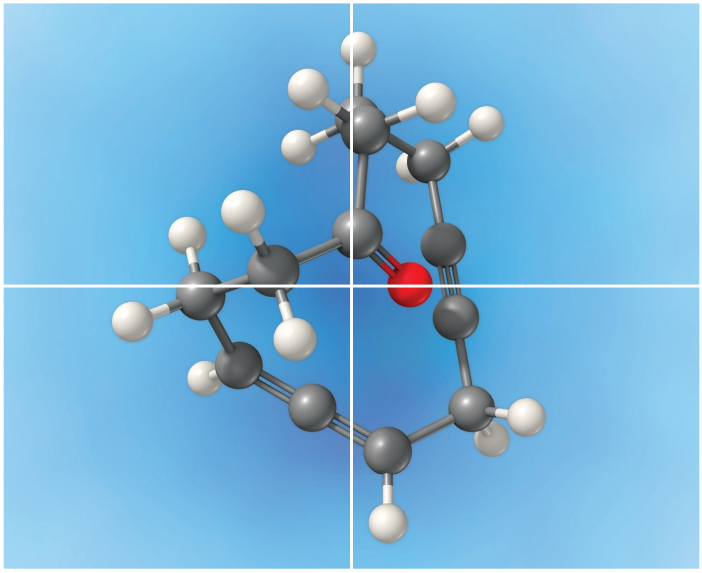
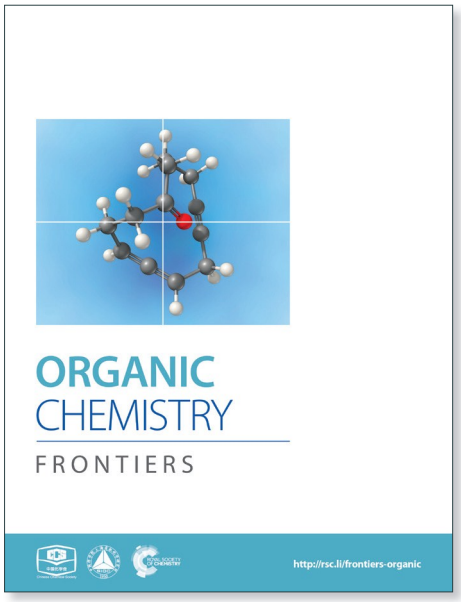
ORGANIC CHEMISTRY

FRONTIERS



Accepted Manuscript



This is an *Accepted Manuscript*, which has been through the Royal Society of Chemistry peer review process and has been accepted for publication.

Accepted Manuscripts are published online shortly after acceptance, before technical editing, formatting and proof reading. Using this free service, authors can make their results available to the community, in citable form, before we publish the edited article. We will replace this *Accepted Manuscript* with the edited and formatted *Advance Article* as soon as it is available.

You can find more information about *Accepted Manuscripts* in the **Information for Authors**.

Please note that technical editing may introduce minor changes to the text and/or graphics, which may alter content. The journal's standard **Terms & Conditions** and the **Ethical guidelines** still apply. In no event shall the Royal Society of Chemistry be held responsible for any errors or omissions in this *Accepted Manuscript* or any consequences arising from the use of any information it contains.

Journal Name

Organic Chemistry Frontiers

Dynamic Article Links ►

Cite this: DOI: 10.1039/c0xx00000x

www.rsc.org/xxxxxx

ARTICLE TYPE

Iodine-Promoted Meyer-Schuster Rearrangement for the Synthesis of α-Iodo Unsaturated Ketones

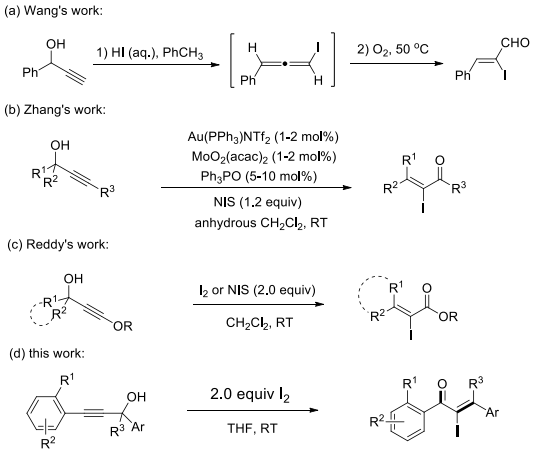
Hai-Tao Zhu,*[a] Ming-Jin Fan,[a] De-Suo Yang,*[a] Xiao-Ling Wang,[a] Sen Ke,[a] Chao-Yang Zhang,[a] and Zheng-Hui Guan*[b]

Received (in XXX, XXX) Xth XXXXXXXXX 20XX, Accepted Xth XXXXXXXXX 20XX

DOI: 10.1039/b000000x

A facile and efficient iodine-promoted Meyer-Schuster rearrangement of propargyl alcohols for the synthesis of α-iodo-α,β-unsaturated ketones is presented. The reaction is concisely conducted at ambient temperature and shows good functional group tolerance.

α-Iodo unsaturated ketones are versatile intermediates which have been used for the synthesis of biologically active heterocyclic compounds[1] and palladium-catalyzed cross coupling.[2] Typically, the direct iodination of unsaturated enones was achieved by 1,4-conjugate addition of a nucleophile to enones sequentially with electrophilic iodination and elimination.[3] Lots of α-iodo enones, such as α-iodo cycloalkenones,[4, 1b, 1d] α-iodo enaminones[5] and α-iodo chalcones[6] were synthesized by the protocol. However, the synthesis of acyclic β-mono/disubstituted α-iodo enones is still a challenging task. Therefore, the development of facile and efficient methods toward these valuable compounds is of great significance.



Scheme 1. Synthesis of α-iodo unsaturated ketenes

Recently, Lewis acid[7] or Brønsted acid[8, 9] catalyzed Meyer-Schuster rearrangements of propargyl alcohols have been developed for the synthesis of useful compounds, such as heterocycles, carbocycles, enones and esters. In 2007, an aqueous HI-promoted Meyer-Schuster rearrangement for the synthesis of α-iodo-α,β-unsaturated aldehydes was developed by Wang and coworker (Scheme 1a).[9] The reaction was achieved through a stepwise mechanism that included the formation of iodoallene intermediates and their oxygen-mediated oxidation. After that, Au and Mo co-catalyzed Meyer-Schuster rearrangement for the synthesis of α-iodo-α,β-unsaturated ketones was developed by Zhang and coworker where an iodonium ion was needed for the Au-I exchange (Scheme 1b).[10] Recently, Reddy et al. reported an iodine-induced Meyer-Schuster rearrangement of 3-alkoxy propargyl alcohols for the synthesis of α-iodo-α,β-unsaturated esters (Scheme 1c).[11] Despite these advances, versatile and efficient methods for the synthesis of α-iodo unsaturated ketones that are easy accessibility and use readily accessible starting materials remain highly desirable. As a part of our ongoing research on the transformations of propargylic alcohols,[12] we herein report a facile iodine-promoted Meyer-Schuster rearrangement of propargylic alcohols for the synthesis of α-iodo unsaturated ketones.

Initially, the methyl-2-(3-hydroxy-3,3-diphenylprop-1-yn-1-yl) benzoate **1a** was selected as the substrate to study Meyer-Schuster rearrangement in the presence of I_2 (1.2 equiv). To our delight, the desired product methyl-2-(2-iodo-3,3-diphenylacryloyl) benzoate **2a** was isolated in 73% yield in THF at room temperature (Table 1, entry 1). The structure of the representative product **2a** was determined by X-ray crystallographic analysis (Figure 1).[13] Increasing the loading of I_2 to 1.5 equivalents, 76% yield of **2a** was obtained (entry 2). And 80% yield of **2a** was achieved in the presence of 2.0 equivalents of I_2 (entry 3). However, the yield was decreased when 3.0 equivalents of I_2 was used (entry 4). The screening of different solvents showed that CH_3CN and CH_3OH were less effective than THF (entries 5-6). Further, no better result was obtained when the reaction temperature was varied (entry 7).

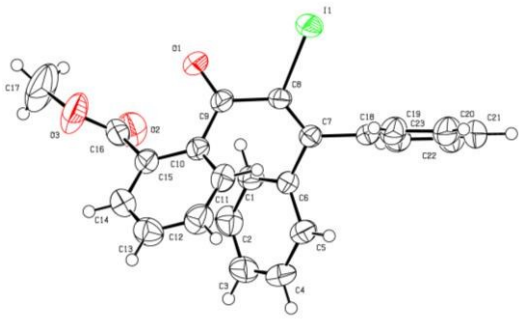
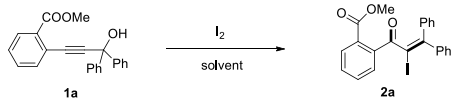


Figure 1. Structure of **2a**

With the optimized reaction conditions established, the scope of the reaction was investigated (Table 2). This iodine-promoted

Meyer-Schuster rearrangement of propargylic alcohols[14] showed high functional group tolerance and proved to be a concise methodology for synthesis of α-iodo enones. A variety of substituents, such as carboalkoxyl, formyl, alkyl, alkoxyl, nitro and halo substituents, tolerated the reaction condition and the corresponding substrates gave α-iodo enones **2a-z** in moderate to good yields. The *o*-carboethoxyl and *o*-methoxyl phenyl-substituted **2b** and **2e**, were smoothly obtained in 85% and 82% yields, respectively. These results suggested that the rearrangement was insensitive to electronic effect of *ortho*-substituent on aryl rings (entries 2 and 5). However, substrate **1i** with no substituent on phenyl ring, gave the corresponding product **2i** in low yield under the optimized

Table 1. Optimization of the iodine-promoted Meyer-Schuster rearrangement of methyl-2-(3-hydroxy-3,3-diphenylprop-1-yn-1-yl) benzoate (**1a**) [a]



1a **2a**

Entry	Solvent	I_2 (equiv.)	Temperature (°C)	Yield[b] (%)
1	THF	1.2	RT	73
2	THF	1.5	RT	76
3	THF	2.0	RT	80
4	THF	3.0	RT	68
5	CH_3CN	1.5	RT	68
6	CH_3OH	1.5	RT	74
7	THF	2.0	80	75

[a] All reactions were run under the following conditions, unless otherwise indicated: 0.2 mmol of **1a** with I_2 in 4 mL of solvent at room temperature. [b] Isolated yield.

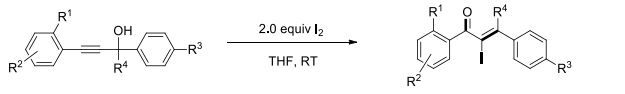
conditions. We also found that *m*- and *p*-carbomethoxyl phenyl-substituents α-iodo enones **2j** and **2k** were not achieved in THF. Fortunately, changing the solvent from THF to CH_3CN, we got better results (entries 9-11). Remarkably, products **2m-q**, having *m*- or *p*- halo (Cl, F) substituents on methyl benzoate ring were afforded in excellent yields (entries 13-17). Substrate **1l** with an electron-withdrawing nitro group showed a bit better result than **1r** with electron-rich methyl group (entries 12 and 18). Moreover, we examined the electronic effects of the substituents on the R^4 and R^3 of the aromatic ring. It was found that electron-withdrawing or electron-donating substituents did not affect this transformation (entries 19-22). Interestingly, aliphatic substituted α-iodo enone **2w** was also obtained in 62% yield (entry 23).

Secondary propargyl alcohols (R^4 = H) did not affect this transition. The methyl 2-(3-hydroxy-3-phenylprop-1-yn-1-yl)-benzoate **1x** produced stereo-selectively the rearrangement product **2x** in good yield (entry 24). However, substrate **1y**, bearing an ethoxycarbonyl on R^1, formed the inseparable mixture (*Z* and *E*) in a 17:1 ratio (entry 25). Compound **1z**, bearing a methyl on R^4, gave the similar result (entry 26).

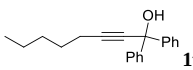
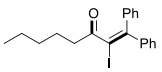
Noteworthily, we also investigated the scale-up of this reaction. The 4 mmol of **1a**, upon exposure to I_2 in THF, afforded the desired product **2a** in 79% yield in 1h. Furthermore, when using IBr as the electrophilic reagent, the desired adduct **2a** was also obtained in 90% yield (Scheme 2). The result indicated that Meyer-Schuster rearrangement is probably induced by iodonium ion.

As shown in Scheme 3, the α-iodo unsaturated ketone **2a** produced by iodo Meyer-Schuster rearrangement can be further transferred in palladium-catalyzed cross-couplings or reductions. For example, the Suzuki coupling of **2a** with *p*-methoxyl phenyl boronic acid afforded the corresponding product **3a** in 45% yield.[15] Reductive lactonization and deiodination of **2a** and **2x** in the presence of $NaBH_4$ produced cyclic compound **4a** and **4x** in 79% and 40% yield, respectively.[16] The structure of **4** was determined by the 1D NMR, 2D NMR and NOESY spectra. (see the Supporting Information).

Table 2. Synthesis of α-iodo-α,β-unsaturated ketones **2** [a]

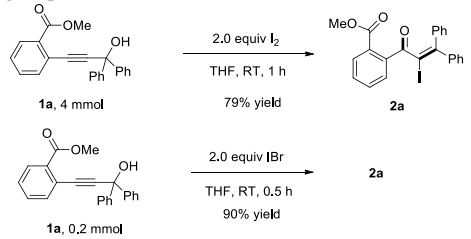


1 **2**

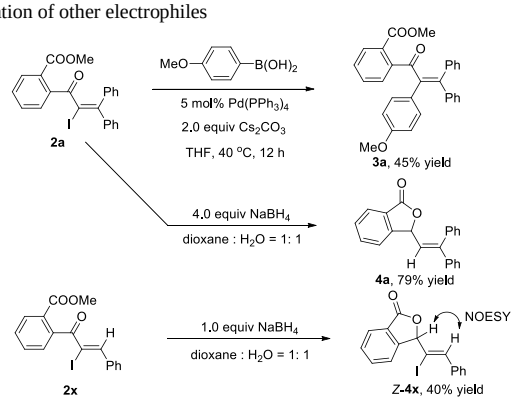
Entry	Substrate (R^1, R^2, R^3, R^4)	Product	Yield[b]
1	R^1 = COOMe, R^2 = H, R^3 = H, R^4 = Ph **1a**	**2a**	80
2	R^1 = COOEt, R^2 = H, R^3 = H, R^4 = Ph **1b**	**2b**	85
3	R^1 = COOBn, R^2 = H, R^3 = H, R^4 = Ph **1c**	**2c**	81
4	R^1 = CHO, R^2 = H, R^3 = H, R^4 = Ph **1d**	**2d**	73
5	R^1 = OMe, R^2 = H, R^3 = H, R^4 = Ph **1e**	**2e**	82
6	R^1 = CH_2COOMe, R^2 = H, R^3 = H, R^4 = Ph	**2f**	93
7	R^1 = H, R^2 = 4-Et, R^3 = H, R^4 = Ph **1g**	**2g**	86
8	R^1 = H, R^2 = 4-OMe, R^3 = H, R^4 = Ph **1h**	**2h**	76
9	R^1 = H, R^2 = H, R^3 = H, R^4 = Ph **1i**	**2i**	84[c]
10	R^1 = H, R^2 = 3-COOMe, R^3 = H, R^4 = Ph **1j**	**2j**	74[c]
11	R^1 = H, R^2 = 4-COOMe, R^3 = H, R^4 = Ph **1k**	**2k**	56[c]
12	R^1 = COOMe, R^2 = 4-NO_2, R^3 = H, R^4 = Ph **1l**	**2l**	86
13	R^1 = COOMe, R^2 = 4-Cl, R^3 = H, R^4 = Ph **1m**	**2m**	92
14	R^1 = COOMe, R^2 = 4-F, R^3 = H, R^4 = Ph **1n**	**2n**	91
15	R^1 = COOMe, R^2 = 3-Cl, R^3 = H, R^4 = Ph **1o**	**2o**	86
16	R^1 = COOMe, R^2 = 5-Cl, R^3 = H, R^4 = Ph **1p**	**2p**	88
17	R^1 = COOMe, R^2 = 5-F, R^3 = H, R^4 = Ph **1q**	**2q**	92
18	R^1 = COOMe, R^2 = 4-Me, R^3 = H, R^4 = Ph **1r**	**2r**	75
19	R^1 = COOMe, R^2 =H, R^3 =Me, R^4 = 4-MeC_6H_4 **1s**	**2s**	88
20	R^1 = COOMe, R^2 = H, R^3 = Cl, R^4 = 4-ClC_6H_4 **1t**	**2t**	85
21	R^1 = COOMe, R^2 = H, R^3 = F, R^4 = 4-FC_6H_4 **1u**	**2u**	81
22	R^1 = COOMe, R^2 = H, R^3 = OMe, R^4 = 4-$OMeC_6H_4$ **1v**	**2v**	76
23	 **1w**  **2w**		62
24	R^1 = COOMe, R^2 = H, R^3 = H, R^4 = H **1x**	**2x**	73 (>19:1)[d]
25	R^1 = COOEt, R^2 = H, R^3 = H, R^4 = H **1y**	**2y**	60 (17:1)[d]
26	R^1 = COOMe, R^2 = H, R^3 = H, R^4 = Me **1z**	**2z**	46 (15:1)[d]

[a] All reactions were run under the following conditions, unless otherwise indicated: 0.2 mmol of **1** with I_2 in 4 mL of THF at room temperature. [b] Isolated yield. [c] The solvent was CH_3CN. [d] The ratio was determined by ^1H NMR.

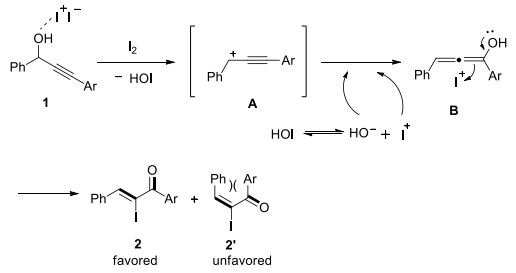
On the basis of the results obtained above, a tentative mechanism was proposed in Scheme 4. Presumably, in the presence of Lewis acidic iodine, the propargyl hydroxyl group of substrate **1** is activated to afforded the intermediate propargyl cation **A** and hypoiodous acid (HOI).[17] Then, **A** reacts with a hydroxyl anion derived from the hypoiodous acid ionization to give allenol intermediate **B**. Finally, **B** is induced by an iodide cation to isomerize and produce major α-iodo unsaturated ketone **2**. The *E* isomer **2′** is unfavorable due to steric hindrance between two aryl groups.



Scheme 2. Scale-up of the iodo Meyer-Schuster rearrangement and application of other electrophiles



Scheme 3. Utilizations of functional groups of α-iodo conjugated enone **2a** and **2x**



Scheme 4. Proposed mechanism for the formation of α-iodo unsaturated ketones

Conclusions

In conclusion, we have developed a concise and efficient approach to synthesize highly substituted α-iodo-α,β-unsaturated ketones from readily accessible propargylic alcohols under mild reaction conditions. The reaction shows high Z-stereoselectivity and the resulting α-iodo enones can be further exploited by cross-couplings and reductions. Application of α-iodo-α,β-unsaturated ketones to the synthesis of useful polycyclic compounds is in progress.

The authors gratefully acknowledge the financial support of this work by Education Department of Shaanxi Province Key Laboratory Project (13JS006). We are also extremely grateful to part of the characterization work supported by the Shannxi Key Laboratory of Phytochemistry, Baoji University of Arts and Sciences.

Experimental Section

General procedure for synthesis of α-iodo unsaturated ketones: To a solution of propargyl alcohol derivatives **1** (0.20 mmol) in THF (4.0 mL) was added I_2 (2.0 equiv, 0.4 mmol) at room temperature. When the reaction was completed, the reaction mixture was quenched by addition of saturated aqueous sodium thiosulfate and extracted with ethyl acetate (3 x 15 mL), washed with water, saturated brine, dried over Na_2SO_4 and evaporated under reduced pressure. The residue was purified by chromatography on silica gel to afford corresponding α-iodo unsaturated ketenes **2**.

Methyl-2-(2-iodo-3,3-diphenylacryloyl)benzoate 2a ^{1}H NMR (400M Hz, $CDCl_3$) δ ppm 7.33 (d, *J* = 7.6 Hz, 2H), 7.32-7.26 (m, 3H), 7.19-7.12 (m, 4H), 6.95-6.91 (m, 5H), 3.90 (s, 3H). ^{13}C NMR (100M Hz,$CDCl_3$) δ ppm 193.3, 168.5, 158.6, 144.8, 139.7, 136.7, 132.1, 131.0, 130.4, 130.1, 129.7, 128.8, 128.7, 128.6, 128.2, 127.9, 101.3, 53.0. IR (neat, cm^{-1}): 2921, 1734, 1654, 1234, 1097, 763. HRMS (ESI) Calcd for $C_{23}H_{17}INaO_3$: M+Na = 491.0115. Found: 491.0121.

Notes and references

[a] *Shannxi Key Laboratory of Phytochemistry, Baoji University of Arts and Sciences, Baoji 721013, China. E-mail: 1888@bjwlxy.edu.cn;*

[b] *Key Laboratory of Synthesis and Natural Functional Molecule Chemistry of Ministry of Education, Department of Chemistry & Materials Science, Northwest University, Xi'an 710127, China. E-mail: guanzhh@nwu.edu.cn.*

1 (a) M. Gartner, J. Qu and G. Helmchen, *J. Org. Chem.*, 2012, **77**, 1186; (b) V. Rauniyar, Z. J. Wang, H. E. Burks, and F. D. Toste, *J. Am. Chem. Soc.*, 2011, **133**, 8486; (c) T. J. Greshock and R. L. Funk, *J. Am. Chem. Soc.*, 2006, **128**, 4946; (d) T. Yao, X. Zhang and R. C. Larock, *J. Am. Chem. Soc.*, 2004, **126**, 11164; (e) M. G. Banwell, B. D. Kelly, O. J. Kokas and D. W. Lupton, *Org. Lett.*, 2003, **5**, 2497; (f) K. C. Nicolaou, D. L. F. Gray, T. Montagnon and S. T. Harrison, *Angew. Chem. Int. Ed.*, 2002, **41**, 996; (h) A. D. William and Y. Kobayashi, *J. Org. Chem.*, 2002, **67**, 8771; (i) N. G. Ramesh, E. H. Heijne, A. J. H. Klunder and B. Zwanenburg, *Tetrahedron*, 2002, **58**, 1361; (j) C.-K. Sha, K. C. Santhosh, C.-T. Tseng and C.-T. Lin, *Chem. Commun.*, 1998, 397.

2 (a) G. Pandey and M. Balakrishnan, *J. Org. Chem.*, 2008, **73**, 8128; (b) N. K. Swamy, L. K. Tatini, J. M. Babu, P. Annamalai and M. Pal, *Chem. Commun.*, 2007, 1035; (c) Q. Yao, E. P. Kinney and Z. Yang, *J. Org. Chem.*, 2003**, 68**, 7528; (d) K. C. Nicolaou, M. P. Jennings and P. Dagneau, *Chem. Commun.*, 2002, 2480; (e) K. Lee , J. Lee and P. H. Lee, *J. Org. Chem.*, 2002, 67, 8265; (f) L. Timbart and J.-C. Cintrat, *Chem. Eur. J.*, 2002, **8**, 1637; (g) S, T. Handy and X. Zhang, *Org. Lett.*, 2001, **3**, 233; (h) M. W. Miller and C. R. Johnson, *J. Org. Chem.*, 1997**, 62**, 1582; (i) R. C. Larock, M. J. Doty, Q. Tian and J. M. Zenner, *J. Org. Chem.*, 1997**, 62**, 7536.

3 (a) C. R. Johnson, J. P. Adams, M. P. Braun, C. B. W. Senanayake, P. M. Wovkulich and M. R. Uskokovic, *Tetrahedron Lett.*, 1992, **33**, 917; (b) D. Elsa; P. Bovonsombat and E. M. Nelis, *Synth. Commun.*, 1997, **27**, 2497.

4 (a) D. F. Taber and J. F. Berry, *J. Org. Chem.*, 2013, **78**, 8437; (b) K. Li and A. Alexakis, *Angew. Chem. Int. Ed.*, 2006, **45**, 7600; (c) P. Bovonsombat, G. J. Angara and E. Mc Nelis, *Tetrahedron Lett.*, 1994, **35**, 6787; (d) C.-K. Sha, C.-Y. Shen, T.-S. Jean, R.-T. Chiu and W.-H. Tseng, *Tetrahedron Lett.*, 1993, **34**, 7641; (e) C.-K. Sha and S. J. Huang, *Tetrahedron Lett.*, 1995, **36**, 6927.

5 (a) J. M. Kim, J. E. Na and J. N. Kim, *Tetrahedron Lett.*, 2003, **44**, 6317; (b) P. J. Campos, J. Arranz and M. A. Rodriguez, *Tetrahedron Lett.*, 1997, **38**, 8397; (c) I. Papoutsis, S. Spyroudis, A. Varvoglis, J. A. Callies and V. V. Zhdankin, *Tetrahedron Lett.*, 1997, **38**, 8401; (d) N. G. Ramesh, N. G. Ramesh, E. H. Heijne, A. J. H. Klunder and B. Zwanenburg, *Tetrahedron Lett.*, 1998, **39**, 3295.

6 (a) G. Liu, P. D. Wilkerson, C. A. Toth and H. Xu, *Org. Lett.*, 2012,

14, 858; (b) A. S. K. Hashmi, T. Haffner, M, Rudolph and F. Rominger, *Eur. J. Org. Chem.*, 2011, 667; (c) P. Bovonsombat, R. Rujiwarangkul, T. Bowornkiengkai, J. Leykajarakul, *Tetrahedron Lett.*, 2007, **48**, 8607; (d) M. E. Krafft, and J. W. Cran, *Synlett*, 2005, 1263; (e) A. Alimardanov and E. Negishi, *Tetrahedron Lett.*, 1999, **40**, 3839.

7 (a) Y. Zhu, L.Sun, P. Lu, and Y. Wang, *ACS Catal.*, 2014, **4**, 1911; (b) M. N. Pennell, P. G. Turner and T. D. Sheppard, *Chem. Eur. J.*, 2012, **18**, 4748; (c) M. Egi, M. Umemura, T. Kawai, S. Akai, *Angew. Chem. Int. Ed.*, 2011, **50**, 12197; (d) D. A. Engel and G. B. Dudley, *Org. Lett.*, 2006, **8**, 4027; (e) E. Jimenez-Nunez, A. M. Echavarren, *Chem. Commun.*, 2007, 333; (f) A. Furstner, P. W. Davies, *Angew. Chem. Int. Ed.*, 2007, **46**, 3410.

8 (a) S.Aiken, K. Booth, C. D. Gabbutt, B. M. Heron, C. R. Rice, A. Charaf-Eddin and D. Jacquemin, *Chem. Commun.*, 2014, 7900; (b) E. V. Banide , Y. Ortin , B. Chamiot , A. Cassidy , J. Niehaus , A. Moore , C. M. Seward , H. Muller-Bunz and M. J. McGlinchey, *Organometallics*, 2008, 27, 4173; (c) R. Sanz, A. Martínez, J. M. Alvarez-Gutierrez and F. Rodriguez, *Eur. J. Org. Chem.*, 2006, **1383**; (d) K. H. Meyer, K. Schuster, *Chem. Ber.*, 1922, **55**, 819; (e) S. Swaminathan, K. V. Narayanan, *Chem. Rev.*, 1971, **71**, 429.

9 S. Chen, J. Wang, *J. Org. Chem.*, 2007, **72**, 4993.

10 L. Ye, L. Zhang, *Org. Lett.*, 2009, **11**, 3646.

11 S. Puri, N. Thirupathi and M. S. Reddy, *Org. Lett.*, 2014, **16**, 5246.

12 (a) H.-T. Zhu, K.-G. Ji, F. Yang, L.-J. Wang, Sh.-Ch. Zhao, A. Shaukat, X.-Y. Liu and Y.-M. Liang, *Org. Lett.*, 2011, **13**, 684; (b) H.-T. Zhu, L.-J. Wang, K.-G. Ji, X.-Y. Liu and Y.-M. Liang, *Chem. Asian J.*, 2012, **7**, 1862; (c) H.-T. Zhu, X. Dong, L.-J. Wang, M.-J. Zhong, X.-Y. Liu and Y.-M. Liang, *Chem. Commun.*, 2012, **48**, 10748.

13 CCDC 1044075 (**2a**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

14 (a) Y. Dou, P. Xing, Z. Huang and B. Jiang, *Chin. J. Chem.*, 2014, **32**, 999; (b) Z. Wang, J. Zheng and P. Huang, *Chin. J. Chem.*, 2012, **30**, 23; (c) X. Dong, X. Xu, H. Hou, Q. Wei, D. Xu, N. Jiao, A. Zhang, S. Zhao and S. Ma, *Chin. J. Org. Chem.*, 2001, **21**, 1142.

15 N. Miyaura and A. Suzuki, *Chem. Rev.*, 1995, **95**, 2457.

16 (a) W. R. Bowman, C. F. Bridge, P. Brookes, M. O. Cloonan and D. C. Leach, *J. Chem. Soc., Perkin Trans. 1*, 2002, 58; (b) A. K. Verma, S. P. Shukla, J. Singh and V. Rustagi, *J. Org. Chem.*, 2011, **76**, 5670.

17 F. Yang, T. Jin, M. Bao and Y. Yamamoto, *Chem. Commun.*, 2011, **47**, 4013.