)	4	31
3[c]	0.01 (2)	8	63
4[c]	0.1 (4.8)	8	72
5[c]	0.1 (10)	8	65

[a] Reaction conditions: −78 °C, KO*t*Bu (3.0 equiv), THF as a solvent. [b] 2,3-Sigma rearrangement product was isolated. [c] *t*BuOK was added in 7–10 portions over 2 h.

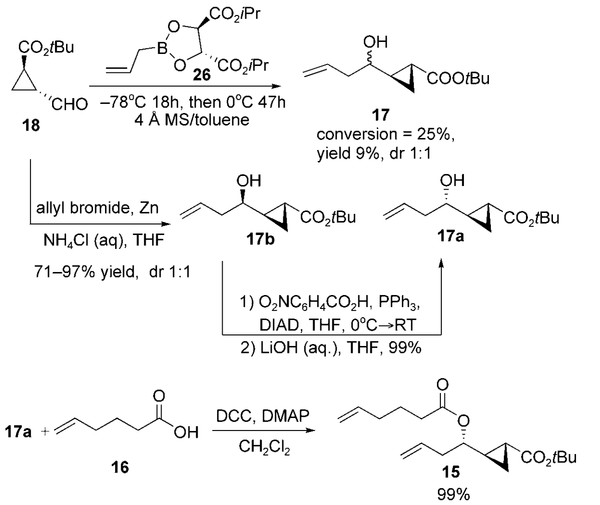


Scheme 2. Mechanism of cyclopropanation.



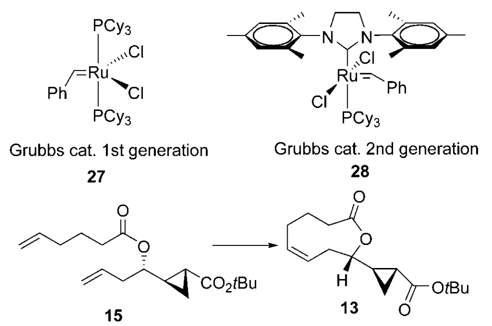
Scheme 3. Synthesis of cyclopropane **18**.

With the cyclopropane **19b** in hand, we first tried its oxidation into the corresponding aldehyde **18** with $NaIO_4$ in the presence of catalytic OsO_4. As shown in Scheme 3, the reaction proceeded very smoothly affording the desired aldehyde in up to 97 % yield. The allylation of **18** was tested with Roush reagent[4] **26**, but the reaction proceeded very slowly. Only 25 % of **18** was converted even after 18 h at −78 °C and a further 47 h at 0 °C. In addition, the diastereomeric ratio was 1:1, probably due to the steric hindrance of the cyclopropane moiety. We were very pleased to find that aldehyde **18** reacted smoothly with allyl bromide in the presence of zinc powder in a mixed solvent of saturated aqueous ammonium chloride and THF,[5] giving alcohol **17a–b** in very high yields. Although the diastereoselectivity remained poor, the two diastereoisomers **17a** and **17b** were separated readily by flash chromatography on silica gel. In addition, isomer **17b** could easily be transformed into the desired isomer **17a** in nearly quantitative yield by the Mitsunobu protocol.[6] Condensation of **17a** with 5-hexenoic acid **16** in CH_2Cl_2 in the presence of dicyclocarbodiimide (DCC) and DMAP afforded compound **15** in 99% yield (Scheme 4).



Scheme 4. Synthesis of **17** and **15**.

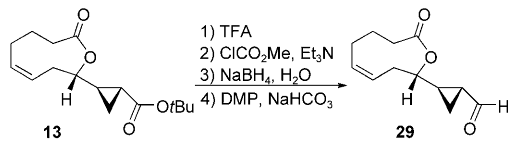
Using 1st generation Grubbs catalyst **27**[7] as the catalyst, ring-closing metathesis of **15** proceeded smoothly in the presence of catalytic amount of $[Ti(OiPr)_4]$[2c,d] giving **13** in 63% yield as shown in Scheme 5. Attempts to further improve the yield by employing the second generation Grubbs' catalyst **28**[8] failed and only 9% yield was obtained. Thus, the formal synthesis of halicholactone was accomplished in five steps in total up to 44.5% yield, much shorter than the 12 steps reported in the literature.[2a] The ^{13}C and ^{1}H NMR spectra of **13** were consistent with those reported by Wills et al.[2a]



reaction conditions	yield
27 (30 mol%), $[Ti(OiPr)_4]$, CH_2Cl_2, reflux, 0.001M	63%
28 (50 mol%), $[Ti(OiPr)_4]$, CH_2Cl_2, reflux, 0.001M	9%

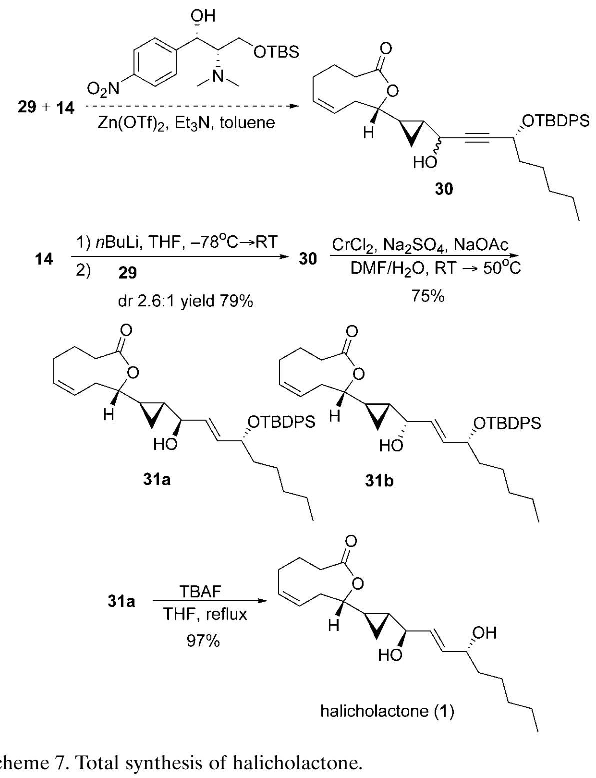
Scheme 5. RCM reaction of **15** to give **13**.

Following Wills' protocol, the transformation of **13** to aldehyde **29** was accomplished in a total 61% yield for four steps.[2a] This process involved the saponification of **13** into the corresponding carboxylic acid, followed by treatment of the acid with methyl chloroformate in the presence of triethylamine. After removal of triethylamine hydrochloride by filtration, the mixed anhydride was reduced with sodium borohydride affording a primary alcohol. Aldehyde **29** was obtained by oxidation of the alcohol with Dess–Martin periodinane (DMP)[9] (Scheme 6).



Scheme 6. Synthesis of aldehyde **29**.

Since the diastereoselectivity of the coupling reaction of aldehyde **30** with (3*S*)-(1*E*,5*Z*)-3-*O*-[(*tert*-butyldiphenylsilyl)-oxy]-1-iodo-1,5-octadiene was poor (nearly 1:2) in the Wills' synthesis,[2a] we tried to improve the selectivity by asymmetric addition of alkyne **14** with aldehyde **29**, followed by reduction reaction of the carbon–carbon triple bond as shown in Scheme 7. Unfortunately, the enantioselective alkynylation of aldehyde **29** catalyzed by a chiral amino alcohol-based ligand,[10] developed by Jiang, did not work probably due to the steric hindrance of the cyclopropane moiety. It was found that the coupling reaction of aldehyde **29** with the lithium salt of alkyne **14** proceeded readily, affording alkynol **30** in good yields with a diastereomeric ratio of 2.6 to 1 (Scheme 7), in which the major one is the desired product. The transformation of **30** to **31** was accomplished by a Cr^{II}-



Scheme 7. Total synthesis of halicholactone.

promoted reduction[11] and the desired isomer **31a** was isolated easily by column chromatography on silica gel. TBAF-mediated deprotection of the TBDPS group afforded halicholactone **1** in 97% yield.

In summary, an enantioselective ylide cyclopropanation has allowed facile access to the main fragment of halicholactone, **13**, with excellent enantioselectivity and diastereoselectivity in five steps, making the synthesis much more practical than those previously reported in the literature. Thus, a total synthesis of halicholactone has been accomplished in 11.2% overall yield, providing the shortest synthetic route thus far.

Experimental Section

Cyclopropanation of *tert*-butyl acrylate: To a stirred suspension of sulfonium salt **20** (3.5 g, 9.0 mmol) and *tert*-butyl acrylate (5.8 g, 45 mmol) in THF (150 mL) at −78°C was added *t*BuOK (3.0 g, 27 mmol) in seven portions over 2 h. After stirring for 4 h at −78°C, the reaction mixture was passed through a short silica gel column, which was eluted with ethyl acetate. After concentration of the combined elution, the residue was purified by flash column chromatography on silica gel (petroleum ether/EtOAc 50:1). Yield: 1.5 g (70%); 97% *ee*. When 0.9 g of salt **20** was used (THF, 100 mL), 0.35 g (76%, 97% *ee*) of the product was obtained. The *ee* cannot be determined by chiral HPLC and was determined based on the *ee* of **18**. $[\alpha]_D^{20}$ = −157.1 (c=1.00, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$/TMS): δ = 5.78 (dd, J=0.4, 18.4 Hz, 1H), 5.49 (dd, J=8.4, 18.4 Hz, 1H), 2.00–1.94 (m, 1H), 1.60–1.56 (m, 1H), 1.44 (s, 9H), 1.32–1.27 (m, 1H), 0.94–0.87 (m, 1H), 0.03 ppm (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.4, 146.1, 129.7, 80.3, 28.1, 27.5, 23.2, 15.6, −1.3 ppm; IR (film): $\tilde{\nu}$ = 3452 (w), 3074 (w), 2955 (m), 2911(s), 1723 (s), 1634 (m), 1461 (w), 1353 (m), 1246 (w), 910 (m), 792 cm^{-1} (s); MS (EI): m/z (%): 240 (1.35) [M^+], 75 (100.00); HRMS (EI): m/z: calcd for $C_{13}H_{24}O_2Si$: 240.1546, found: 240.1556 [M^+].

RCM reaction for the synthesis of compound 13: A solution of **15** (154 mg, 0.5 mmol) and freshly distilled [Ti(O*i*Pr)$_4$] (43 mg, 0.15 mol) in dry CH_2Cl_2 (500 mL) was refluxed for 1.5 h under an nitrogen atmosphere. After the addition of first generation Grubbs' catalyst (123 mg, 0.15 mol), the resulting solution was refluxed for 60 h. The mixture was cooled to room temperature and then exposed to air with stirring for 4 h. Silica gel (ca. 2 g) was added and the resulting mixture was stirred at room temperature for 1 h, passed through a short silica gel column, which was eluted with ethyl acetate. After concentration of the elution, the residue was purified by flash column chromatography on silica gel (petroleum ether/EtOAc 15:1). Yield: 88 mg (63%); $[\alpha]_D^{20}$ = −87.7 (c=1.20, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$/TMS): δ = 5.49–5.45 (m, 2H), 4.27 (ddd, J=1.6, 7.2, 10.8 Hz, 1H), 2.55–2.46 (m, 2H), 2.37–2.29 (m, 1H), 2.27–2.23 (m, 1H), 2.18–2.13 (m, 1H), 2.09–2.04 (m, 2H), 1.82–1.72 (m, 1H), 1.67–1.60 (m, 2H), 1.45 (s, 9H), 1.18–1.13 (m, 1H), 0.86–0.81 ppm (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.0, 172.6, 134.8, 124.3, 80.4, 74.6, 33.7, 33.5, 28.1, 26.4, 25.2, 24.5, 19.5, 12.5 ppm; IR (film): $\tilde{\nu}$ = 3081 (w), 2978 (m), 2919 (m),1719 (s), 1638 (w), 1457 (w), 1368 (m), 1151 (s), 1087 (w), 999 (w), 917 (m), 803 cm^{-1} (m); MS (ESI): m/z (%): 303.1 [M^++Na]; HRMS (EI): m/z: calcd for $C_{16}H_{24}O_4$: 280.1675, found: 280.1674 [M^+].

Halicholactone (1): To a solution of **31a** (40 mg, 0.07 mmol) in THF (2 mL) was added TBAF (66 mg, 0.21 mmol). The solution was refluxed for 3 h, concentrated and the residue was purified by chromatography on silica gel (petroleum ether/EtOAc 10:3) to give the product **1** as colorless oil (22 mg, 97%). $[\alpha]_D^{20}$ = −94.7 (c=0.61, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$/TMS): δ=5.80–5.71 (m, 2H), 5.51–5.43 (m, 2H), 4.22 (ddd, J=1.6, 8.4, 10.8 Hz, 1H), 4.11 (q, J=6.4 Hz, 1H), 3.69 (dd, J=4.0, 7.6 Hz, 1H), 2.53–2.43 (m, 2H), 2.33–2.22 (m, 2H), 2.17–2.12 (m, 1H), 2.10–2.02 (m, 2H), 1.83–1.72 (m, 3H), 1.56–1.46 (m, 2H), 1.43–1.30 (m, 6H), 1.13–1.08 (m, 1H), 1.06–1.00 (m, 1H), 0.89 (t, J=7.2 Hz, 3H), 0.71 (ddd, J=5.6, 5.6, 8.8 Hz, 1H), 0.60 ppm (ddd J=5.2, 5.2, 8.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.1, 134.6, 133.9, 131.6, 124.6, 76.2, 74.1, 72.2, 37.2, 33.8, 33.5, 31.7, 26.4, 25.2, 25.0, 23.4, 22.5, 19.4, 14.0, 8.2 ppm; IR (film): $\tilde{\nu}$ = 3410 (br), 2928 (s), 2857 (s), 1738 (s), 1712 cm^{-1} (s); MS (ESI): m/z: 359.1 [M+Na$^+$]; HRMS (ESI): m/z: calcd for $C_{20}H_{32}O_4Na$: 359.2206, found: 359.2193 [M+Na$^+$].

Acknowledgements

We are grateful for the financial support from the Natural Sciences Foundation of China (Grant No. 20821002 and 20672131), the Major State Basic Research Development Program (Grant No. 2009CB825300), The Chinese Academy of Sciences, and The Science and Technology Commission of Shanghai Municipality.

Keywords: cyclopropanation · halicholactone · ring-closing metathesis · total synthesis · ylides

[1] a) H. Niwa, K. Wakamatsu, K. Yamada, *Tetrahedron Lett.* **1989**, *30*, 4543–4546; b) D. G. Nagle, W. H. Gerwick, *Tetrahedron Lett.* **1990**, *31*, 2995–2998; c) D. G. Nagle, W. H. Gerwick, *J. Org. Chem.* **1994**, *59*, 7227–7237; d) Y. Seo, K. W. Cho, J.-R. Rho, J. Shin, B.-M. Kwon, S.-H. Bok, J.-I. Song, *Tetrahedron* **1996**, *52*, 10583–10596. For structure revision of solandelactone E, F: J. E. Davoren, S. F. Martin, *J. Am. Chem. Soc.* **2007**, *129*, 510–511.

[2] a) D. J. Critcher, S. Connolly, M. Wills, *J. Org. Chem.* **1997**, *62*, 6638–6657; b) D. K. Mohapatra, A. Datta, *J. Org. Chem.* **1998**, *63*, 642–646; c) Y. Baba, G. Saha, S. Nakao, C. Iwata, T. Tanaka, T. Ibuka, H. Ohishi, Y. Takemoto, *J. Org. Chem.* **2001**, *66*, 81–88; d) T. Takahashi, H. Watanabe, T. Kitahara, *Heterocycles* **2002**, *58*, 99–104; e) D. K. Mohapatra, K. A. Durugkar, *ARKIVOC* **2004**, 146–155.

[3] For reviews: a) Y. Tang, S. Ye, X.-L. Sun, *Synlett* **2005**, 2720–2730; b) X.-L. Sun, Y. Tang, *Acc. Chem. Res.* **2008**, *41*, 937–948. For recent examples: c) S. Ye, Z.-Z. Huang, C.-A. Xia, Y. Tang, L.-X. Dai, *J. Am. Chem. Soc.* **2002**, *124*, 2432–2433; d) W.-W. Liao, K. Li, Y. Tang, *J. Am. Chem. Soc.* **2003**, *125*, 13030–13031; e) X.-M. Deng, P. Cai, S. Ye, X.-L. Sun, W.-W. Liao, K. Li, Y. Tang, Y.-D. Wu, L.-X. Dai, *J. Am. Chem. Soc.* **2006**, *128*, 9730–9740; f) L.-W. Ye, X.-L. Sun, Q.-G. Wang, Y. Tang, *Angew. Chem.* **2007**, *119*, 6055–6058; *Angew. Chem. Int. Ed.* **2007**, *46*, 5951–5954; g) Q.-G. Wang, X.-M. Deng, B.-H. Zhu, L.-W. Ye, X.-L. Sun, Y. Tang, *J. Am. Chem. Soc.* **2008**, *130*, 5408–5409.

[4] W. R. Roush, K. Ando, L. K. Hoong, *J. Am. Chem. Soc.* **1985**, *107*, 8186–8190.

[5] P. Barbier, *C. R. Acad. Sci.* **1899**, 110.

[6] O. Mitsunobu, M. Yamada, *Bull. Chem. Soc. Jpn.* **1967**, *40*, 2380–2382.

[7] a) G. C. Fu, R. H. Grubbs, *J. Am. Chem. Soc.* **1992**, *114*, 5426–5427; b) G. C. Fu, R. H. Grubbs, *J. Am. Chem. Soc.* **1992**, *114*, 7324–7325; c) R. H. Grubbs, J. S. Miller, G. C. Fu, *Acc. Chem. Res.* **1995**, *28*, 446–452.

[8] M. Scholl, S. Ding, C. W. Lee, R. H. Grubbs, *Org. Lett.* **1999**, *1*, 953–956.

[9] a) D. B. Dess, J. C. Martin, *J. Org. Chem.* **1983**, *48*, 4155–4156.

[10] B. Jiang, Z. Chen, W. Xiong, *Chem. Commun.* **2002**, 1524–1525.

[11] a) C. E. Castro, R. D. Stephen, *J. Am. Chem. Soc.* **1964**, *86*, 4358–4363; b) D. Brillon, D. Deslongchamps, *Can. J. Chem.* **1987**, *65*, 56–68.

Received: June 19, 2009
Published online: September 24, 2009