

CrossMark
click for updatesCite this: *Chem. Sci.*, 2016, 7, 5934

Rhodium catalyzed diastereoselective synthesis of 2,2,3,3-tetrasubstituted indolines from *N*-sulfonyl-1,2,3-triazoles and *ortho*-vinylanilines†

Dongari Yadagiri, Angula Chandra Shekar Reddy and Pazhamalai Anbarasan*

An efficient diastereoselective rhodium catalyzed synthesis of indolines possessing two contiguous tetrasubstituted carbon centers has been achieved with good to excellent yields using *ortho*-vinylanilines and iminocarbenes derived from *N*-sulfonyl-1,2,3-triazoles. The reaction affords excellent *cis*-diastereoselectivity through the initial formation of a *N*-ylide followed by intramolecular trapping with unactivated alkenes *via* an ene-type reaction with a well-organized transition state, namely intramolecular carbenylative amination of alkenes. The developed transformation was further extended to the successful synthesis of tricyclic compounds, imidazoindolines, through reduction and hypervalent iodine mediated oxidative cyclization.

Received 8th March 2016

Accepted 19th May 2016

DOI: 10.1039/c6sc01075j

www.rsc.org/chemicalscience

Introduction

2,3-Multisubstituted indolines are widely present in various alkaloid natural products and therapeutically important molecules possessing diverse biological activities.¹ Representative examples include minfiensine, vindoline and strychnine, which exhibit significant anticancer activities (Fig. 1).² Hence, over several decades 2,3-multisubstituted indolines have attracted great synthetic interest.³

Most of the known traditional methods involve different functionalizations of (ox)indole derivatives.⁴ Recently, these methods have been replaced with transition metal catalyzed⁵ or free radical⁶ construction of indoline either through C–C or C–N bond forming reactions.⁷ Hu and co-workers⁸ utilized the intramolecular trapping of ammonium ylides, generated from diazo carbonyl compounds and an amine, with either a polar

double bond-like ketone or an activated alkene for the synthesis of 2,2,3-trisubstituted indolines. Although the intramolecular trapping of ammonium ylides with activated double bonds has been studied, trapping with an unactivated alkene, such as styrene which would afford 2,3-multisubstituted indolines, is very rare and highly desirable.

Over the past few years, *N*-sulfonyl-1,2,3-triazoles have emerged as a valuable resource for the generation of imino carbenes, a new reactive intermediate in organic synthesis.⁹ Unlike the traditional α -oxocarbenes, imino carbenes possess unique reactivity due to the presence of both an electrophilic carbene and nucleophilic nitrogen. This has been utilized in the construction of pharmaceutically important nitrogen based building blocks and heterocycles, through various carbene induced transformations.¹⁰ For instance, Fokin *et al.*¹¹ and Yoo *et al.*¹² demonstrated a formal stereoselective 1,3-insertion of rhodium imino carbenes into the N–H bond of amine derivatives through the generation of a *N*-ylide (Scheme 1).

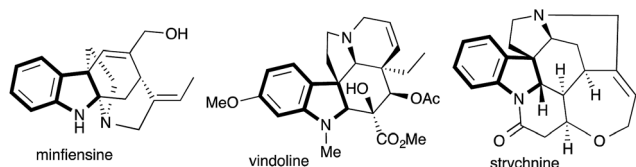
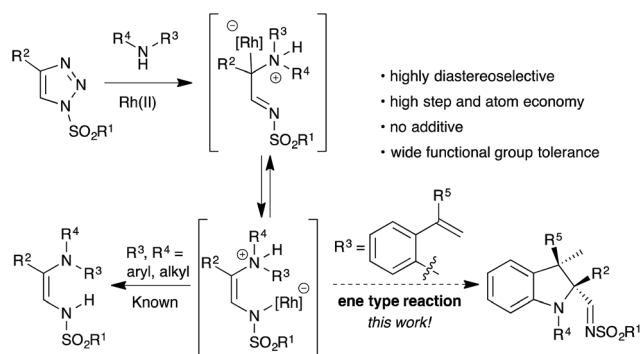


Fig. 1 Representative examples of indoline alkaloids.

Department of Chemistry, Indian Institute of Technology Madras, Chennai 600036, India. E-mail: anbarasansp@iitm.ac.in; Web: <http://chem.iitm.ac.in/faculty/anbarasan/profanbu/>

† Electronic supplementary information (ESI) available. CCDC 1438963 and 1438964. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c6sc01075j

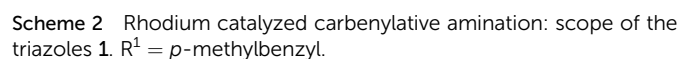


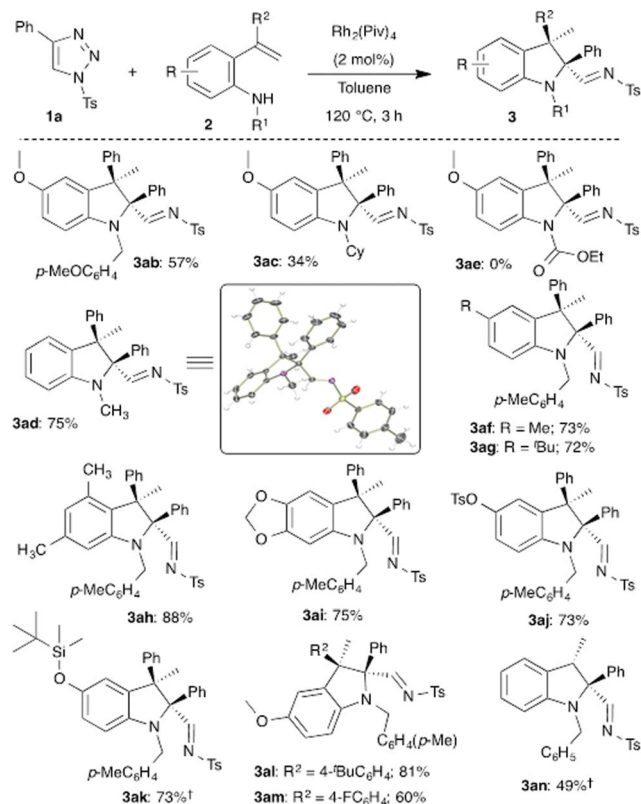
Scheme 1 Rhodium-catalyzed reactions of *N*-sulfonyl-1,2,3-triazoles.

Encouraged by this result, next, the influence of the catalyst was examined. Changing $\text{Rh}_2(\text{OAc})_4$ to a bulkier catalyst such as $\text{Rh}_2(\text{Oct})_4$ or $\text{Rh}_2(\text{Piv})_4$ showed a significant improvement in the yield (Table 1, entries 3–4). Next, screening of $\text{Rh}_2(\text{TBSP})_4$ and $\text{Rh}_2(\text{S-NTTL})_4$, chiral rhodium catalysts, under similar conditions afforded **3aa** in diminished yield (Table 1, entries 5–6). Unfortunately, no appreciable enantioselectivity was observed. Similarly, a low yield of **3aa** was observed with other solvents such as benzene and 1,2-DCE (Table 1, entries 7–8). Gratifyingly,

Next, the scope in relation to *ortho*-vinylanilines **2** was investigated using the optimized conditions. Initially, the effect of the substituent on the nitrogen was examined. *p*-Methoxybenzyl and methyl substituted aniline derivatives provided indolines **3ab** and **3ad** in good yield (Scheme 3). The structure and relative stereochemistry of indole **3ad** was unambiguously confirmed using single crystal X-ray analysis.¹⁴ A sterically

^a Isolated yields. ^b 1 mol% of Rh₂(Piv)₄. R = *p*-methylbenzyl.

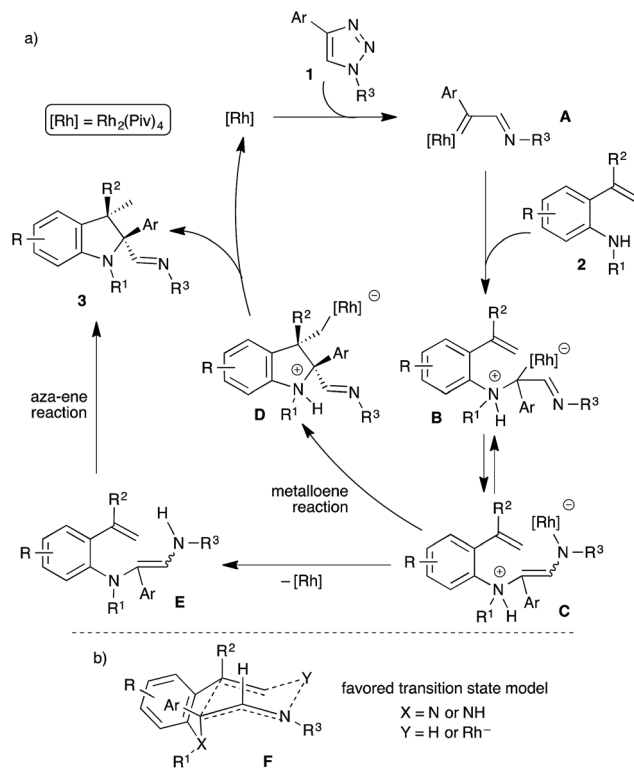




Scheme 3 Rhodium catalyzed carbenylative amination: scope of the *o*-vinylanilines **2**. †NMR yield.

hindered cyclohexyl substituted aniline provided **3ac** in relatively low yield. Unfortunately, having an electron-withdrawing substituent on the nitrogen did not afford the expected product **3ae**. Subsequently, screening of different substituents on the aromatic ring of the aniline was carried out. Electronically and sterically different substituents on the aromatic ring were well tolerated, especially, reactive functional groups such as acetal, sulfonate and silyl ether groups were untouched under the reaction conditions, and led to the formation of the corresponding indolines (**3af–3ak**) with good to excellent yields. Different C3-substituted indolines **3al** and **3am** were also obtained in 81% and 60% yield, respectively, from the corresponding alkene derivative. Furthermore, 2,2,3-trisubstituted indoline **3an** was also synthesized, employing the present method, in 49% yield with excellent diastereoselectivity from a simple vinyl substituted aniline.

Diastereoselective formation of the tetrasubstituted indolines can be explained with the following plausible mechanism (Scheme 4a). The reaction starts with the generation of rhodium carbenoid **A** from the *N*-sulfonyl-1,2,3-triazole using the rhodium catalyst,⁹ which on subsequent reaction with the *o*-vinylaniline **2** would afford the ammonium ylide **B**. A 1,3-rhodium shift in the ammonium ylide **B** would produce the zwitterion **C**. Formation of indoline **3** from **C** could be rationalized with two pathways: (1) a rhodium promoted intramolecular metalloene¹⁵ reaction of **C** would generate the cyclized intermediate **D** with high diastereoselectivity, and

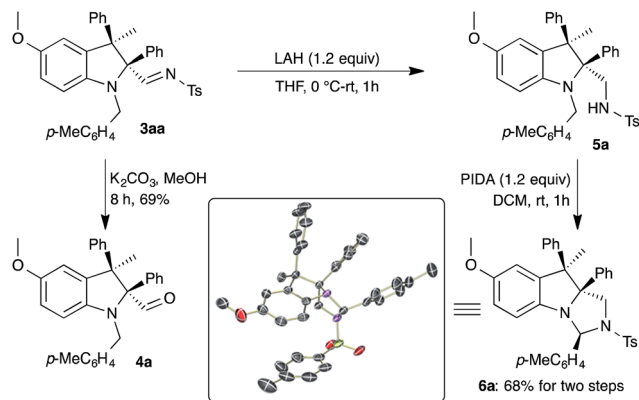


Scheme 4 (a) Plausible mechanism; (b) proposed transition state for the ene-type reaction.

a following protonation of rhodium species **D** would furnish the product **3** along with regeneration of the rhodium catalyst which continues the catalytic cycle. (2) Initial protonation of rhodium species **C** to provide enamine **E** followed by an intramolecular aza-ene reaction¹⁶ would afford the observed product **3**. To investigate the feasible pathways, various attempts were made to isolate the enamine **E**. Unfortunately, all our attempts either resulted in no reaction or the formation of product **3**, formation of enamine **E** was not observed. Hence, at this point both the pathways are equally possible. As can be seen in Scheme 4a, the *cis*-diastereoselectivity possibly arises from an intramolecular ene-type reaction. To explain the observed stereochemistry, a plausible transition state model is proposed (Scheme 4b). The 1,3-rhodium shift or the formation of an enamine through intramolecular protonation could afford preferentially the *Z*-alkene.¹¹ Subsequent cyclization through a six membered ene-type transition state **F** is highly favourable, where intramolecular interactions between [Rh] or H and the alkene would facilitate the cyclization and the *cis*-diastereoisomer could be obtained.

After successful demonstration of the generality of the carbenylative amination, synthetic applications of the substituted indolines **3** were revealed *via* the manifestation of readily available functional groups. Reaction of **3aa** with K₂CO₃ and methanol afforded the corresponding aldehyde **4a** in 69% yield (Scheme 5). On the other hand, conversion of the imine moiety in **3aa** to a sulfonamide (**5a**) was achieved through reduction with LAH. Next, a hypervalent iodine mediated cyclization¹⁷ of





Scheme 5 Synthesis of imidazoindoline 6a.

5a was envisaged for the synthesis of a nitrogen based tricyclic compound. The reaction of sulfonamide **5a** with (diacetoxyiodo) benzene (PIDA) in DCM at room temperature afforded imidazoindoline **6a** in 68% yield over two steps, as a single diastereomer. The formation of **6a** can be explained as due to oxidation of the tertiary amine in **5a** with PIDA to provide an iminium ion followed by cyclization. The structure of **6a** was unambiguously confirmed using single crystal X-ray analysis¹⁸ (see ESI†).

The developed two-step protocol was subsequently applied to functionally different indolines **3**. In general, all of the indolines that were examined afforded the imidazoindolines **6b–k** in good yield under the two-step reduction and oxidative cyclization sequence (Scheme 6). It is important to note that the oxidative cyclization tolerates oxidation prone electron rich

arene and thiophene substituents as well as electron deficient arenes, and led to the synthesis of the corresponding imidazoindolines **6d–j** in good yield. Interestingly, replacement of *N*-Bn with *N*-Me also provided the imidazoindoline **6k** in 69% yield.

Conclusions

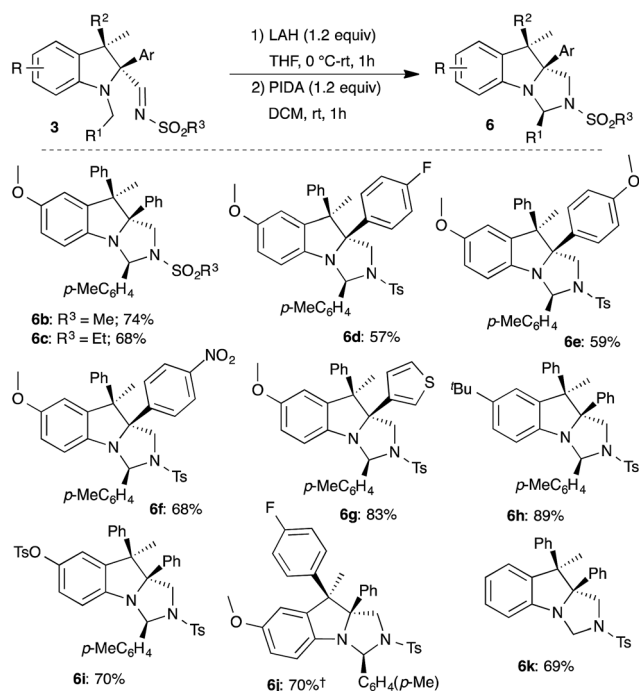
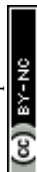
In conclusion, an efficient rhodium catalyzed formal carbenylative amination of *ortho*-vinylanilines with iminocarbenes derived from *N*-sulfonyl-1,2,3-triazoles has been accomplished for the diastereoselective synthesis of indolines possessing two contiguous tetrasubstituted carbon centers. The reaction affords excellent *cis*-diastereoselectivity through the initial formation of a *N*-ylide, followed by trapping with unactivated alkenes *via* an ene-type reaction with a well-organized transition state. The present method tolerates various reactive functional groups, which allows the synthesis of various indoline derivatives in good to excellent yield. The developed transformation was further extended to the successful synthesis of tricyclic compounds, imidazoindolines, through reduction and hyper-valent iodine mediated oxidative cyclization.

Acknowledgements

We thank the Department of Science and Technology (DST), New Delhi, India (Project No. SR/S1/OC-48/2012) for funding this work. DY thanks IITM and ACSR thanks CSIR for fellowships. We also thank Mr Ramkumar for single crystal analysis support.

Notes and references

- (a) E. Fattorusso and O. Tagliatela-Scafati, *Modern Alkaloids: Structure, Isolation, Synthesis, and Biology*, 2008; (b) D. Crich and A. Banerjee, *Acc. Chem. Res.*, 2007, **40**, 151–161; (c) M. A. Jordan and L. Wilson, *Nat. Rev. Cancer*, 2004, **4**, 253–265.
- (a) A. Ramirez and S. Garcia-Rubio, *Curr. Med. Chem.*, 2003, **10**, 1891–1915; (b) J. Liu, J. Zhu, L. Tang, W. Wen, S. Lv and R. Yu, *World J. Microbiol. Biotechnol.*, 2014, **30**, 175–180; (c) M. Serasanambati, S. R. Chilakapati, P. K. Manikonda, J. R. Kanala and D. R. Chilakapati, *Nat. Prod. Res.*, 2014, **29**, 484–490; (d) J. Chen, Y. Qu, D. Wang, P. Peng, H. Cai, Y. Gao, Z. Chen and B. Cai, *Molecules*, 2014, **19**, 4395–4408.
- D. Zhang, H. Song and Y. Qin, *Acc. Chem. Res.*, 2011, **44**, 447–457.
- (a) Q. Cai and S.-L. You, *Org. Lett.*, 2012, **14**, 3040–3043; (b) S. Kirchberg, R. Frohlich and A. Studer, *Angew. Chem., Int. Ed.*, 2009, **48**, 4235–4238; (c) S. Beaumont, V. Pons, P. Retailleau, R. H. Dodd and P. Dauban, *Angew. Chem., Int. Ed.*, 2010, **49**, 1634–1637.
- (a) A. Minatti and S. L. Buchwald, *Org. Lett.*, 2008, **10**, 2721–2724; (b) A. B. Dounay, P. G. Humphreys, L. E. Overman and A. D. Wroblewski, *J. Am. Chem. Soc.*, 2008, **130**, 5368–5377; (c) Y. Yasui, T. Kinugawa and Y. Takemoto, *Chem. Commun.*, 2009, 4275; (d) T. Watanabe, S. Oishi, N. Fujii and

Scheme 6 Synthesis of imidazoindolines **6**. ¹H NMR yield.

- H. Ohno, *Org. Lett.*, 2008, **10**, 1759–1762; (e) D. M. Schultz and J. P. Wolfe, *Org. Lett.*, 2010, **12**, 1028–1031.
- 6 (a) F. Brucelle and P. Renaud, *J. Org. Chem.*, 2013, **78**, 6245–6252; (b) R. Viswanathan, C. R. Smith, E. N. Prabhakaran and J. N. Johnston, *J. Org. Chem.*, 2008, **73**, 3040–3046; (c) D. L. J. Clive, J. Peng, S. P. Fletcher, V. E. Ziffle and D. Wingert, *J. Org. Chem.*, 2008, **73**, 2330–2344; (d) H. Fuwa and M. Sasaki, *Org. Lett.*, 2007, **9**, 3347–3350.
- 7 (a) C. D. Gilmore, K. M. Allan and B. M. Stoltz, *J. Am. Chem. Soc.*, 2008, **130**, 1558–1559; (b) Z. Wang, W. Wan, H. Jiang and J. Hao, *J. Org. Chem.*, 2007, **72**, 9364–9367; (c) J. R. Dunetz and R. L. Danheiser, *J. Am. Chem. Soc.*, 2005, **127**, 5776–5777.
- 8 (a) C. Jing, D. Xing and W. Hu, *Chem. Commun.*, 2014, **50**, 951–953; (b) L. Jiang, R. Xu, Z. Kang, Y. Feng, F. Sun and W. Hu, *J. Org. Chem.*, 2014, **79**, 8440–8446.
- 9 (a) P. Anbarasan, D. Yadagiri and S. Rajasekar, *Synthesis*, 2014, **46**, 3004–3023; (b) H. M. L. Davies and J. S. Alford, *Chem. Soc. Rev.*, 2014, **43**, 5151–5162.
- 10 (a) T. Miura, Y. Fujimoto, Y. Funakoshi and M. Murakami, *Angew. Chem., Int. Ed.*, 2015, **54**, 9967–9970; (b) Y. Yang, M.-B. Zhou, X.-H. Ouyang, R. Pi, R.-J. Song and J.-H. Li, *Angew. Chem., Int. Ed.*, 2015, **54**, 6595–6599; (c) Y. Jiang, X.-Y. Tang and M. Shi, *Chem. Commun.*, 2015, **51**, 2122–2125; (d) Y. Wang, X. Lei and Y. Tang, *Chem. Commun.*, 2015, **51**, 4507–4510; (e) J. Pospech, R. Ferraccioli, H. Neumann and M. Beller, *Chem.-Asian J.*, 2015, **10**, 2624–2630; (f) Y. Shi, X. Yu and C.-Y. Li, *Eur. J. Org. Chem.*, 2015, 6429–6433; (g) J. He, Z. Man, Y. Shi and C.-Y. Li, *J. Org. Chem.*, 2015, **80**, 4816–4823; (h) B. Seo, W. H. Jeon, J. Kim, S. Kim and P. H. Lee, *J. Org. Chem.*, 2015, **80**, 722–732; (i) S. Shin, Y. Park, C.-E. Kim, J.-Y. Son and P. H. Lee, *J. Org. Chem.*, 2015, **80**, 5859–5869; (j) V. N. G. Lindsay, H. M. F. Viart and R. Sarpong, *J. Am. Chem. Soc.*, 2015, **137**, 8368–8371; (k) M.-H. Shen, Y.-P. Pan, Z.-H. Jia, X.-T. Ren, P. Zhang and H.-D. Xu, *Org. Biomol. Chem.*, 2015, **13**, 4851–4854; (l) D. J. Jung, H. J. Jeon, J. H. Lee and S.-g. Lee, *Org. Lett.*, 2015, **17**, 3498–3501; (m) E. Lee, T. Ryu, E. Shin, J.-Y. Son, W. Choi and P. H. Lee, *Org. Lett.*, 2015, **17**, 2470–2473; (n) T. Miura, Y. Funakoshi, Y. Fujimoto, J. Nakahashi and M. Murakami, *Org. Lett.*, 2015, **17**, 2454–2457; (o) H.-D. Xu, K. Xu, H. Zhou, Z.-H. Jia, H. Wu, X.-L. Lu and M.-H. Shen, *Synthesis*, 2015, **47**, 641–646; (p) Y. Jiang, R. Sun, Q. Wang, X.-Y. Tang and M. Shi, *Chem. Commun.*, 2015, **51**, 16968–16971; (q) S. Chuprakov, S. W. Kwok, L. Zhang, L. Lercher and V. V. Fokin, *J. Am. Chem. Soc.*, 2009, **131**, 18034–18035; (r) N. Grimster, L. Zhang and V. V. Fokin, *J. Am. Chem. Soc.*, 2010, **132**, 2510–2511; (s) J. C. Culhane and V. V. Fokin, *Org. Lett.*, 2011, **13**, 4578–4580; (t) M. Zibinsky and V. V. Fokin, *Org. Lett.*, 2011, **13**, 4870–4872; (u) J. S. Alford and H. M. L. Davies, *Org. Lett.*, 2012, **14**, 6020–6023.
- 11 S. Chuprakov, B. T. Worrell, N. Selander, R. K. Sit and V. V. Fokin, *J. Am. Chem. Soc.*, 2014, **136**, 195–202.
- 12 D. J. Lee and E. J. Yoo, *Org. Lett.*, 2015, **17**, 1830–1833.
- 13 (a) S. Rajasekar, D. Yadagiri and P. Anbarasan, *Chem.-Eur. J.*, 2015, **21**, 17079–17084; (b) D. Yadagiri and P. Anbarasan, *Chem. Sci.*, 2015, **6**, 5847–5852; (c) D. Yadagiri and P. Anbarasan, *Chem.-Eur. J.*, 2013, **19**, 15115–15119; (d) D. Yadagiri and P. Anbarasan, *Org. Lett.*, 2014, **16**, 2510–2513; (e) S. Rajasekar and P. Anbarasan, *J. Org. Chem.*, 2014, **79**, 8428–8434.
- 14 CCDC 1438964† contains supplementary crystallographic data for the compound **3ad**.
- 15 (a) W. Oppolzer, *Angew. Chem., Int. Ed.*, 1989, **28**, 38–52; (b) T. J. J. Muller, in *Comprehensive Organic Synthesis II*, Elsevier, Amsterdam, 2nd edn, 2014, pp. 1–65.
- 16 (a) W. Tan, B.-X. Du, X. Li, X. Zhu, F. Shi and S.-J. Tu, *J. Org. Chem.*, 2014, **79**, 4635–4643; (b) W. Adam and O. Krebs, *Chem. Rev.*, 2003, **103**, 4131–4146; (c) J.-H. Zhang, M.-X. Wang and Z.-T. Huang, *Tetrahedron Lett.*, 1998, **39**, 9237–9240; (d) J.-H. Zhang, M.-X. Wang and Z.-T. Huang, *J. Chem. Res., Synop.*, 1998, 486–487.
- 17 (a) R. Samanta, K. Matcha and A. P. Antonchick, *Eur. J. Org. Chem.*, 2013, 5769–5804; (b) F. V. Singh and T. Wirth, *Chem.-Asian J.*, 2014, **9**, 950–971.
- 18 CCDC 1438963† contains supplementary crystallographic data for the compound **6a**.

