ChemComm

Cite this: *Chem. Commun.*, 2011, **47**, 6969–6971

www.rsc.org/chemcomm

COMMUNICATION

One pot iridium-catalyzed asymmetrical double allylations of sodium sulfide: a fast and economic way to construct chiral C_2-symmetric bis(1-substituted-allyl)sulfane†

Shengcai Zheng,[a] Weiqing Huang,[a] Ning Gao,[a] Ruimin Cui,[a] Min Zhang[a] and Xiaoming Zhao*[a]

Received 6th April 2011, Accepted 3rd May 2011
DOI: 10.1039/c1cc11930c

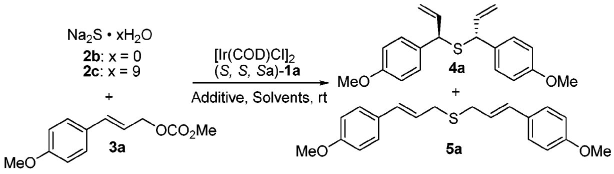
One pot asymmetrical double allylations of sodium sulfide catalyzed by an iridium complex along with a combination of caesium fluoride and water in dichloromethane have been realized and the double allylation products with two C–S bond chiral centers were obtained in 67–99% yields with *b/l* 81/19–99/1, dr 85/15–99/1, and 96–99% ee.

The allyl sulfides, the important organosulfur components of garlic oil, have received great attention because of their anticancer activity.[1] Especially chiral allicin and diallyl sulfides are most abundant in the garlic oil.[2] Organosulfur compounds with a chiral carbon–sulfur bond are of great importance to organocatalysis[3] and medicinal chemistry.[4] Therefore, a new synthetic method for the preparation of chiral allyl sulfides is very desirable. Obviously, transition metal-catalyzed asymmetrical allylation of a sulfur nucleophile is a straightforward access for the preparation of chiral allyl sulfides.[5] However, few studies on this context were disclosed presumably since sulfur nucleophiles can poison transition metal catalysts.[6]

Iridium-catalyzed asymmetric allylic substitution has become an efficient way to synthesize chiral allylic compounds with both high regioselectivity and enantioselectivity. A wide range of carbo[7] and heteroatom (*e.g.*, N,[8] O,[9] and S)[5l–p] nucleophiles have been extensively investigated during the past decade. The utilization of an inorganic sulfur nucleophile (*e.g.*, Na_2S) in enantioselective allylic substitution is even more intriguing and atom-economical. Nevertheless, until today there is no report that sodium sulfide can serve as a nucleophile in transition-metal-catalyzed allylation substitutions. Herein we first report the highly efficient iridium-catalyzed double allylations of sodium sulfide with a variety of allyl methyl carbonates with excellent regio-, diastereo-, and enantioselectivity.

Preliminary studies using sodium hydrogensulfide **2a** as the nucleophile and $[Ir(COD)Cl]_2$/phosphoramidite ligand **1a**[10,11] as the catalyst for an allylation of allylic carbonate **3a** were performed (Table 1). Initially examining this reaction in dichloromethane (DCM) at room temperature formed the black precipitate and no desired product was observed (entry 1). The utilization of sodium sulfide **2b** instead of **2a** produced the complex products (entry 2). Interestingly, the reaction with Cs_2CO_3 afforded the double allylation product **4a** with two C–S bond chiral centers in 20% yield with **4a**/**5a** 99/1, 93/7 dr, and 99% ee (entry 3). Further screening of several additives including CsF, KF, CsCl, and LiCl revealed that the reaction with CsF furnished the highest yield (39%) with **4a**/**5a** 99/1,

Table 1 Optimizing reaction conditions for Ir-catalyzed double allylations of sodium sulfide **2**[a]



Entry	Add.[b]	Sol.(s)	NaNu **2**	Yield[c] (%)	**4a/5a**[d]	dr[e]	ee[e] (%)
1	—	DCM	NaHS	N.R.	—	—	—
2	—	DCM	Na_2S	Comp.	—	—	—
3	Cs_2CO_3	DCM	Na_2S	20	>99/1	93/7	>99
4	CsF	DCM	Na_2S	39	>99/1	98/2	>99
5	KF	DCM	Na_2S	22	—	97/3	84
6	CsCl	DCM	Na_2S	34	>99/1	87/13	94
7	LiCl	DCM	Na_2S	8	—	97/3	>99
8[f]	—	H_2O/DCM	Na_2S	42	>99/1	97/3	>99
9[f]	CsF	H_2O/DCM	Na_2S	83	>99/1	97/3	>99
10	$CsOH\cdot H_2O$	DCM	Na_2S	64	>99/1	98/2	92
11	CsF	DCM	$Na_2S\cdot 9H_2O$	99	>99/1	98/2	>99
12	—	DCM	$Na_2S\cdot 9H_2O$	34	—	98/2	>99
13	CsF	THF	$Na_2S\cdot 9H_2O$	24	—	94/6	>99
14	CsF	Toluene	$Na_2S\cdot 9H_2O$	33	—	91/9	>99

[a] Reaction conditions: 1 mol% of $[Ir(COD)Cl]_2$, 2 mol% of **1a**, 200 mol% of **2a**, and 100 mol% of **3a** (0.1 M) at 25 °C. [b] 300 mol% of additive for entries 2–6, 8–10, and 11–13. [c] Isolated yields. [d] Determined by ^1H NMR of the crude reaction mixture. [e] Determined by a chiral HPLC analysis (Chiralpak AD–H column). [f] H_2O/DCM = 1/20.

---

[a] *Department of Chemistry, Tongji University, 1239 Siping Road, Shanghai, 200092, PR. China. E-mail: xmzhao08@mail.tongji.edu.cn*
[b] *Key Laboratory of Organofluorine Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 354 Fenglin Road, Shanghai 200032, PR. China*

† Electronic supplementary information (ESI) available: Experimental procedures and analysis data for new compounds, CIF file of (*R*,*R*)-**6f**. CCDC 819903. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c1cc11930c.

dr 98/2, and 99% ee (entries 4–7). Using H_2O/DCM[12] as the solvents led to somewhat improved yield (42%) of **4a** (entry 8). It is noted that a combination of CsF and H_2O dramatically enhanced the yield from 42% to 83% (entry 8 *vs.* entry 9). The employment of the more basic $CsOH{\cdot}H_2O$ reduced the yield to 64% (entry 9 *vs.* entry 10). We were gratified to discover that the use of a more economic reagent, sodium sulfide hydrate ($Na_2S{\cdot}9H_2O$) **2c**, along with CsF gave much better results than that of anhydrous sodium sulfide **2b** without influencing regio-, diastereo-, and enantioselectivity (entry 11 *vs.* entry 9). In contrast, a significant decrease in the reaction efficiency was observed in the absence of CsF under identical conditions (entry 11 *vs.* entry 12). These results strongly suggest that an optimal and small amount of water together with CsF is very beneficial to Ir-catalyzed allylation of sodium sulfide. Other solvents such as THF and toluene were also used but poor results were obtained (entries 13 and 14). Thus, the reaction conditions presented in entry 11 of Table 1 were defined as the standard conditions for further study.

Further evaluation of the varied chiral ligands **1a**,[10,11] **1b**,[11] **1c**,[10] **1d**,[13] and **1e**[14] (Fig. 1) was carried out under the optimized conditions. All of **1a–1c** gave the same excellent regio-, diastereo-, and enantioselectivity and only **1a** resulted in 99% yield (entries 1–3, Table 2). Notably, the reaction completely failed when **1d** was tested (entry 4); and the reaction with a stereochemically simpler ligand **1e** afforded the desired products in 81% yield and 99% ee but with a lower diastereoselectivity (entry 5).

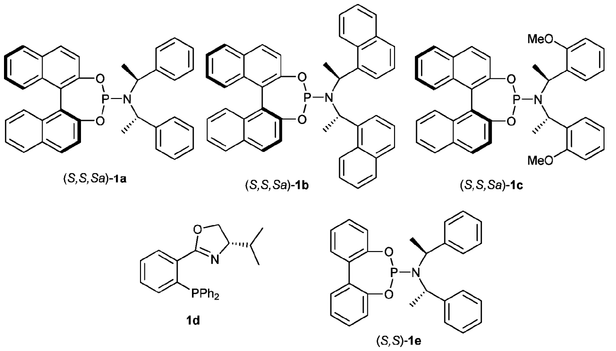


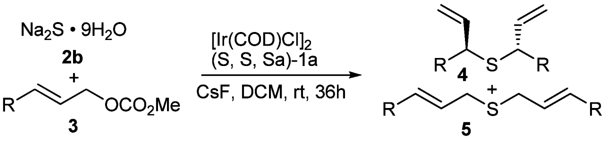
Fig. 1 Chiral ligands **1a–e**.

Table 2 Screening chiral ligands[a]

Entry	Ligand	*T*/h	Yield[b] (%)	**4a**/**5a**[c]	DL/*meso*[d]	ee[e] (%)
1	**1a**	36	99	99/1	98/2	>99
2	**1b**	48	74	99/1	98/2	>99
3	**1c**	48	99	99/1	98/2	>99
4	**1d**	48	N. R.[f]	—	—	—
5	**1e**	48	81	99/1	80/20	>99

[a] Reaction conditions as described in entry 11 of Table 1. [b] Isolated yields. [c] Determined by ^1H NMR of the crude reaction mixture. [d] Determined by a chiral HPLC analysis. [e] Determined by a chiral HPLC analysis (Phenomenex cellulose-1). [f] N. R. = no reaction.

Table 3 Ir-catalyzed regio-, diastereo-, and enantioselective double allylations of sodium sulfide hydrate with allyl methyl carbonates[a]



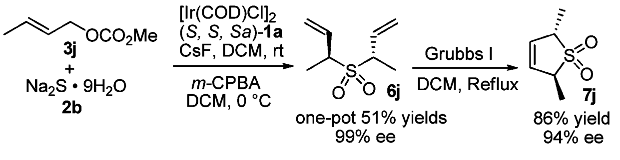
Entry	R	4	Yield[b] (%)	**4**/**5**[c]	DL/*meso*[d]	ee[d] (%)
1	4-$MeOC_6H_4$	**4a**	99	>99/1	97/3	>99
2	3-$MeOC_6H_4$	**4b**	99	>99/1	97/3	97
3	4-MeC_6H_4	**4c**	99	>99/1	96/4	>99
4	Ph	**4d**	99	96/4	95/5	96
5	4-ClC_6H_4	**4e**	80	>99/1	96/4	>99
6	4-BrC_6H_4	**4f**	72	98/2	97/3	>99
7	3-$CF_3C_6H_4$	**4g**	67	97/3	96/4	>99
8	2-Thienyl	**4h**	77	>99/1	99/1	>99
9	Et	**4i**	84	81/19	85/15	98
10[e]	Me	**4j**	—	87/13	89/11	99

Reaction conditions:[a] 1 mol% of $[Ir(COD)Cl]_2$, 2 mol% of **1a**, 300 mol% of CsF, 300 mol% of **2b**, and 100 mol% **3** (0.1 M) in DCM at 25 °C. [b] Isolated yields. [c] Determined by ^1H NMR of the crude reaction mixture. [d] Determined by a chiral HPLC analysis. [e] Determined by ^1H NMR and HPLC of a derivative **6j** because of the volatilization of **4j**.

Having established the optimal conditions, we further explored the scope and generality of this allylation (Table 3). The phenyl- and aromatic allyl methyl carbonates **3a–d** with electron-donating groups (*e.g.*, 4-OMe, 3-OMe, and 4-Me) on the phenyl ring yielded the desired products in 99% yields with excellent regioselectivity (96/4–99/1), diastereoselectivity (95/5–97/3) and enantioselectivity (96–99% ee) (entries 1–4). The hetero- and aromatic allyl methyl carbonates **3e–h** with electron-withdrawing groups (*e.g.*, 4-Cl, 4-Br, and 3-CF_3) on the phenyl ring afforded the desired products **4e–h** in 67–80% yields with excellent regioselectivity (97/3–99/1), diastereoselectivity (96/4–99/1) and enantioselectivity (>99% ee) (entries 5–8). The aliphatic allylic carbonates are the effective substrates as well as the inseparable products **4i**[15] and **4j**[16] with a small amount of the linear product were observed in these cases (entries 9–10).

Moreover, X-ray diffraction analysis of compound **6f**, generated from **4f** in the enantiopure form, reveals its absolute configuration as (*R*,*R*) (see the ESI†).

The power of this methodology was demonstrated by a fast, efficient, and economical synthesis of a 4-carbon building block, 2,5-disubstituted-2,5-dihydrothiophene1,1-dioxide **7**,[17] an equivalent of 2,5-disubstituted tetrahydrothiophene[18] which is a dienophile as well. The ring-closing metathesis (RCM) of (*S*)-3-((*S*)-but-3-en-2-ylsulfonyl)but-1-ene **6j**, which was prepared *via* an allylation of **3j** with **2b** under the optimal conditions, followed by the oxidation in one pot, with a Grubbs catalyst furnished (2*S*,5*S*)-2,5-dimethyl-2,5-dihydrothiophene1,1-dioxide **7j**[17a] in 86% yield with 94% ee (Scheme 1). To the best of our knowledge, this is the first sample for RCM of **6** to **7** in the enatiopure form. In addition, subsequent reduction[18]



Scheme 1 The ring-closing metathesis of **6j**.

and hydrogenation of **7j** could furnish (2*S*,5*S*)-2,5-dimethyltetrahydrothiophene which has been widely used as a C_2 catalyst for the asymmetric epoxidation of aldehydes.[3a–c]

In conclusion, we have developed highly regio-, diastereo-, and enantioselective iridium-catalyzed double allylations of sodium sulfide hydrate with a variety of allyl methyl carbonates. This is the first example that sodium sulfide is used as an atom-economical inorganic nucleophile in transition-metal-catalyzed allylation substitutions. It is interesting to note that the double allylation reaction efficiently generates two C–S chiral centers in one pot. This work also highlights the importance of an optimal amount of water in iridium-catalyzed allylation reactions when sodium sulfide is employed as an inorganic sulfur nucleophile. We are currently investigating applications of this methodology to generate chiral allylic sulfides with unique and additional functionalities.

We gratefully acknowledge Pu Jiang Program of Shanghai (2010), Innovative Program of Shanghai Education Committee (09ZZ36), the NSFC (20942003), 985 Program of Tongji University for generous financial support.

Notes and references

1 (*a*) H. Wang, J. Yang, S. Hsieh and L. Sheen, *J. Agric. Food Chem.*, 2010, **58**, 7096; (*b*) J. S. Yang, G. W. Chen, T. C. Hsia, H. C. Ho, C. C. Ho, M. W. Lin, S. S. Lin, R. D. Yeh, S. W. Ip, H. F. Lu and J. G. Chung, *Food Chem. Toxicol.*, 2009, **47**, 171; (*c*) C. C. Wu, J. G. Chung, S. J. Tsai, J. H. Yang and L. Y. Sheen, *Food Chem. Toxicol.*, 2004, **42**, 1937; (*d*) A. A. Powolny and S. V. Singh, *Cancer Lett.*, 2008, **269**, 305.

2 L. D. Lawson, S. G. Wood and B. G. Hughes, *Planta Med.*, 1991, **57**, 263.

3 For reviews see: (*a*) A. Li, L. Dai and V. K. Aggarwal, *Chem. Rev.*, 1997, **86**, 2341; (*b*) V. K. Aggarwal and J. Richardson, *Chem. Commun.*, 2003, 2644; (*c*) V. K. Aggarwal and C. Winn, *Acc. Chem. Res.*, 2004, **37**, 611; (*d*) J. Zanardi, D. Lamazure, S. Miniere, V. Reboul and P. Metzner, *J. Org. Chem.*, 2002, **67**, 9083; (*e*) K. Tanaka, T. Hori, T. Osaka, K. Noguchi and M. Hirano, *Org. Lett.*, 2007, **9**, 4881.

4 (*a*) R. Eskandari, D. A. Kuntz, D. R. Rose and B. M. Pinto, *Org. Lett.*, 2010, **12**, 1632; (*b*) Y. Yoshimura, K. Asami, T. Imamichi, T. Okuda, K. Shiraki and H. Takahata, *J. Org. Chem.*, 2010, **75**, 4161; (*c*) L. D. Patterson and M. J. Miller, *J. Org. Chem.*, 2010, **75**, 1289; (*d*) J. S. S. Rountree and P. V. Murphy, *Org. Lett.*, 2009, **11**, 871; (*e*) S. A. Testero, P. I. O'Daniel, Q. Shi, M. Lee, D. Hesek, A. Ishiwata, B. C. Noll and S. Mobashery, *Org. Lett.*, 2009, **11**, 2515; (*f*) A. J. P. Mortimer, A. E. Aliev, D. A. Tocher and M. J. Porter, *Org. Lett.*, 2008, **10**, 5477; (*g*) R. T. Dere and X. Zhu, *Org. Lett.*, 2008, **10**, 4641.

5 For a review in the area, see: (*a*) T. Kondo and M. Mitsdo, *Chem. Rev.*, 2000, **100**, 3205; (*b*) H. Eichelmann and H. J. Gais, *Tetrahedron: Asymmetry*, 1995, **6**, 643; (*c*) B. M. Trost, M. J. Krische, R. Radinov and G. Zanoni, *J. Am. Chem. Soc.*, 1996, **118**, 6297; (*d*) B. M. Trost, M. L. Crawley and C. B. Lee, *J. Am. Chem. Soc.*, 2000, **122**, 6120; (*e*) F. X. Felpin and Y. Landais, *J. Org. Chem.*, 2005, **70**, 6441; (*f*) S. Chandrasekhar, V. Jagadeshwar, B. Saritha and C. Narsihmulu, *J. Org. Chem.*, 2005, **70**, 6506; (*g*) Y. Yatsumonji, Y. Ishida, A. Tsubouchi and T. Takeda, *Org. Lett.*, 2007, **9**, 4603; (*h*) L. E. Overman, S. W. Roberts and H. F. Sneddon, *Org. Lett.*, 2008, **10**, 1485; (*i*) M. Jegelka and B. Plietker, *Org. Lett.*, 2009, **11**, 3462; (*j*) B. Alexey, H. F. Zaitsev, P. S. Caldwell and L. F. V. Pregosin, *Chem.–Eur. J.*, 2009, **15**, 6468; (*k*) T. Kondo, Y. Morisaki, S. Uenoyama, K. Wada and T. Mitsudo, *J. Am. Chem. Soc.*, 1999, **121**, 8657; (*l*) Q. Xu, W. Liu, L. Dai and S. You, *J. Org. Chem.*, 2010, **75**, 4615; (*m*) Q. Xu, L. Dai and S. You, *Org. Lett.*, 2010, **12**, 800; (*n*) M. Ueda and J. F. Hartwig, *Org. Lett.*, 2010, **12**, 92; (*o*) S. Zheng, N. Gao, W. Liu, D. Liu, X. Zhao and T. Cohen, *Org. Lett.*, 2010, **12**, 4454; (*p*) N. Gao, S. Zheng, W. Yang and X. Zhao, *Org. Lett.*, 2011, **13**, 1514.

6 (*a*) L. L. Hegedus and R. W. McCabe, *Catalyst Poisoning*, Marcel Dekker, New York, 1984; (*b*) A. T. Hutton, in *Comprehensive Coordination Chemistry*, ed. G. Wilkinson, R. D. Gillard and J. A. McCleverty, Pergamon, Oxford, UK, vol. 5, 1984, p. 1151.

7 (*a*) A. Alexakis and D. Polet, *Org. Lett.*, 2004, **6**, 3529; (*b*) T. Graening and J. F. Hartwig, *J. Am. Chem. Soc.*, 2005, **127**, 17192; (*c*) D. J. Weix and J. F. Hartwig, *J. Am. Chem. Soc.*, 2007, **129**, 7720; (*d*) G. Helmchen, A. Dahnz, P. Duebon, M. Schelwies and R. Weihofen, *Chem. Commun.*, 2007, 675; (*e*) A. Alexakis, S. Hajjaji, E. D. Polet and X. Rathgeb, *Org. Lett.*, 2007, **9**, 3393; (*f*) H. He, X. Zheng, Y. Li, L. Dai and S. You, *Org. Lett.*, 2007, **9**, 4339; (*g*) W. Liu, H. He, L. Dai and S. You, *Org. Lett.*, 2008, **10**, 1815; (*h*) G. Onodera, K. Watabe, M. Matsubara, K. Oda, S. Kezuka and R. Takeuchi, *Adv. Synth. Catal.*, 2008, **350**, 2725; (*i*) W. Liu, H. He, L. Dai and S. You, *Synthesis*, 2009, 2076; (*j*) H. He, W. Liu, L. Dai and S. You, *J. Am. Chem. Soc.*, 2009, **131**, 8346; (*k*) W. Liu, S. Zheng, H. He, X. Zhao, L. Dai and S. You, *Chem. Commun.*, 2009, 6604; (*l*) S. Spiess, J. A. Raskatov, C. Gnamm, K. Broner and G. Helmchen, *Chem.–Eur. J.*, 2009, **15**, 11087.

8 (*a*) T. Ohmura and J. F. Hartwig, *J. Am. Chem. Soc.*, 2002, **124**, 15164; (*b*) K. Tissot-Croset, D. Polet and A. Alexakis, *Angew. Chem., Int. Ed.*, 2004, **43**, 2426; (*c*) C. Welter, A. Dahnz, B. Brunner, S. Streiff, P. Dubon and G. Helmchen, *Org. Lett.*, 2005, **7**, 1239; (*d*) M. J. Pouy, A. Leitner, D. J. Weix, S. Ueno and J. F. Hartwig, *Org. Lett.*, 2007, **9**, 3949.

9 (*a*) C. T. Shu and J. F. Hartwig, *Angew. Chem., Int. Ed.*, 2004, **43**, 4794; (*b*) I. Lyothier, C. Defieber and E. M. Carreira, *Angew. Chem., Int. Ed.*, 2006, **45**, 6204; (*c*) S. Ueno and J. F. Hartwig, *Angew. Chem., Int. Ed.*, 2008, **47**, 1928; (*d*) M. Gartner, S. Mader, K. Seehafer and G. Helmchen, *J. Am. Chem. Soc.*, 2011, **133**, 2072.

10 K. Tissot-Croset, D. Polet, S. Gille, C. Hawner and A. Alexakis, *Synthesis*, 2004, 2586.

11 L. A. Arnold, R. Imbos, A. Mandoli, A. H. M. de Vries, R. Naasz and B. L. Feringa, *Tetrahedron*, 2000, **56**, 2865.

12 A mixture of DCM and H_2O as the solvent was employed in Pd-catalyzed asymmetric allylation using $NaSO_2Ph$ as the nucleophile and for details, see: B. M. Trost, M. J. Krische, R. Radinov and G. Zanoni, *J. Am. Chem. Soc.*, 1996, **118**, 6297.

13 (*a*) P. v. Matt and A. Pfaltz, *Angew. Chem., Int. Ed. Engl.*, 1993, **32**, 566; (*b*) J. Sprinz and G. Helmchen, *Tetrahedron Lett.*, 1995, **34**, 1769.

14 A. Alexakis, S. Rosset, J. Allamand, S. March, F. Guillen and C. Benhaim, *Synlett*, 2001, 1375.

15 The diallyl thioether **4i** has been prepared in the racemic form and for the details, see: R. Delaby, L. Piaux and A. Guillemonat, *Compt. Rend.*, 1937, **205**, 609.

16 The diallyl thioether **4j**, a low boiling point and foul smelling product, has been prepared in the racemic form and for details, see: (*a*) G. A. Tolstrikov, *Zh. Org. Khim.*, 1981, **17**, 251; (*b*) H. N. Hafez and A. B. A. El-Gazzar, *Bioorg. Med. Chem. Lett.*, 2008, **18**, 5222; (*c*) K. I. Molvi, K. K. Vasu, S. G. Yerande, V. Sudarsanam and N. Haque, *Eur. J. Med. Chem.*, 2007, **42**, 1049; (*d*) J. B. Sperry and D. L. Wright, *Curr. Opin. Drug Discovery Dev.*, 2005, **86**, 723.

17 The useful building block **7j** has been prepared in the racemic form through the 1,4 addition of sulfur dioxide to conjugated acyclic dienes and for details, see: (*a*) H. J. Backer, J. Strating and C. M. H. Kool, *Rec. Trav. Chim. Pays-Bas*, 1939, **58**, 778; (*b*) W. L. Mock, *J. Am. Chem. Soc.*, 1966, **88**, 2857; (*c*) S. D. McGregor and D. M. Lemal, *J. Am. Chem. Soc.*, 1966, **88**, 2858; (*d*) J. Saltiel and L. Metts, *J. Am. Chem. Soc.*, 1967, **89**, 2232; (*e*) W. L. Mock, *J. Am. Chem. Soc.*, 1975, **97**, 3666; (*f*) W. L. Mock, *J. Am. Chem. Soc.*, 1975, **97**, 3673; (*g*) Q. Yao, *Org. Lett.*, 2002, **4**, 427; (*h*) K. Oh, *Org. Lett.*, 2007, **9**, 2973; (*i*) M. T. Mwangi, M. D. Schulz and N. B. Bowden, *Org. Lett.*, 2009, **11**, 33; (*j*) M. G. Brant, C. M. Bromba and J. E. Wulff, *J. Org. Chem.*, 2010, **75**, 6312; (*k*) M. G. Brant, C. M. Bromba and J. E. Wulff, *J. Org. Chem.*, 2010, **75**, 6312.

18 (*a*) F. G. Bordwell and W. H. McKellin, *J. Am. Chem. Soc.*, 1951, **73**, 2251; (*b*) Y. Handa, J. Inanaga and M. Yamaguchi, *J. Chem. Soc., Chem. Commun.*, 1989, 298; (*c*) N. Somasundaram, K. Pitchumani and C. Srinivasan, *J. Chem. Soc., Chem. Commun.*, 1994, 1473; (*d*) E. Akgun, K. Mahmood and C. A. Mathis, *J. Chem. Soc., Chem. Commun.*, 1994, 761.