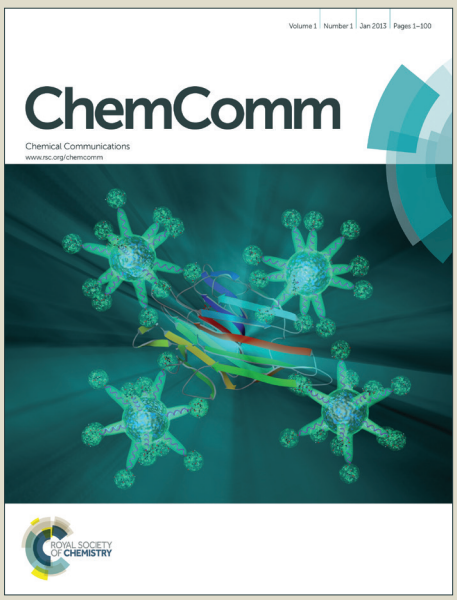
# ChemComm

Accepted Manuscript





ROYAL SOCIETY OF CHEMISTRY

www.rsc.org/chemcomm

Journal Name

COMMUNICATION

# Pd(II)-Catalyzed Formal [4+1] Cycloadditions of Diazoacetates and Aryl Propargyl Alcohols to Form 2, 5-Dihydrofurans

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

www.rsc.org/

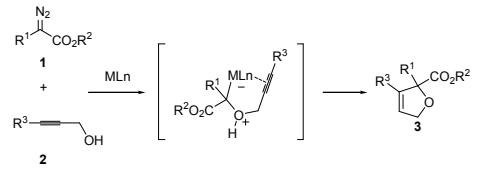
Taoda Shi,[†a] Xin Guo,[†a] Shenghan Teng [a] and Wenhao Hu[*a,b]

**A Pd(II)-catalyzed formal [4+1] cycloaddition of aryl diazoacetates and aryl propargyl alcohols is reported to afford 2,5-dihydrofuran derivatives as the dominant product over other traditional ones. The auto-tandem catalytic process is proposed to occur via Pd(II)-catalyzed intermolecular oxonium ylide formation and subsequent intramolecular trapping of the ylide with Pd(II)-activated alkynes.**

The development of new chemical strategies for rapid access to complex structures is an important goal for organic chemists. Auto-tandem catalysis, in which two or more mechanistically distinct reactions are promoted by a single catalyst, has the advantages of atom economy, operational simplicity, catalyst and process efficiency.[1]

Palladium is a versatile transition metal with intriguing reactivity towards various functional groups. For example, palladium(II) salts have been shown to efficiently activate alkynes for the intramolecular addition of enolate-type nucleophiles to construct carbo- or heterocycles.[2] They have also drawn growing attention in carbenoid chemistry such as cross-coupling reactions[3], X-H insertions[4] and ylide-trapping processes.[5]

Transition metal-catalyzed reactions of diazo compounds and propargyl alcohols or homopropargyl alcohols have been studied by several groups (Scheme 1). Wood and co-workers reported that diazoketones and propargyl alcohols underwent [2, 3]- or [3, 3]-sigmatropic rearrangement depending on the Rh(II) catalyst of choice.[6] Davies et al. reported that rhodium(II)-catalyzed reactions of tertiary propargyl alcohols with methyl aryl/styryldiazoacetates result in tandem reactions, consisting of oxonium ylide formation followed by [2, 3]-sigmatropic rearrangement.[7] Recently, Hatakeyama et al. reported a formal [4+1]-cycloaddition of homopropargylic alcohols with diazodicarbonyl compounds, which involves stepwise Rh(II)-catalyzed O–H insertion/$ZnCl_2$-catalyzed Conia-ene cyclization sequence.[8] Up to now, electrophiles such as imines, aldehydes, ketones, α, β-unsaturated ketoesters, and diazenes have been successfully utilized to trap protic oxonium ylides.[9] However, alkynes, as building blocks or versatile intermediates for compounds with value in biochemistry and material sciences[10] have not yet been explored to trap these ylides. Inspired by the versatility of palladium catalyst in ylide formation and alkyne activation, we hypothesized that the trapping of oxonium ylide with alkynes would be realized with diazoacetates and propargyl alcohols catalyzed by a proper transition metal catalyst with both ylide-generating and π-bond activating properties (Scheme 1). Herein we present our findings.



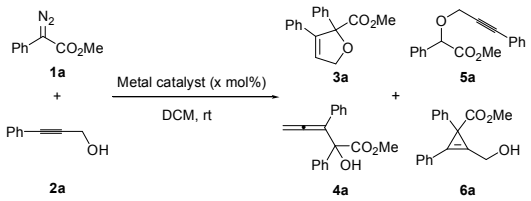

**Scheme 1** Concept of transition metal-catalyzed trapping of oxonium ylide with alkynes.

Proof of principle studies were carried out with phenyl diazoacetate **1a** and phenyl propargyl alcohol **2a** as substrates for reactions in dichloromethane at room temperature. A series of transition metal catalysts were screened. Besides the traditional 2, 3-sigmatropic rearrangement product **4a**[6, 7], O-H insertion product **5a**, and cyclopropene **6a**, a new 2, 5-dihydrofuran derivative **3a**, which was not reported before, was also observed in most cases. The product distribution varied with the use of different catalysts. The O–H insertion product **5a** was the only product with $Rh_2(OAc)_4$ as the catalyst, which is consistent with the results reported by Davies (Table 1, Entry 1).[7] When the reaction was catalyzed with copper(I) salts with non-coordinating anions (Table 1, Entry 2 and Entry 3), the ratio of the cycloaddition product **3a** and 2, 3-sigmatropic rearrangement product **4a** increased. However, **5a** was dominant when the reaction was catalyzed

[a] *Institute of Drug Discovery and Development, East China Normal University, Shanghai Engineering Research Centre for Molecular Therapeutics and New Drug Development, Shanghai, 200062 (China).*
[b] *Department of Chemistry, East China Normal University, Shanghai，200062.*
† The authors contributed equally. Electronic Supplementary Information (ESI) available: Experimental procedures and spectra data for compounds **3a**-**3t**, **4a**- **6a** and **7**- **9**. See DOI: 10.1039/x0xx00000x

by CuCl or CuI (Table 1, Entries 4 and 5), which was used to catalyze a formal

**Table 1** Development of transition metal-catalyzed [4+1] cycloaddition protocol.



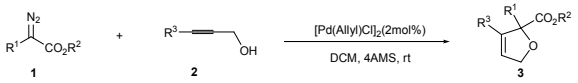

| Entry | M (x mol%) | **3a**: **4a**: **5a**: **6a**[a] | Conversion[a](%) | Yield of **3a**[b](%) |
|---|---|---|---|---|
| 1 | $[Rh_2(OAc)_4]$ (1) | 0: 0: 100: 0 | 100 | - |
| 2 | $Cu(OTf)_2$ (10) | 50: 30: 5: 15 | 100 | 50 |
| 3 | $Cu(CH_3CN)_4PF_6$ (10) | 32:36: 32: 0 | 100 | 28 |
| 4 | CuCl (10) | 11: 5: 84: 0 | 100 | - |
| 5[c] | CuI (10) | 0: 0: 100: 0 | 100 | - |
| 6[d] | CuI(10)/phenanthroline(10) | - | <5 | - |
| 7 | AgOTf (10) | 13: 12: 49:26 | 100 | 10 |
| 8 | $AgSbF_6$ (10) | 30: 8: 32: 30 | 100 | 25 |
| 9 | $AuCl_3$ (2) | - | <5 | - |
| 10 | $[\{Ir(cod)Cl\}_2]$ (2) | - | <5 | - |
| 11 | $PdCl_2$ (5) | 10: 10: 80: 0 | 100 | - |
| 12 | $Pd(PPh_3)_2Cl_2$ (5) | - | <5 | - |
| 13 | $Pd(CH_3CN)_2Cl_2$ (5) | 19: 72: 0: 9 | 100 | 15 |
| 14 | $Pd(OAc)_2$(5) | 13:50:38:0 | 100 | 9 |
| 15 | $Pd(OAc)_2$(10)/$Et_3N$(50) | 0: 0: 100: 0 | 32 | - |
| 16 | $[\{PdCl(\eta^3\text{-}C_3H_5)\}_2]$ (5) | 65: 5:30: 0 | 100 | 60 |
| 17 | $[\{PdCl(\eta^3\text{-}C_3H_5)\}_2]$ (2) | 63: 6 :31: 0 | 100 | 60 |
| 18[e] | $[\{PdCl(\eta^3\text{-}C_3H_5)\}_2]$ (2) | 79: 7 : 14: 0 | 100 | 70 |
| 19[f] | $[\{PdCl(\eta^3\text{-}C_3H_5)\}_2]$ (2) | 0: 0: 100: 0 | 100 | - |
| 20[g] | $[\{PdCl(\eta^3\text{-}C_3H_5)\}_2]$ (2) | 0: 0: 100: 0 | 100 | - |

[a] Determined by crude HNMR of the reaction mixture. [b] Isolated yield after column chromatography. [c] The reaction was performed in DCE at 90℃. [d] The reaction was performed in DCE at 80℃. [e] 200mg of activated 4A molecular sieves was added. [f] The reaction was performed in DCM at 40℃. [f] The reaction was performed in DCE at 60℃.

[4+1] cycloaddition between diazoacetates and α, β-acetylenic ketones to form trisubstituted furans[11]. Catalyzed by Cu(I) or Pd(II) complex with phenanthroline[12], $PPh_3$ or $Et_3N$[13] as ligands or additives, only the dimer of **1a** was observed (Table 1, Entry 6). Meanwhile, the 2, 3-sigmatropic rearrangement product **4a** was more favoured when $Pd(CH_3CN)_2Cl_2$ was used (Table 1, Entry 13). In contrast, in Davies's result, similar products were only obtained with secondary and tertiary propargylic alcohols, indicating that $Pd(CH_3CN)_2Cl_2$-associated oxonium ylide is more electronically favourable for 2, 3-sigmatropic rearrangement than Rh(II)-associated oxonium ylide. The cyclopropenation product **6a** could be observed only in four cases with a lower ratio than the total amount of the other products (Table 1, entries 2, 7, 8 and 9), indicating that the formation of the oxonium ylide via reaction of the hydroxyl moiety with metal carbenes is more favourable.[13] We were pleased to find that $[PdCl(\eta^3\text{-}C_3H_5)]_2$ turned out to be the optimal catalyst for the formal [4+1] cycloaddition product **3a** (Table 1, entry 16). The catalyst loading could be lowered to 2 mol% without decreased ratio of **3a** (Table 1, entry 17), and the yield could be increased to 70% when 4A molecular sieves was added (Table 1, entry 18). When the reaction was performed at higher temperatures, the O-H insertion product **5a** was observed as the dominant product (Table 1, entrie 19 and 20). Hence, the optimal condition for the cyclization reactions was with 2 mol% of $[PdCl(\eta^3\text{-}C_3H_5)]_2$ as catalyst, dichloromethane as solvent, and 4A molecular sieves as an additive.

With the optimized conditions, the substrate scope was examined. As illustrated in Table 2, the aryl diazoacetates gave corresponding 2, 5-dihydrofurans in good yields (Table2, entries 1-8). However, only dimers and O-H insertion products were observed with EDA and diazo ketones. Then, the scope of substituted aryl propargyl alcohols was examined with the reaction of diazoesters **1h** (Table 2, entries 9-14) and **1a** (Table 2, entries 15-20), and significant substitution effect was observed. While the aryl propargyl alcohols bearing halides or electron-donating substituents afforded moderate to good yields of the cyclization products (Table 2, entries 12-17), only O-H insertion product was observed when aryl propargyl alcohols bearing an electron-withdrawing group such as $NO_2$ were used. Instead of cycloaddition products, O-H insertion products and dimers of the diazoesters were dominant for propargyl alcohols ($R_3$ = Methyl, H, $CO_2Bn$), tertiary propargyl alcohols and homopropargyl alcohols.

**Table 2** Substrate scope of the diazoacetates and propargyl alcohols.[a]

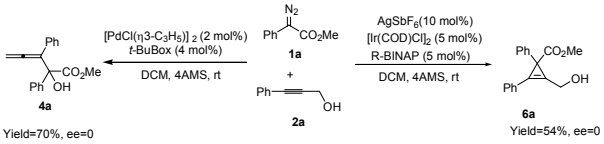



1 2 3

| Entry | $R^1$ | $R^2$ | $R^3$ | Yield (%)[b] |
|---|---|---|---|---|
| 1 | Ph | MeO | Ph | 70 |
| 2 | *P*-Br-$C_6H_4$ | MeO | Ph | 60 |
| 3 | *m*-Cl-$C_6H_4$ | MeO | Ph | 54 |
| 4 | *P*-Cl-$C_6H_4$ | MeO | Ph | 69 |
| 5 | *p*-MeO-$C_6H_4$ | MeO | Ph | 72 |
| 6 | 3, 4-$(MeO)_2$-$C_6H_3$ | MeO | Ph | 74 |
| 7 | 3, 4, 5-$(MeO)_3$-$C_6H_2$ | MeO | Ph | 78 |
| 8 | Ph | BnO | Ph | 59 |
| 9 | 3, 4, 5-$(MeO)_3$-$C_6H_2$ | MeO | *p*-Br-$C_6H_4$ | 58 |
| 10 | 3, 4, 5-$(MeO)_3$-$C_6H_2$ | MeO | *m*-Br-$C_6H_4$ | 54 |
| 11 | 3, 4, 5-$(MeO)_3$-$C_6H_2$ | MeO | *p*-Me-$C_6H_4$ | 62 |
| 12 | 3, 4, 5-$(MeO)_3$-$C_6H_2$ | MeO | *m*-Me-$C_6H_4$ | 63 |
| 13 | 3, 4, 5-$(MeO)_3$-$C_6H_2$ | MeO | *p*-Cl-$C_6H_4$ | 58 |
| 14 | 3, 4, 5-$(MeO)_3$-$C_6H_2$ | MeO | 3, 5-$(Me)_2$-$C_6H_4$ | 51 |
| 15 | Ph | MeO | *p*-MeO-$C_6H_4$ | 64 |
| 16 | Ph | MeO | *p*-Me-$C_6H_4$ | 60 |
| 17 | Ph | MeO | *m*-Me-$C_6H_4$ | 61 |
| 18 | Ph | MeO | *p*-Br-$C_6H_4$ | 50 |
| 19 | Ph | MeO | *p*-Cl-$C_6H_4$ | 55 |
| 20 | Ph | MeO | *m*-Br-$C_6H_4$ | 52 |

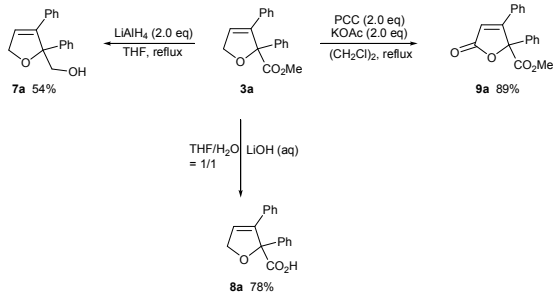
[a] Standard reaction conditions: **1** (0.3mmol, 1.5equiv) in dichloromethane (4 mL) was added to a solution of **2**(0.2mmol, 1.0 equiv), $[PdCl(\eta^3\text{-}C_3H_5)]_2$ (0.004mmol, 2mol %) in dichloromethane (8 mL) over 1 h at rt. [b]Isolated yield after column chromatography.

In our initial effort for asymmetric catalysis, we found that the 2, 3-sigmatropic rearrangement product **4a** was isolated as the dominant product when the catalyst combination of $[PdCl(\eta^3\text{-}C_3H_5)]_2$ and t-BuBox was used, although no enantioselectivity was observed. It's complementary to Davies' method, which is not effective for primary alcohols (Scheme 2). However, the cyclopropenation product **6a** was dominant when the catalyst combination of [Ir(COD)Cl], $AgSbF_6$ and BINAP was used, indicating that the reaction of the Ir(I) carbenoid with the internal alkyne moiety is more favourable than with the hydroxy group in the ylide-forming process, which is present in the other three reaction pathways. Thus, control of chemoselectivity toward each of the four reaction pathways could be realized with the choice of a specific catalytic system.




**Scheme 2** Control of the reaction of **1a** and **2a** towards 2,3-sigmatropic rearrangement or cyclopropenation.

2, 5-Dihydrofurans are synthetically and biologically interesting structural motif.[14] To demonstrate the synthetic value of the 2, 5-hydrofurans, **3a** was easily transformed into the corresponding alcohol **7a**, acid **8a** and furan-2-ketone **9a**[15], with 54%, 89%, and 78% yield respectively (Scheme 3). The structure of **8a** was unambiguously confirmed by X-ray crystallographic analysis (Figure 1).[16]




**Scheme 3** Derivation of the [4+1] cycloaddition product **3a**.

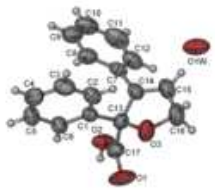
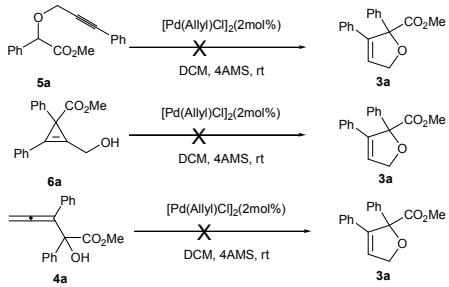


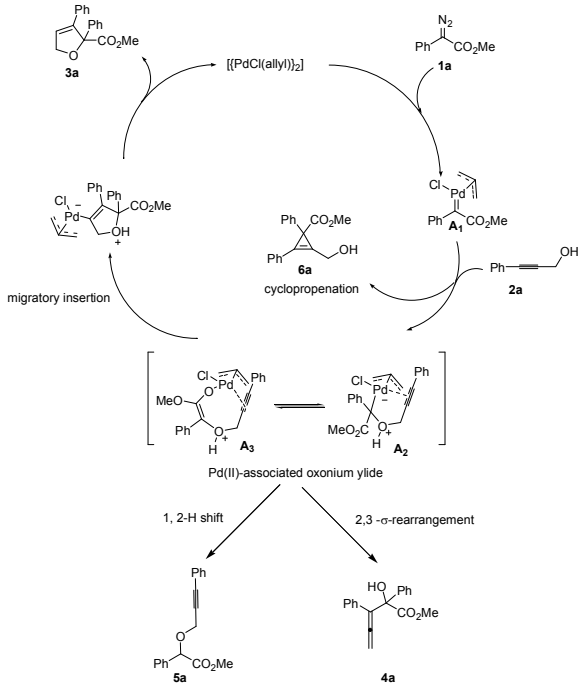
**Fig 1** ORTEP illustration of **8a·$H_2O$**.




**Scheme 4** Control reactions.

In order to investigate the reaction pathway of the Pd(II)-catalyzed formal [4+1] cyclization, several control reactions were conducted (Scheme 4). Compounds **4a**, **5a,** and **6a** were isolated and each subjected to the standard reaction conditions catalyzed by $[PdCl(\eta^3\text{-}C_3H_5)]_2$. As a result, the cyclization product **3a** was not detected, excluding the formation of **3a** from **4a**, **5a** or **6a**. A plausible mechanism was proposed as shown in Scheme 5. Diazoacetate **1a** was

decomposed by $[PdCl(\eta^3\text{-}C_3H_5)]_2$, forming palladium carbenoid $\mathbf{A_1}$. The palladium-associated oxonium ylide $\mathbf{A_2}$, which is in equilibrium with palladium enolate $\mathbf{A_3}$, was formed in situ from $\mathbf{A_1}$ and propargyl alcohol **2a**. $\mathbf{A_2}$ or $\mathbf{A_3}$ led to **3a** via a proposed migratory insertion of the activated C≡C triple bond into the Pd(II)-C bond. **4a** and **5a** were also formed from oxonium ylide $\mathbf{A_2}$ via 2, 3-σ-rearrangement and 1, 2-proton shift, while **6a** was formed from $\mathbf{A_1}$ and **2a** via cyclopropenation. The formation of $\mathbf{A_2}$ is more favourable than **6a** due to the high electrophilic character of the carbene carbon that favors the hydroxyl attack.




**Scheme 5** Proposed mechanism of the [4+1] cycloaddition.

In conclusion, we have developed a Pd(II)-catalyzed formal [4+1] cyclization of diazoacetates and aryl propargyl alcohols, furnishing 2, 5-dihydrofuran derivatives as the dominant product over those from other traditional reaction pathways. This is the first example of trapping of oxonium ylides with alkynes. In this auto-tandem catalytic process, the Pd(II) catalyst not only catalyzed the formation of the protic oxonium ylide, but also activated the alkyne moiety to trap the highly active intermediate.

We are grateful for financial support from NSFC (21125209 and 21332003), the Ministry of Science and Technology (MOST) of China (2011CB808600), STCSM of Shanghai (12JC1403800).

## Notes and references

1 D. Fogg and E. Santos, *Coord. Chem. Rev*., 2004, **248**, 2365; J. Gleason and A. Ajamain, *Angew. Chem. Int. Ed*., 2004, **43**, 3754; S. Chang, *Chem. Soc. Rev*., 2004, **33**, 302; R. Baker and G. Bazan, *Chem. Rev*., 2005, **105**, 1001; J.-C. Wasilke, S. J. Obrey, R. T. Baker and G. C. Bazan, *Chem. Rev*., 2005, **105**, 1001; A. M. Walji and D. W. C. MacMillan, *Synlett* 2007, 1477.

2 G. Balme, D. Bouyssi and N. Monteiro, Palladium-catalyzed reactions involving attack on palladium-alkyne, and related π-complexes by carbon nucleophiles. In Handbook of Organopalladium Chemistry for Organic Synthesis; E.-i. Negishi, Ed.; Wiley: New York, 2002, Vol. 2, pp 2245-2265; G. Balme, D. Bouyssi, T. Lomberget and N. Monteiro, Synthesis 2003, 2115; G. Balme, E. Bossharth and N. Monteiro, *Eur. J. Org. Chem.* 2003, 4101.

3 Z. H. Zhang, Y. Y. Liu, M. X. Gong, X. K. Zhao, Y. Zhang and J. B. Wang, *Angew. Chem. Int. Ed*. 2010, **49**, 1139; Q. Xiao, Y. Zhang and J. B. Wang, *Acc. Chem. Res*. 2013, **46**, 236; Q. Xiao, B. Wang, L. Tian, Y. Yang, J. Ma, Y. Zhang, S. Chen and J. Wang. *Angew. Chem. Int. Ed.* 2013, **52**, 9305; Z.-S. Chen, X.-H. Duan, P.-X. Zhou, S. Ali, J.-Y. Luo and Y.-M. Liang, *Angew. Chem. Int. Ed*. 2012, **51**, 1370; J. Barluenga and C. Valds, *Angew. Chem. Int. Ed.* 2011, **50**, 7486; K. Yang, J. Zhang, Y. Li, B. Cheng, L. Zhao and H. Zhai, *Org. Lett*., 2013, **15**, 808; H. Wang, X. Yang, Y. Liu and S. Bi, *Organometallics* 2014, **33**, 1404.

4 X.-L. Xie, S.-F. Zhu, J.-X. Guo, Y. Cai and Q.-L. Zhou, *Angew. Chem. Int. Ed*. 2014, **53**, 2978; Y. Zhu, X. Liu, S. Dong, Y. Zhou, W. Li, L. Lin and X. Feng, *Angew. Chem. Int. Ed*. 2014, **53**, 1636; G. Liu, J. Li, L. Qiu, L. Liu, G. Xu, B. Ma and J. Sun, *Org. Biomol. Chem*., 2013, **11**, 5998; D. Ding, G. Liu, G. Xu, J. Li, G. Wang and J. Sun, *Org. Biomol. Chem*., 2014, **12**, 2533.

5 D. Zhang, H. Qiu, L. Jiang, F. Lv, C. Ma and W. Hu, *Angew. Chem. Int. Ed*. 2013, **52**, 13356.

6 G. A. Moniz and J. L.Wood, *J. Am. Chem. Soc*. 2001, **123**, 5095.

7 Z. Li, V. Boyarskikh, J. H. Hansen, J. Autschbach, D. G. Musaev and H. M. L. Davies, *J. Am. Chem. Soc*. 2012, **134**, 15497.

8 F. Urabe, S. Miyamoto, K. Takahashi, J. Ishihara and S. Hatakeyama, *Org. Lett*., 2014, **16**, 1004.

9 X. Guo and W. Hu, *Acc. Chem. Res*., 2013, **46**, 2427.

10 F. Dénès, A. Pérez-Luna and F. Chemla, *Chem. Rev*. 2010, **110**, 2366; X. Zeng, *Chem. Rev*., 2013, **113**, 6864; R. Chinchilla and C. Nájera, *Chem. Rev*. 2014, **114**, 1783.

11 L.-B. Zhao, Z.-H. Guan, Y. Han, Y.-X. Xie, S. He, and Y.-M. Liang, *J. Org. Chem*. 2007, **72**, 10276.

12 L. Zhou, J. Ma, Y. Zhang and J. Wang, *Tetrahedron Lett*., 2011, **52** , 5484.

13 J. F. Briones and H. M. L. Davies, *J. Am. Chem. Soc*., 2012, **134**, 11916.

14 B. H. Lipshutz, *Chem. Rev*. 1986, **86**, 795; M. M. Faul and B. E. Huff, *Chem. Rev*. 2000, **100**, 2407.

15 Y. Wang, K. Zheng and R. Hong, *J. Am. Chem. Soc*., 2012, **134**, 4096; M. Akiyama,Y. Isoda, M. Nishimoto, A. Kobayashi, D. Togawa, N. Hirao, A. Kuboki and S. Ohira, *Tetrahedron Lett*., 2005, **46**, 7483.

16 CCDC 1035999 contains the supplementary crystallographic data for **8a**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.