Organic & Biomolecular Chemistry

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Thermal induced intramolecular [2 + 2] cycloaddition of allene-ACPs†

Cite this: *Org. Biomol. Chem.*, 2013, **11**, 3949

Received 2nd May 2013,
Accepted 4th May 2013

DOI: 10.1039/c3ob40911b

www.rsc.org/obc

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A facile synthetic method for preparation of bicyclo[4.2.0] nitrogen heterocycles has been developed *via* a thermal induced intramolecular [2 + 2] cycloaddition reaction of allene-ACPs. The DFT calculations indicate that this intramolecular cycloaddition proceeds in a concerted manner and a strained small ring is essential.

During the past few decades, allene chemistry has been revealed as an established member of the weaponry utilized in modern synthetic chemistry.[1] Cycloaddition reactions that occur without the use of additional reagents or catalysts and without creating any waste have attracted much attention in recent years as an ideal process in terms of atom economy.[2] The allene moiety represents an excellent partner for [2 + 2] cycloaddition with alkenes and alkynes, affording the corresponding cyclobutane and cyclobutene skeletons in a single step. The importance of the cyclobutane or cyclobutene containing compounds both as target molecules and as useful building blocks for the construction of more complex molecular structures has been widely demonstrated.[3] Thus far, the [2 + 2] cycloaddition of allenes has been studied upon photoirradiation[4,5] or under thermal-induced conditions.[6] More recently, transition metal catalyzed [2 + 2] cycloaddition of allenes has been also disclosed along with applications in natural product synthesis.[7]

Methylenecyclopropanes (MCPs), as highly strained but readily accessible molecules, can undergo a variety of ring-opening reactions in the presence of transition metals or Lewis acids because the relief of ring strain can provide a potent thermodynamic driving force.[8,9] These ring-opening processes can trigger various reactions of MCPs with other substrates, giving efficient access to enhanced molecular complexity in organic syntheses.[10] However, only a few examples of [2 + 2] cycloaddition of methylene- and alkylidenecyclopropanes have been developed so far. In 2006, Nakamura, Yamamoto and co-workers first reported silver salt-catalyzed or thermal induced [2 + 2] cycloaddition of imines to (alkoxymethylene)cyclopropanes, giving the desired cycloadducts in moderate to good yields.[11] They also disclosed the [2 + 2] cycloaddition reaction of (benzyloxymethylene)cyclopropane with alkylidenemalononitriles at ambient pressure upon heating, affording the corresponding cyclobutane derivatives in high yields.[12] Since Yamamoto and co-workers first reported the Pd-catalyzed chemical transformation of aniline-tethered alkylidenecyclopropanes,[13] recently we found a convenient synthetic method of functionalized pyrrolo[1,2-*a*]indoles *via* a thermal induced [3 + 2] cyclization reaction of aniline-tethered alkylidenecyclopropanes with aldehydes.[14] These interesting findings have encouraged us to further explore more useful transformations with these special MCPs or their derivatives such as *N*-(buta-2,3-dienyl)-2-(cyclopropylidenemethyl)anilines **1**, which could be easily prepared according to the previous literature (see the ESI†).[15]

We found that upon heating **1** at 110 °C in toluene, the bicyclo[4.2.0] nitrogen heterocycles **2** could be obtained in good yields *via* an intramolecular [2 + 2] cycloaddition process, affording a novel synthetic approach to the useful bicyclo [4.2.0] nitrogen heterocycles. In this paper, we wish to report the details of this interesting transformation.

We initially investigated the thermal induced [2 + 2] cycloaddition reaction of aniline-tethered alkylidenecyclopropane **1a** in different solvents at different temperatures and the results are summarized in Table 1. The reaction of **1a** in THF at 60 °C did not give any new product (Table 1, entry 1). Using toluene as the solvent and raising the reaction temperature to 80 °C, no reaction occurred (Table 1, entry 2). Raising the reaction temperature to 110 °C produced the corresponding [2 + 2] cycloaddition product **2a** in 80% yield (Table 1, entry 3). Its structure has been unambiguously determined by X-ray diffraction. Its

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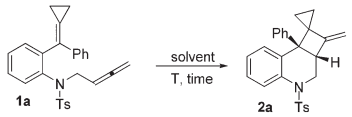
†Electronic supplementary information (ESI) available: Experimental procedures, characterization data of new compounds. CCDC 885057 and 895654. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c3ob40911b

Table 1 Optimization of the reaction conditions of thermal induced intramolecular [2 + 2] cycloaddition of **1a**



Entry	Solvent	*T*/°C	Time/h	Yield[a] (%)
1	THF	60	18	0
2	Toluene	80	12	0
3	Toluene	110	36	80
4	*ortho*-Xylene	130	12	89
5	*ortho*-Xylene	140	8	91

[a] Isolated yield.

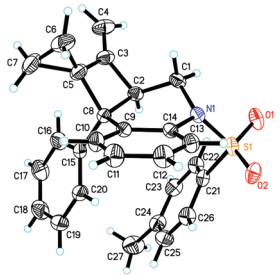


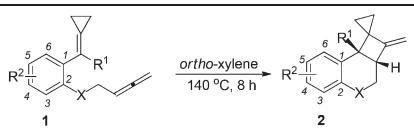
Fig. 1 ORTEP drawing of **2a**.

ORTEP drawing is presented in Fig. 1 and the corresponding CIF data have been presented in the ESI.†[16] Upon heating **1a** at 130 °C in *ortho*-xylene within 12 h, **2a** was obtained in 89% yield (Table 1, entry 4) and carrying out the reaction at 140 °C led to the formation of **2a** in 91% yield (Table 1, entry 5).

Under the optimized reaction conditions (0.1 mmol **1** in 1.0 mL *ortho*-xylene at 140 °C), we next examined the substrate scope of this reaction and the results are shown in Table 2. As for substrates **1b–1d**, in which R^1 = 4-MeC_6H_4, 4-ClC_6H_4, 4-FC_6H_4, the reactions proceeded smoothly to furnish the desired products **2b–2d** in 62–77% yields, regardless of whether they have electron-rich or electron-poor aromatic rings (Table 2, entries 1–3). When aromatic R^2 has a 5-Cl or a 4-MeO substituent, the reactions still proceeded efficiently to afford the desired products **2e** and **2f** in 67–81% yields (Table 2, entries 4 and 5). Changing X to NSO_2(*o*-$NO_2C_6H_4$), NNs, NBs, NSO_2Ph, NAc and NBz, the reactions also proceeded smoothly, furnishing the desired products **2g–2l** in 65–82% yields (Table 2, entries 6–11). When R^1 is a methyl group, the reaction took place very well to afford the desired product **2m** in 76% yield at 170 °C in 1,2-dichlorobenzene (Table 2, entry 12). However, **1n** could not be transformed to **2n** presumably due to the steric effect of the *ortho*-substituent in the aromatic R^1 group (Table 2, entry 13). Changing the R^1 group to a hydrogen atom or changing X to an oxygen atom, no reactions occurred (Table 2, entries 14 and 15). We also attempted to use $Au(PPh_3)Cl$, AgOTf, $Au(PPh_3)Cl$/AgOTf or $Pd(PPh_3)_4$ as a catalyst in this [2 + 2] cycloaddition reaction at lower temperature (about 80 °C), but no reaction occurred.

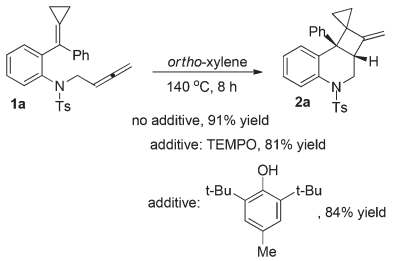
To gain more mechanistic insights into this intramolecular [2 + 2] cycloaddition reaction, several control experiments were performed as shown in Scheme 1. These control experiments confirmed that this cyclization reaction under the optimized conditions was unaffected by the addition of the radical inhibitors such as TEMPO (2.0 equiv.) and 2,6-di-*tert*-butyl-4-methylphenol (BHT) (2.0 equiv.), rendering unlikely the intervention of a radical pathway. However, considering that the short-life biradical intermediate in a solvent cage may not be

Table 2 Substrate scope of intramolecular [2 + 2] cycloaddition of *N*-(buta-2,3-dienyl)-2-(cyclopropylidenemethyl)anilines **1**[a]

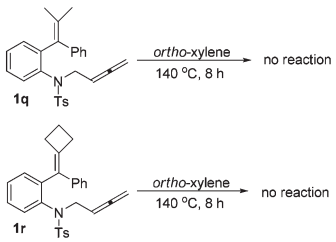


Entry	Substrate	R^1	R^2	X	Product 2	Yield[b] (%)
1	**1b**	4-MeC_6H_4	H	NTs	**2b**	77
2	**1c**	4-ClC_6H_4	H	NTs	**2c**	70
3	**1d**	4-FC_6H_4	H	NTs	**2d**	62
4	**1e**	C_6H_5	5-Cl	NTs	**2e**	67
5	**1f**	C_6H_5	4-MeO	NTs	**2f**	81
6	**1g**	C_6H_5	H	NSO_2(*o*-$NO_2C_6H_4$)	**2g**	78
7	**1h**	C_6H_5	H	NNs	**2h**	78
8	**1i**	C_6H_5	H	NBs	**2i**	65
9	**1j**	C_6H_5	H	NSO_2Ph	**2j**	73
10	**1k**	C_6H_5	H	NAc	**2k**	82
11	**1l**	C_6H_5	H	NBz	**2l**	82
12	**1m**	Me	H	NTs	**2m**	76[c]
13	**1n**	2-ClC_6H_4	5-Cl	NTs	**2n**	—
14	**1o**	H	H	NTs	**2o**	—
15	**1p**	C_6H_5	4-MeO	O	**2p**	—

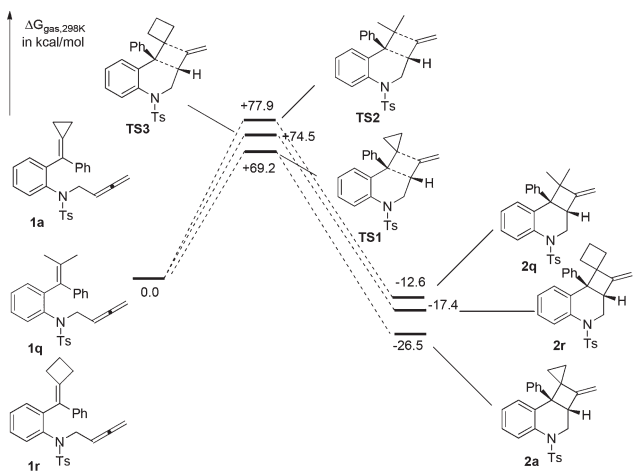
[a] Reaction conditions: 1 (0.1 mmol), *ortho*-xylene (1.0 mL), 140 °C, 8 h. [b] Isolated yield. [c] 1,2-Dicholorobenzene (1.0 mL), 170 °C, 8 h.



Scheme 1 Control experiments of **1a** in the presence of TEMPO or 2,6-di-*tert*-butyl-4-methylphenol.



Scheme 2 Control experiments of **1q** and **1r** under the standard conditions.

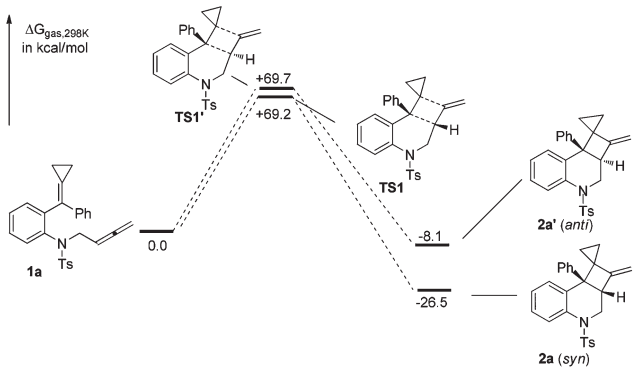


Scheme 3 A theoretical investigation of the reaction pathways.

captured by the radical inhibitors such as TEMPO and BHT, a free radical pathway cannot be completely ruled out at the present stage.

The other control experiments were also performed as shown in Scheme 2. These substrates **1q** and **1r**, which have no cyclopropane moiety, could not be converted into the desired products under the standard conditions, indicating that the strained small ring is essential in this intramolecular [2 + 2] cycloaddition reaction.

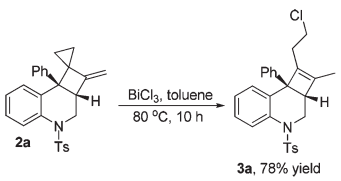
In order to further elucidate the mechanism of this intramolecular [2 + 2] cycloaddition reaction, we have theoretically investigated the reaction pathways as shown in Scheme 3 (for the details, see the ESI†). All calculations have been performed at the B3LYP/6-31G(d) level with the Gaussian 09 program.[17] The DFT calculations indicate that this intramolecular [2 + 2]



Scheme 4 A theoretical investigation of the formation of products **2a** and **2a′**.

cyclization reaction of **1a** is a concerted cycloaddition rather than a two-step reaction[11,12] with an energy barrier of 69.2 kcal mol^{-1}, which accounts for the fact that the reaction requires high temperature. For comparison, we also calculated the reaction pathways of **1q** and **1r**, respectively. The calculation results show that the reactions of **1q** and **1r** have higher energy barriers than that of **1a** by 8.7 kcal mol^{-1} and 5.3 kcal mol^{-1}, respectively, indicating that the reactions of **1q** and **1r** require higher temperature or harsh reaction conditions. In addition, the corresponding products **2q** and **2r** are thermodynamically less stable than product **2a** by 13.9 kcal mol^{-1} and 9.1 kcal mol^{-1}, respectively. These results may explain why we did not obtain the corresponding products **2q** and **2r** in the above experiments under the standard reaction conditions. Subsequently, we theoretically investigated the reaction pathway for the formation of *anti*-product **2a′**. The calculation results showed that the energy barrier (69.7 kcal mol^{-1}) is slightly higher than that for the formation of *syn*-product **2a** (69.2 kcal mol^{-1}) (Scheme 4). However, the *syn*-product **2a** is more stable than the *anti*-product **2a′** by 18.4 kcal mol^{-1}, which may account for the fact that the *syn*-product **2a** is exclusively obtained in our experiments.

The cyclobutane group of the obtained bicyclo[4.2.0] nitrogen heterocycles can be converted into the cyclobutene group along with the ring opening of cyclopropane. For example, product **2a** can be easily transformed into product **3a** in 78% yield by treatment of $BiCl_3$ (2.0 equiv.) in toluene at 80 °C for 10 h (Scheme 5). This is a new type of 2a,3,4,8b-tetrahydrocyclobuta[*c*]quinoline derivatives which have not been intensively studied so far. Its structure has been unambiguously determined by X-ray diffraction. Its ORTEP drawing and the corresponding CIF data have been presented in the ESI.†[16]



Scheme 5 Transformation of compound **2a** to **3a**.

In summary, a facile synthetic method for preparation of functionalized bicyclo[4.2.0] nitrogen heterocycles has been developed *via* a thermal induced intramolecular [2 + 2] cycloaddition reaction of *N*-(buta-2,3-dienyl)-2-(cyclopropylidenemethyl)anilines and the DFT calculations indicate that this intramolecular cycloaddition proceeds *via* a concerted manner and a strained small ring is essential. The products **2** and the transformed product **3a** have important structure motifs in organic and medicinal chemistry. The potential utilization and extension of the scope of this synthetic methodology are currently under investigation.

Acknowledgements

We thank the Shanghai Municipal Committee of Science and Technology (11JC1402600), the National Basic Research Program of China (973) (2009CB825300), and the National Natural Science Foundation of China (21072206, 20472096, 20872162, 20672127, 21102166, 20732008 and 21121062) for financial support.

Notes and references

1 (*a*) S. Ma, *Chem. Rev.*, 2005, **105**, 2829–2871; (*b*) D. J. Pasto, *Tetrahedron*, 1984, **40**, 2805–2827.

2 (*a*) B. M. Trost, *Acc. Chem. Res.*, 2002, **35**, 695–705; (*b*) B. M. Trost, *Science*, 1991, **254**, 1471–1477.

3 (*a*) E. Lee-Ruff and G. Mladenova, *Chem. Rev.*, 2003, **103**, 1449–1483; (*b*) J. C. Namyslo and D. Kaufmann, *Chem. Rev.*, 2003, **103**, 1485–1538.

4 B. Alcaide, P. Almendros and C. Aragoncillo, *Chem. Soc. Rev.*, 2010, **39**, 783–816.

5 S. A. Fleming, in *Molecular and Supramolecular Photochemistry: Synthetic Organic Photochemistry*, ed. A. G. Griesbeck and J. Mattay, Dekker, New York, 2005, vol. 12, pp. 141–160.

6 (*a*) M. R. Siebert, J. M. Osbourn, K. M. Brummond and D. J. Tantillo, *J. Am. Chem. Soc.*, 2010, **132**, 11952–11966; (*b*) H. Ohno, T. Mizutani, Y. Kadoh, K. Miyamura and T. Tanaka, *Angew. Chem., Int. Ed.*, 2005, **117**, 5243–5245; (*c*) H. Ohno, T. Mizutani, Y. Kadoh, A. Aso, K. Miyamura, N. Fujii and T. Tanaka, *J. Org. Chem.*, 2007, **72**, 4378–4389; (*d*) Y. Horino, M. Kimura, S. Tanaka, T. Okajima and Y. Tamaru, *Chem.–Eur. J.*, 2003, **9**, 2419–2438; (*e*) J. H. Lukas, A. P. Kouwenhoven and F. Baardman, *Angew. Chem., Int. Ed.*, 1975, **14**, 709–710.

7 (*a*) M. R. Luzung, P. Mauleón and F. D. Toste, *J. Am. Chem. Soc.*, 2007, **129**, 12402–12403; (*b*) M. Gulías, A. Collado, B. Trillo, F. López, E. Oñate, M. A. Esteruelas and J. L. Mascareñas, *J. Am. Chem. Soc.*, 2011, **133**, 7660–7663; (*c*) H. Faustino, P. Bernal, L. Castedo, F. López and J. L. Mascareñas, *Adv. Synth. Catal.*, 2012, **354**, 1658–1664.

8 For selected reviews, see: (*a*) N. C. Henry, M. Y. Wong, W. T. Chun and C. Y. Yu, *Chem. Rev.*, 1989, **89**, 165–198; (*b*) M. Rubin, M. Rubina and V. Gevorgyan, *Chem. Rev.*, 2007, **107**, 3117–3179; (*c*) I. Nakamura and Y. Yamamoto, *Adv. Synth. Catal.*, 2002, **344**, 111–129; (*d*) A. Brandi, S. Cicchi, F. M. Cordero and A. Goti, *Chem. Rev.*, 2003, **103**, 1213–1270; (*e*) M. Lautens, W. Klute and W. Tam, *Chem. Rev.*, 1996, **96**, 49–92; (*f*) M. S. Baird, in *Carbocyclic Three- and Four-Membered Ring Compounds*, ed. A. de Meijere, Thieme, Stuttgart, Germany, 1997, vol. E17d, pp. 2759–2779; (*g*) H. Maeda and K. Mizuno, *J. Synth. Org. Chem. Jpn.*, 2004, **62**, 1014–1025; (*h*) L.-X. Shao and M. Shi, *Curr. Org. Chem.*, 2007, **11**, 1135–1137; (*i*) A. de Meijere, S. I. Kozhushkov and A. F. Khlebnikov, *Top. Curr. Chem.*, 2000, **207**, 89–147; (*j*) A. de Meijere and S. I. A. Kozhushkov, *Eur. J. Org. Chem.*, 2000, 3809–3822; (*k*) A. de Meijere, S. I. Kozhushkov, T. Spath, M. von Seebach, S. Lohr, H. Nuske, T. Pohomann, M. Es-Sayed and S. Bräe, *Pure Appl. Chem.*, 2000, **72**, 1745–1756; (*l*) E. Smolensky, M. Kapon and M. S. Eisen, *Organometallics*, 2007, **26**, 4510–4527; (*m*) S. Purser, P. R. Moore, S. Swallow and V. Gouverneur, *Chem. Soc. Rev.*, 2008, **37**, 320–330; (*n*) M. Cheeseman, I. R. Davies, P. Axe, A. L. Johnson and S. D. Bull, *Org. Biomol. Chem.*, 2009, **7**, 3537–3548; (*o*) M. Shi, L.-X. Shao, J.-M. Lu, Y. Wei, K. Mizuno and H. Maeda, *Chem. Rev.*, 2010, **110**, 5883–5913; (*p*) H. Pellissier, *Tetrahedron*, 2010, **66**, 8341–8375; (*q*) G. Audran and H. Pellissier, *Adv. Synth. Catal.*, 2010, **352**, 575–608; (*r*) A. Masarwa and I. Marek, *Chem.–Eur. J.*, 2010, **16**, 9712–9721; (*s*) L. Yu and R. Guo, *Org. Prep. Proced. Int.*, 2011, **43**, 209–259; (*t*) M. Shi, J.-M. Lu, Y. Wei and L.-X. Shao, *Acc. Chem. Res.*, 2012, **45**, 641–652.

9 For recent contributions from our group and others, see: (*a*) M. Shi, L. P. Liu and J. Tang, *J. Am. Chem. Soc.*, 2006, **128**, 7430–7431; (*b*) L.-X. Shao, B. Xu, J.-W. Huang and M. Shi, *Chem.–Eur. J.*, 2006, **12**, 510–517; (*c*) M. Shi, B. Xu and J.-W. Huang, *Org. Lett.*, 2004, **6**, 1175–1178; (*d*) G.-Q. Tian and M. Shi, *Org. Lett.*, 2007, **9**, 4917–4920; (*e*) L.-X. Shao, Y.-X. Li and M. Shi, *Chem.–Eur. J.*, 2007, **13**, 862–869; (*f*) M. Lautens and W. Han, *J. Am. Chem. Soc.*, 2002, **124**, 6312–6316; (*g*) M. Lautens, W. Han and J. H. Liu, *J. Am. Chem. Soc.*, 2003, **125**, 4028–4029; (*h*) M. E. Scott and M. Lautens, *Org. Lett.*, 2005, **7**, 3045–3047; (*i*) L. Lu, G. Chen and S. Ma, *Org. Lett.*, 2006, **8**, 835–838; (*j*) S. Simaan, A. Masarwa, P. Bertus and I. Marek, *Angew. Chem., Int. Ed.*, 2006, **45**, 3963–3965; (*k*) A. Masarwa, A. Stanger and I. Marek, *Angew. Chem., Int. Ed.*, 2007, **46**, 8039–8042; (*l*) M. E. Scott, Y. Bethuel and M. Lautens, *J. Am. Chem. Soc.*, 2007, **129**, 1482–1483; (*m*) W. Li and M. Shi, *Tetrahedron*, 2007, **63**, 11016–11020; (*n*) X. Huang and Y. Yang, *Org. Lett.*, 2007, **9**, 1667–1670; (*o*) C. Taillier and M. Lautens, *Org. Lett.*, 2007, **9**, 591–593; (*p*) M. E. Scott and M. Lautens, *J. Org. Chem.*, 2008, **73**, 8154–8162; (*q*) S. Simaan, A. F. G. Goldberg, S. Rosset and I. Marek, *Chem.–Eur. J.*, 2010, **16**, 774–778; (*r*) X. Y. Tang and M. Shi, *Eur. J. Org. Chem.*, 2010, 4106–4110; (*s*) Z. Zhang and M. Shi, *Tetrahedron Lett.*, 2011, **52**, 6541–6544; (*t*) K. Chen, M. Jiang, Z. Zhang, Y. Wei and M. Shi, *Eur. J. Org. Chem.*, 2011, 7189–7193; (*u*) D. H. Zhang, Y. Wei and M. Shi,

Chem.–Eur. J., 2012, **18**, 7026–7029; (*v*) L. Ackermann, S. I. Kozhushkov and D. S. Yufit, *Chem.–Eur. J.*, 2012, **18**, 12068–12077.

10 (*a*) N. Tsukada, A. Shibuya, I. Nakamura and Y. Yamamoto, *J. Am. Chem. Soc.*, 1997, **119**, 8123–8124; (*b*) A. Fürstner and C. Aïsa, *J. Am. Chem. Soc.*, 2006, **128**, 6306–6307; (*c*) C. Aïsa and A. Fürstner, *J. Am. Chem. Soc.*, 2007, **129**, 14836–14837.

11 I. Nakamura, T. Nemoto, Y. Yamamoto and A. de Meijere, *Angew. Chem., Int. Ed.*, 2006, **45**, 5176–5179.

12 I. Nakamura, R. Nagata, T. Nemoto, M. Terada, Y. Yamamoto, T. Späth and A. de Meijere, *Eur. J. Org. Chem.*, 2007, 4479–4482.

13 A. I. Siriwardana, M. Kamada, I. Nakamura and Y. Yamamoto, *J. Org. Chem.*, 2005, **70**, 5932–5937.

14 K. Chen, Z. Zhang, Y. Wei and M. Shi, *Chem. Commun.*, 2012, **48**, 7696–7698.

15 (*a*) J. A. Stafford and J. E. McMurry, *Tetrahedron Lett.*, 1988, **29**, 2531–2534; (*b*) S. Husinec, M. Petkovic, V. Savic and M. Simic, *Synthesis*, 2012, 399–408.

16 The crystal data of **2a** and **3a** have been deposited in CCDC with numbers 885057 and 895654.

17 M. J. Frisch, *et al.*, *GAUSSIAN 09 (Revision A.01)*, Gaussian, Inc., Wallingford, CT, 2009.