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Divergent synthesis of indole-fused polycycles via Rh(II)-catalyzed intramolecular [3 + 2] cycloaddition and C–H functionalization of indolyltriazoles†

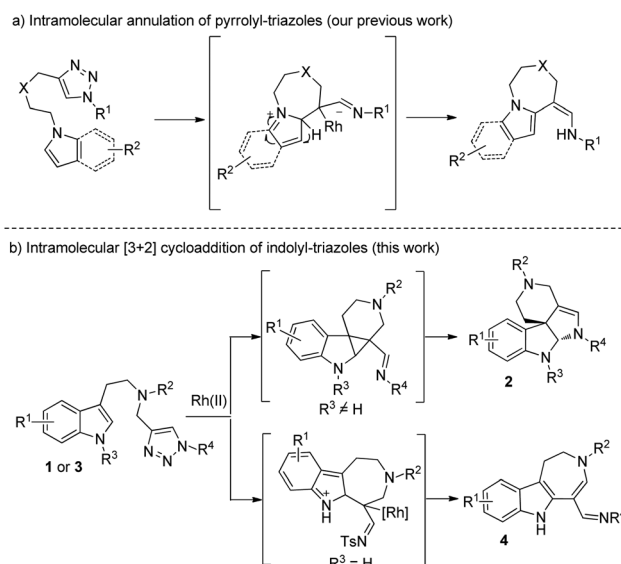
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Rh(II)-catalyzed divergent synthesis of polycyclic indolines and azepino[4,5-*b*]indoles through intramolecular [3 + 2] cycloaddition and C–H functionalization of indoles with *N*-sulfonyl 1,2,3-triazoles is described. The reaction pathways are controlled by the substituent type of indole.

Indole derivatives present a key structural motif in many natural products and medicinal molecules, which exhibit a wide range of promising biological activities.¹ In particular, indole-fused *N*-heterocycles, such as indoline² and azepino[4,5-*b*]indole³ derivatives, are most attractive due to their wide existence in a number of natural products and pharmaceutical reagents. Thus, many synthetic methods have been developed to construct these compounds in recent years.⁴ Because a sequential reaction to synthesize such a complex and useful motif is of great importance, we herein disclose a divergent synthesis of polycyclic indolines and azepino[4,5-*b*]indoles from readily available indolyltriazoles. The reaction pathways are switchable according to different substituents at the indole N1 position: if the nitrogen is protected, the reaction goes through a formal [3 + 2] cycloaddition to yield polycyclic indolines **2**, while for the non-protected indole substrate, the reaction delivers azepino[4,5-*b*]indoles **3** via C–H functionalization.

N-Sulfonyl-1,2,3-triazoles, which can be simply prepared from terminal alkynes by copper-catalyzed 1,3-dipolar cycloaddition with *N*-sulfonyl azides, have recently attracted much attention.⁵ As reported by Fokin, Gevorgyan, Murakami and Davies, *N*-sulfonyl triazoles, as precursors of α -imino metal carbenes, can be effectively decomposed in the presence of a suitable metal catalyst⁶ and undergo various interesting and useful transformations, such as cyclopropanation,⁷ transannulation,⁸ C–H bond insertion,⁹ X–H (X = heteroatoms) bond insertions¹⁰ and other novel reactions based on the inherent

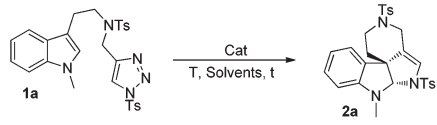
properties of metal carbenes.¹¹ Previously, we^{9b} also developed an intramolecular annulation of 1-sulfonyl-1,2,3-triazoles with pyrroles and indoles to construct indole fused azepine derivatives (Scheme 1a). To continue our research interest in indole chemistry, we envisaged that 4-methyl-*N*-(2-(1-methyl-1*H*-indol-3-yl)ethyl)-*N*-((1-tosyl-1*H*-1,2,3-triazol-4-yl)methyl)benzenesulfonamide **1a** could either undergo intramolecular [3 + 2] cycloaddition/ring expansion or C–H functionalization in the presence of a dirhodium complex (Scheme 1b). To our delight, indoline derivatives **2** were obtained after treatment of **1** (R^3 is not H) with the rhodium catalyst. Moreover, for non-protected substrates ($R^3 = H$), the reaction gave the desired azepine



Scheme 1 Previous work and this work.

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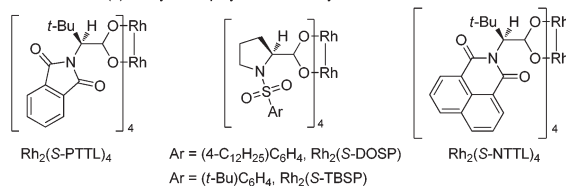
† Electronic supplementary information (ESI) available: Experimental procedures and characterization data of new compounds. CCDC 1018373 and 1018374. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c5qo00216h

Table 1 Optimization of the reaction conditions of rhodium-catalyzed tandem reaction of **1a**


Entry ^a	Cat.	T (°C)	Solvent	Time	Yield ^b (%) 2a
1	Rh ₂ (Piv) ₄	60	DCM	3 h	26
2	Rh ₂ (Piv) ₄	Rt	DCM	24 h	21
3	Rh ₂ (Piv) ₄	80	DCM	3 h	30
4	Rh ₂ (Piv) ₄	80	DCE	3 h	8 ^d
5	Rh ₂ (Piv) ₄	110	DCE	3 h	Trace ^d
6	Rh ₂ (Oct) ₄	80	DCM	3 h	41
7	Rh ₂ (Oct) ₄	120	DCE	3 h	Trace ^d
8	Rh ₂ (esp) ₂	80	DCM	3 h	35
9	Rh ₂ (OAc) ₄	80	DCM	3 h	13 ^d
10	Rh ₂ (S-PTTL) ₄	75	DCM	3 h	75
11	Rh ₂ (S-NTTL) ₄	75	DCM	3 h	71
12	Rh ₂ S-DOSP) ₄	75	DCM	3 h	28
13	Rh ₂ S-TBSP) ₄	75	DCM	3 h	48
14 ^c	Rh ₂ (S-PTTL) ₄	75	Cyclohexane	3 h	65
15 ^c	Rh₂(S-PTTL)₄	75	Cyclohexane : DCM = 5 : 1	3 h	77 (67)^e
16 ^f	—	75	DCM	3 h	—

^a Reaction conditions: **1a** (0.2 mmol), and Rh cat. (2 mol%) were stirred in 2 ml of solvent. ^b Yields of isolated product. ^c The solvent was 6 ml. ^d Tested by ¹H NMR. ^e 2.0 mmol scale, 1.1 g of **1a** (67% yield). ^f When the reaction was conducted without a catalyst, no reaction took place.

Chiral rhodium(II) catalysts employed in this study:



derivatives **4** after C–H functionalization. The structures of **2a** and **4a** were unambiguously determined by X-ray diffraction.¹²

To optimize the reaction conditions, we started to screen different Rh(II) complexes, temperature as well as solvents, using **1a** as the model substrate. As can be seen from Table 1, when the reaction was catalyzed by Rh₂(Piv)₄ (2 mol%) in DCM (dichloromethane) for 3 h at different temperatures, the corresponding product **2a** was obtained in 21–30% yields (Table 1, entries 1–3). On changing the solvent to DCE and performing the reaction at 80 °C, the yield of **2a** was only 8%, and by further increasing the reaction temperature to 110 °C, the reaction was very complex with no desired product detected (Table 1, entries 4–5). Other achiral dirhodium tetracarboxylates were also investigated, and all of these catalysts turned out to be of poor efficiency to this reaction (Table 1, entries 6–9). Then, we tried several chiral dirhodium complexes, which were proved to give better results than achiral catalysts in some reported cases.^{11a,8h} To our delight, when Rh₂(S-PTTL)₄ was employed as a catalyst, the yield of **2a** increased to 75% (Table 1, entry 10). Other chiral rhodium catalysts such as Rh₂(S-NTTL), Rh₂(S-DOSP)₄ and Rh₂(S-TBSP)₄ were found less effective than Rh₂(S-PTTL)₄, affording the desired product **2a** in 28–71% yields, respectively (Table 1, entries 11–13). Next,

solvent effects were tested and it was found that using a mixed solvent of cyclohexane and DCM (5 : 1) would benefit the formation of **2a** (77%) (Table 1, entries 14 and 15). The reaction did not take place without a catalyst under otherwise identical standard reaction conditions (Table 1, entry 16). In addition, the reaction of **1a** could also run at a gram scale and the corresponding product of **2a** was obtained in 67% yield (Table 1, entry 15).

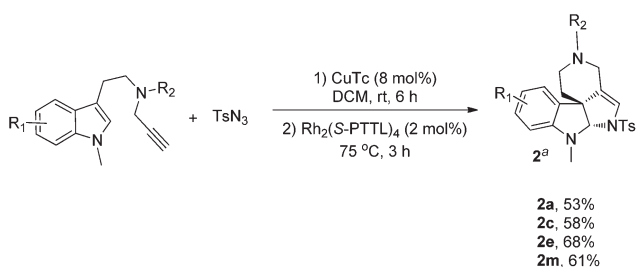
With the optimized reaction conditions in hand, we next investigated the scope and limitations of this reaction and the results are summarized in Table 2. As for substrates **1b–1g**, the reactions proceeded smoothly to afford the corresponding products **2b–2g** in good yields, and the electronic properties of the substituents on indole didn't have significant influence on the reaction outcomes. When indole was protected by ethyl, *n*-butyl or allyl groups (R³), the corresponding products **2h–2j** were obtained in 53–79% yields. Other sulfonyl substituents (R²) were also well tolerated and the desired products **2k–2n** were delivered in 62–92% yields. Moreover, changing the protecting group of triazole (R⁴) instead of Ts, such as Ms, the reaction also went on well to give **2o** in 66% yield.

As a further study of the cycloaddition reaction, we next conducted a one-pot synthesis of the products **2** from terminal

Table 2 Scope of the reaction for the synthesis of **2**^a

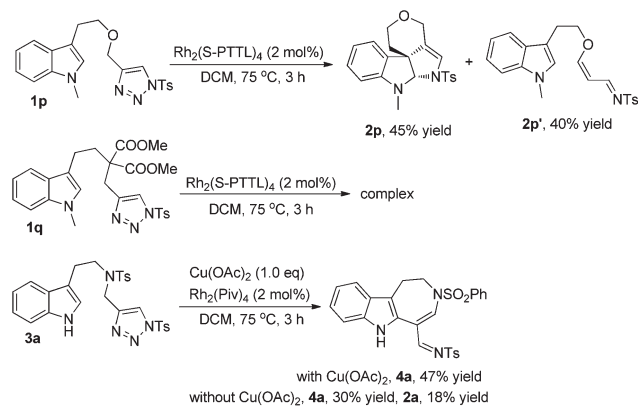
^a Reaction conditions: 0.2 mmol of **1** and $\text{Rh}_2(\text{S-PTTL})_4$ (2 mol%) were stirred in dry solvent (cyclohexane : DCM = 5 : 1) in a 10 ml sealed tube.

^b Yields of isolated products.



Scheme 2 One-pot synthesis of polycyclic pyrroloindolines. Reaction conditions: (1) alkyne (0.2 mmol), TsN_3 (0.2 mmol) and CuTc (8 mol%) were stirred in 2 mL of DCM at rt for 6 h. (2) $\text{Rh}_2(\text{S-PTTL})_4$ (2 mol%) was added and the reaction mixture was heated at 75 °C for 3 h. ^aIsolated yield.

alkyne (Scheme 2). On treatment of alkynes (0.2 mmol) with TsN_3 (0.2 mmol) in the presence of CuTc (0.016 mmol) in DCM (2.0 mL) at rt under Ar, a triazole intermediate was



Scheme 3 Further substrate scope study.

formed, then $\text{Rh}_2(\text{S-PTTL})_4$ was added under Ar and the reaction was heated for 3 h at 75 °C. After completion, the reaction mixture was directly subjected to flash column chromatography to give the products **2a**, **2b**, **2e** and **2m** in moderate yields.

To extend the substrate scope, we also examined other types of indolytriazoles. As can be seen from Scheme 3, when oxygen tethered tryptopholtriazole **1p** was treated with $\text{Rh}_2(\text{S-PTTL})_4$ in DCM at 75 °C for 3 h, the desired spiro derivative **2p** was obtained in 45% yield as well as the acrolein imine byproduct **2p'** derived from β -H elimination in 40% yield. However, when substrate **1q** with a *gem*-diester linker was treated under the standard reaction conditions, the reaction became very complex and no desired product was observed as tested by ¹H NMR of the crude reaction mixture. Interestingly, when indoly-triazole **3a** with a free NH group ($\text{R}^3 = \text{H}$) was employed as the substrate, the reaction gave azepine derivative **4a** in 47% yield upon heating in DCM at 75 °C for 3 h when 1.0 eq. of $\text{Cu}(\text{OAc})_2$ was added to the reaction mixture. In comparison, the reaction gave both **4a** and **2a** in 30% and 18% yields without $\text{Cu}(\text{OAc})_2$, indicating that the copper salt plays an important role in controlling the reaction selectivity.

The formation of **4a** stimulated our interest to further investigate the scope and limitations of this reaction. After screening the reaction conditions, it was found that using 2 mol% $\text{Rh}_2(\text{Piv})_4$ and 1.0 eq. $\text{Cu}(\text{OAc})_2$ as additives, the reaction gave the best results (for more information, please see Table S1 in the ESI[†]). As can be seen from Table 3, the corresponding azepine derivatives **4b–4e** could be obtained in 20–43% yields. The relatively low yield of the reaction might be due to the instability of the products.¹³

A plausible mechanism is outlined in Scheme 4. Initially, denitrogenation of **1** in the presence of a $\text{Rh}(\text{II})$ complex gives an azavinyl carbene intermediate **A**. According to Davies's report,^{7f} if the indole substrate is protected by an alkyl group, then the cyclopropanation of the indole double bond by rhodium carbene takes place to yield intermediate **B**, which then undergoes ring expansion to give intermediate **D**. After ring closure, the final product **2** is obtained. On the other

Table 3 Scope of the reaction for the synthesis of **4**^a

^a Reaction conditions: triazole (0.2 mmol), Cu (OAc) (0.2 mmol) and Rh(II) (0.2 mol%) were added to a flask, then DCM was added under Ar and the reaction mixture was heated at 75 °C for 3 h. ^b Isolated yield.

**Scheme 4** A proposed mechanism.

hand, if R^3 is a proton, a Friedel–Crafts reaction occurs, giving product **4** instead *via* intermediate **C**. Intramolecular H bonding may exist between the indole N–H and the imine group, which could stabilize intermediate **C**, therefore, the formation of **4** is more favored than **2**. When $\text{Cu}(\text{OAc})_2$ is added to the reaction system, the interaction between copper and imine is even more stronger than the H bonding to stabilize intermediate **C**, giving higher selectivity.

In summary, we have developed a novel and effective method to synthesize a series of polycyclic pyrroloindolines and azepino[4,5-*b*]indoles *via* rhodium(II) catalyzed intramolecular [3 + 2] cycloaddition or C–H functionalization of indolyltriazoles. The reaction pathways are dependent on the substituents at the indole N1 position: when R^3 is an alkyl group, the reaction delivers pyrroloindolines, while non-protected substrates result in azepino[4,5-*b*]indoles. Further investigations to extend the substrate scope as well as to examine the mechanistic details more extensively are currently underway in our laboratory.

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Notes and references

- (a) R. J. Sundberg, *The Chemistry of Indoles*, Academic Press, New York, 1970; (b) *Alkaloids Chemical and Biological Perspectives*, ed. S. W. Pelletier, Wiley-Interscience, New York, 1983, vol. 4, p. 211; (c) R. J. Sundberg, *Indoles*, Academic Press, San Diego, 1996; (d) J. P. Michael, *Nat. Prod. Rep.*, 1998, **15**, 571; (e) D. J. Faulkner, *Nat. Prod. Rep.*, 1999, **16**, 155–198; (f) M. Lounasmaa and A. Tolvanen, *Nat. Prod. Rep.*, 2000, **17**, 175; (g) S. Cacchi and G. Fabrizi, *Chem. Rev.*, 2005, **105**, 2873–2920; (h) G. R. Humphrey and J. T. Kuethe, *Chem. Rev.*, 2006, **106**, 2875.
- (a) R. Robinson, *Experientia*, 1946, **2**, 28; (b) S. M. Verbitski, C. L. Mayne, R. A. Davis, G. P. Concepcion and C. M. Ireland, *J. Org. Chem.*, 2002, **67**, 7124; (c) R. Jadulco, R. A. Edrada, R. Ebel, A. Berg, K. Schaumann, V. Wray, K. Steube and P. Proksch, *J. Nat. Prod.*, 2004, **67**, 78.
- R. M. Shaheen, D. W. Davis, W. Liu, B. K. Zebrowski, M. R. Wilson, C. D. Bucana, D. J. McConkey, G. McMahon and L. M. Ellis, *Cancer Res.*, 1999, **59**, 5412.
- For synthesis of indoline, see: (a) K. M. Depew, S. P. Mardsen, D. Zatorska, A. Zatorska, W. G. Bornmann and S. J. Danishefsky, *J. Am. Chem. Soc.*, 1999, **121**, 11953; (b) V. R. Espejo, X. B. Li and J. D. Rainier, *J. Am. Chem. Soc.*, 2010, **132**, 8282; (c) A. Steven and L. E. Overman, *Angew. Chem., Int. Ed.*, 2007, **46**, 5488; (d) L. E. Overman and D. V. Paone, *J. Am. Chem. Soc.*, 2001, **123**, 9465; (e) J. F. Austin, S. G. Kim, C. J. Sinz, W. J. Xiao and D. W. C. MacMillan, *Proc. Natl. Acad. Sci. U. S. A.*, 2004, **101**, 5482; (f) S. Ma, X. Han, S. Krishnan, S. C. Virgil and B. M. Stoltz, *Angew. Chem., Int. Ed.*, 2009, **48**, 8037; (g) D. Crich and A. Banerjee, *Acc. Chem. Res.*, 2007, **40**, 151; (h) J. Kim and M. Movassaghi, *Chem. Soc. Rev.*, 2009, **38**, 3035; (i) P. Ruiz-Sanchis, S. A. Savina, F. Albericio and M. Alvarez, *Chem. – Eur. J.*, 2011, **17**, 1388. For synthesis of indole fused azepine, see: (j) C. Ferrer and A. M. Echavarren, *Angew. Chem., Int. Ed.*, 2006, **45**, 1105; (k) J. T. Lundquist, D. C. Harnish, C. Y. Kim, J. F. Mehlmann, R. J. Unwalla, K. M. Phipps, M. L. Crawley, T. Commons, D. M. Green, W.-X. Xu, W. T. Hum, J. E. Eta, I. Feingold, V. Patel, M. J. Evans, K.-D. Lai, L. B. Marcucci, P. E. Mahaney and J. E. Wrobel, *J. Med. Chem.*, 2010, **53**, 1774; (l) X. Zhong, Y. Li, J. Zhang, W.-X. Zhang, S.-X. Wang and F.-S. Han, *Chem. Commun.*, 2014, **50**, 11181.
- (a) J. Raushel and V. V. Fokin, *Org. Lett.*, 2010, **12**, 4952; (b) Y. Liu, X. Wang, J. Xu, Q. Zhang, Y. Zhao and Y. Hu, *Tetrahedron*, 2011, **67**, 6294; (c) E. J. Yoo, M. Ahlquist, S. H. Kim, I. Bae, V. V. Fokin, K. B. Sharpless and S. Chang, *Angew. Chem., Int. Ed.*, 2007, **46**, 1730.

- 6 For leading reviews, see: (a) B. Chattopadhyay and V. Gevorgyan, *Angew. Chem., Int. Ed.*, 2012, **51**, 862; (b) A. V. Gulevich and V. Gevorgyan, *Angew. Chem., Int. Ed.*, 2013, **52**, 1371; (c) H. M. L. Davies and J. S. Alford, *Chem. Soc. Rev.*, 2014, **43**, 5151. For pioneering examples, see: (d) T. Horneff, S. Chuprakov, N. Chernyak, V. Gevorgyan and V. V. Fokin, *J. Am. Chem. Soc.*, 2008, **130**, 14972; (e) T. Miura, M. Yamauchi and M. Murakami, *Chem. Commun.*, 2009, 1470; (f) J. S. Alford and H. M. L. Davies, *Org. Lett.*, 2012, **14**, 6020.
- 7 (a) S. Chuprakov, S. W. Kwok, L. Zhang, L. Lercher and V. V. Fokin, *J. Am. Chem. Soc.*, 2009, **131**, 18034; (b) N. P. Grimster, L. Zhang and V. V. Fokin, *J. Am. Chem. Soc.*, 2010, **132**, 2510; (c) J. C. Culhane and V. V. Fokin, *Org. Lett.*, 2011, **13**, 4578; (d) M. Zibinsky and V. V. Fokin, *Org. Lett.*, 2011, **13**, 4870; (e) B. T. Parr and H. M. L. Davies, *Angew. Chem., Int. Ed.*, 2013, **52**, 10044; (f) J. E. Spangler and H. M. L. Davies, *J. Am. Chem. Soc.*, 2013, **135**, 6802; (g) H. Shang, Y. Wang, Y. Tian, J. Feng and Y. Tang, *Angew. Chem., Int. Ed.*, 2014, **53**, 5662; (h) E. E. Schultz, V. N. G. Lindsay and R. Sarpong, *Angew. Chem., Int. Ed.*, 2014, **53**, 9904; (i) J. S. Alford and H. M. L. Davies, *J. Am. Chem. Soc.*, 2014, **136**, 10266.
- 8 (a) S. W. Kwok, L. Zhang, N. P. Grimster and V. V. Fokin, *Angew. Chem., Int. Ed.*, 2014, **53**, 3452; (b) M. Zibinsky and V. V. Fokin, *Angew. Chem., Int. Ed.*, 2013, **52**, 1507; (c) T. Miura, T. Tanaka, K. Hiraga, S. G. Stewart and M. Murakami, *J. Am. Chem. Soc.*, 2013, **135**, 13652; (d) B. Chattopadhyay and V. Gevorgyan, *Org. Lett.*, 2011, **13**, 3746; (e) Y. Shi and V. Gevorgyan, *Org. Lett.*, 2013, **15**, 5394; (f) E. E. Schultz and R. Sarpong, *J. Am. Chem. Soc.*, 2013, **135**, 4696; (g) S. Chuprakov, S. W. Kwok and V. V. Fokin, *J. Am. Chem. Soc.*, 2013, **135**, 4652; (h) B. T. Parr, S. A. Green and H. M. L. Davies, *J. Am. Chem. Soc.*, 2013, **135**, 4716; (i) Y. Xing, G. Sheng, J. Wang, P. Lu and Y. Wang, *Org. Lett.*, 2014, **16**, 1244; (j) X. Ma, S. Pan, H. Wang and W. Chen, *Org. Lett.*, 2014, **16**, 4554; (k) D. J. Lee, H. S. Han, J. Shin and E. J. Yoo, *J. Am. Chem. Soc.*, 2014, **136**, 11606.
- 9 (a) S. Chuprakov, J. A. Malik, M. Zibinsky and V. V. Fokin, *J. Am. Chem. Soc.*, 2011, **133**, 10352; (b) J.-M. Yang, C.-Z. Zhu, X.-Y. Tang and M. Shi, *Angew. Chem., Int. Ed.*, 2014, **53**, 5142; (c) D. Yadagiri and P. Anbarasan, *Org. Lett.*, 2014, **16**, 2510.
- 10 (a) T. Miura, T. Biyajima, T. Fujii and M. Murakami, *J. Am. Chem. Soc.*, 2012, **134**, 194; (b) T. Miura, T. Tanaka, T. Biyajima, A. Yada and M. Murakami, *Angew. Chem., Int. Ed.*, 2013, **52**, 3883; (c) S. Chuprakov, B. T. Worrell, N. Selander, R. K. Sit and V. V. Fokin, *J. Am. Chem. Soc.*, 2014, **136**, 195.
- 11 (a) N. Selander, B. T. Worrell, S. Chuprakov, S. Velaparthi and V. V. Fokin, *J. Am. Chem. Soc.*, 2012, **134**, 14670; (b) N. Selander and V. V. Fokin, *J. Am. Chem. Soc.*, 2012, **134**, 2477; (c) T. Miura, Y. Funakoshi, M. Morimoto, T. Biyajima and M. Murakami, *J. Am. Chem. Soc.*, 2012, **134**, 17440; (d) R. Liu, M. Zhang, G. Winston-McPherson and W. Tang, *Chem. Commun.*, 2013, **49**, 4376; (e) T. Miura, T. Tanaka, A. Yada and M. Murakami, *Chem. Lett.*, 2013, **42**, 1308; (f) J. S. Alford, J. E. Spangler and H. M. L. Davies, *J. Am. Chem. Soc.*, 2013, **135**, 11712; (g) K. Chen, Z.-Z. Zhu, Y.-S. Zhang, X.-Y. Tang and M. Shi, *Angew. Chem., Int. Ed.*, 2014, **53**, 6645; (h) T. Miura, Y. Funakoshi, T. Tanaka and M. Murakami, *Org. Lett.*, 2014, **16**, 2760; (i) T. Miura, T. Nakamuro, K. Hiraga and M. Murakami, *Chem. Commun.*, 2014, **50**, 10474; (j) Y.-Z. Zhao, H.-B. Yang, X.-Y. Tang and M. Shi, *Chem. – Eur. J.*, 2015, **21**, 3562; (k) Y. Wang, X. Lei and Y. Tang, *Chem. Commun.*, 2015, **51**, 4507.
- 12 The crystal data of **2a** and **4a** have been deposited in CCDC with numbers 1018373 and 1018374.
- 13 The deprotection of Bn or allyl groups of **2n** and **2j** under various conditions turned out to be unsuccessful, the formation of a complex product mixture indicated that the corresponding products might be unstable. For more details, please see the ESI.†

