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Phosphine-Catalyzed Intramolecular Rauhut-Currier Reaction: Enantioselective Synthesis of Hydro-2H-Indole Derivatives

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A highly enantioselective intramolecular Rauhut-Currier reaction catalyzed by a multifunctional chiral aminophosphine catalyst was reported. A series of hydro-2*H*-indole derivatives that bear an all-carbon quaternary center were obtained in high yields (up to 94%), excellent diastereo- and enantioselectivity (up to >20:1 d.r. and >99% ee). And this reaction could be performed on a gram scale using 2 mol% catalyst loading.

Nitrogen-containing heterocycles are ubiquitous core structures of various biologically active compounds, natural products, and pharmaceutical agents. For example, Aporphine alkaloids telisatin A and B showed cytotoxic activity against three human cancer cell (GSC-7901, K562, and SPCA-1). Solanidine mainly present as glycosides, can inhibit proliferation and exhibit obvious antitumor effect (Fig. 1).[1] In this context, various synthetic strategies have been devised in recent years for the synthesis of hydro-2*H*-indole derivatives.[2] Despite the fact that much progress has been made in the construction of nitrogen-containing cores, most of them was focused on the racemic transformations. The development of an enantioselective protocol for the synthesis of such skeloton, employing readily available starting materials and reagents under user-friendly synthetic conditions, is still a formidable challenge and in great demand. Herein, we reported our methodology of organophosphine-catalyzed

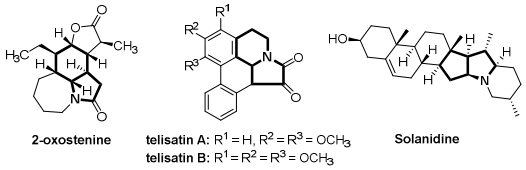
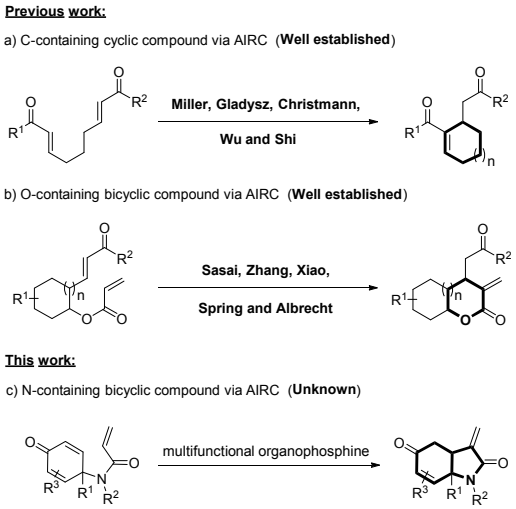


Fig. 1 Nitrogen-containing bioactive molecules.

enantioselective intramolecular RC reaction toward nitrogen-containing skeletons bearing two vicinal chiral centers from simple precusors. Most significantly, the catalyst loading could be decreased down to 2 mol% without deminishing the efficiency.



Scheme 1. Reported asymmetric intramolecular Rauhut-Currier (AIRC) reaction and our work.

Over the past decade, enantioselective nucleophilic phosphine catalysis has captured considerable attention and been developed as a practical approach to structurally diverse and synthetically valuable skelotons.[3] Among them, the Rauhut-Currier (RC) reaction, also known as the vinylogous Morita-Baylis-Hillman reaction, involves the coupling of one active alkene/latent enolate to another Michael acceptor, creating a new C-C bond between the α-position of one activated alkene and the β-position of a second alkene with the catalysis of a nucleophilic catalyst, was first reported by Rauhut and Currier in 1963.[4] However, less progress has been made on this reaction during the past decades due to the lack of efficient control of the selectivity.[5] The pioneering

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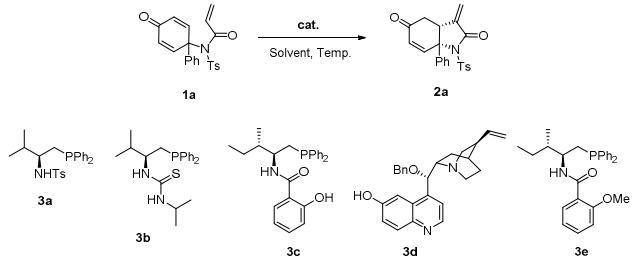
methodological studies of the intramolecular version of RC reaction that employed bis-enone substrates were demonstrated by Krische *et al.* and Roush *et al.* respectively, in 2002.[6] Later on, attractive systems based on achiral catalysis have been developed for the RC process.[7] The first breakthrough in the enantioselective RC reaction was reported by Aroyan and Miller in 2007.[8] And the past decade has seen remarkable advance in enantioselective RC reactions, and many excellent examples describing enantioselective intermolecular and intramolecular RC reaction have been reported.[9] And it is very meaningful to synthesis fields that those tactics had been successfully applied in the synthesis of several natural products.[10] It is noteworthy that in contrast to rich literature reports on the construction C-containing and O-containing cyclic compounds with the asymmetric intramolecular RC strategies (AIRC) (Scheme 1a, 1b), there wasn't an isolated example up to date on the AIRC reaction involving the construction N-containing cyclic compounds. During the submitting of this manuscript, Takizawa and Sasai has reported a very brilliant asymmetric intramolecular RC work.[11] Inspired by these previous work and as part of our continual interest in asymmetric nucleophilic phosphine catalysis, we were, therefore, very interested in developing such a process (Scheme 1c).

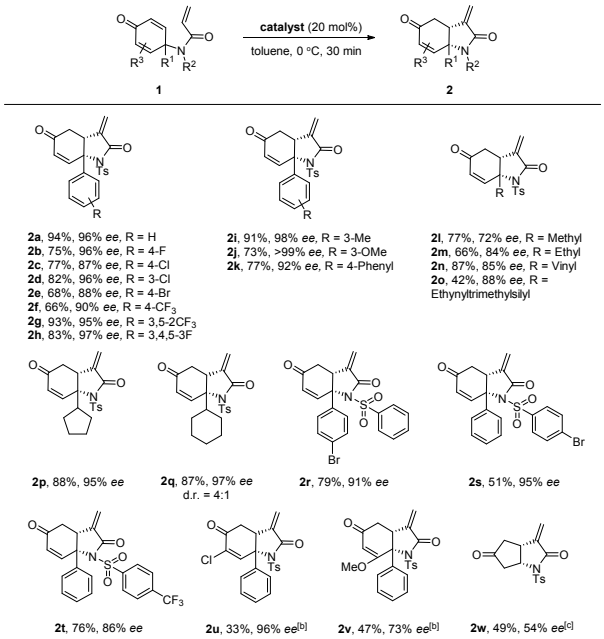
Table 1. Optimization of the Reaction Conditions[a]



entry	Cat. [%]	solvent	*T* [°C]	yield[b] [%]	ee[c] [%]
1	PPh_3 (20)	toluene	20	64	-
2	**3a** (20)	toluene	20	88	95
3	**3b** (20)	toluene	20	59	71
4	**3c** (20)	toluene	20	99	96
5	**3d** (20)	toluene	20	82	78
6	**3e** (20)	toluene	20	73	58
7	**3c** (20)	$CHCl_3$	20	76	94
8	**3c** (20)	toluene	10	82	93
9[d]	**3c** (20)	toluene	0	94	96
10[d]	**3c** (20)	toluene	-10	83	96
11[e]	**3c** (20)	toluene	-20	84	95

[a]Unless otherwise specified, all reactions were carried out with **1a** (0.1 mmol) in solvent (1.0 mL) with 15 min. [b]Yields of isolated products. [c]Determined by HPLC analysis using a chiral stationary phase. [d]Reaction with 30 min. [e]Reaction with 180 min.

We began our investigation by selecting phenyl-substituted cyclohexadienone **1a** as a prototypical substrate. To our delight, PPh_3 can smoothly catalyze the RC reaction in 20 °C within 15 min with 64% yield, and then we tested various chiral phosphine catalyst **3a**, **3b**, **3c** and cinchona derived **3d** (Table 1 entries 2-5). The outcome showed that multifunctional phosphine catalyst **3c** displayed the best results (99% yield, 95.5% ee). The methylated catalyst **3e** was used to elucidate the effect of the phenolic hydroxy group. As expected, although the reaction proceeded with good yields, the ee value decreased sharply to 58% (Table 1, entry 6), which unveiled the importance of hydrogen bonding in stereo-control. To additionally improve the enantioselectivity of the reaction, solvent and temperature screening was performed and toluene was found to be the best solvent. In additon, the enantiometric excess was further improved when conducted at 0 °C.



Scheme 2. [a]Unless otherwise specified, all reactions were carried out with **1** (0.1 mmol) in toluene (1.0 mL) within 30 min. [b]Reaction with 0 °C, 60 min. [c]Reaction with 25 °C, 6 h.

With the optimized reaction conditions in hand, we subsequently established the scope of the reaction (Scheme 2). The reaction was applicable to a wide range of different aryl substituents on the starting materials. High yields and excellent enantioselectivities were attained regardless of the electronic properties (Scheme 2, **2a**-**2k**). Variation of the alkyl substituent from methyl to ethyl was tolerated and the corresponding cyclized products **2l**, **2m** were obtained in good yield with 72-88% ee. Substrates **1n** and **1o**, which contain vinyl or ethynyl side chains, also worked well and the desired products **2n** and **2o** were isolated in good yield and ee. A slightly lower yield or ee may due to a smaller steric hindrance in starting material among **1l** to **1n**. Furthermore, cyclopentyl and cyclohexanyl substituted product could be obtained in an acceptable yield and enantioselectivity. Several different sulfonyl groups on nitrogen atom also give satisfactory results (Scheme 2, **2r**-**2t**). The chlorine and methoxy-substituted

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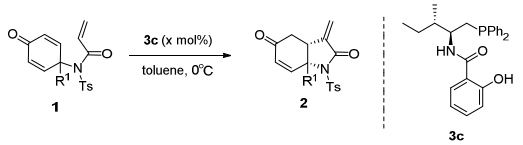
cyclohexadienones substrate resulted in low yield and good ee (Scheme 2, **2u**-**2v**). Notably, substrate **1w**, which is derived from furfuryl alcohol, offers an opportunity to construct bicycle hydropyrrole scaffolds with two contiguous chiral centers, albeit with poor yield and ee value. The relative configuration of hydroindole skeleton was determined unambiguously to be *cis* configuration by using single crystal X-ray analysis conducted on a representative RC product **2b**.[12] It should be noted that only one single diastereomer was obtained in all cases except **2q**.

In order to display the potential applicability of this protocol, we performed the reaction on a gram scale using 4 mmol of substrate. Firstly, 20 mol% **3c** was used as the catalyst in 40 mL toluene (the same catalyst concentration as the optimized reaction conditions) providing **2a** in 81% yield and 96% ee (Table 2, entry 2). We were delighted to find that when the catalyst loading was decreased to 2 mol%, the reaction still smoothly proceeded in 5 mL toluene to provide **2a** in 82% yield and 99.5% ee (Table 2, entry 6). The gram-scale reactions were also performed in the presence of 2 mol% catalyst to obtain **2b**, **2d**, and **2i** in good yields and excellent ee values within acceptable reaction time from 40 min to 3 h (Table 2, entries 7-9).

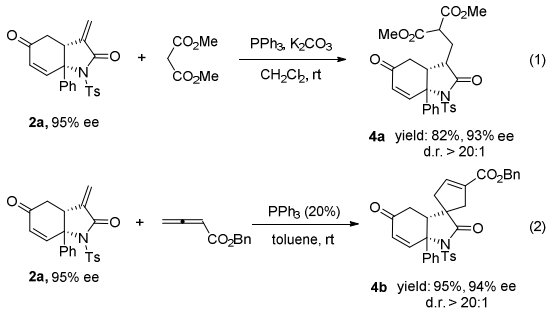
Table 2. RC reactions on a multigram scale.



entry	R^1	x	toluene [mL]	product	yield[a] [%]	ee[b] [%]
1[c,f]	H	20	1	**2a**, 37mg	94	96
2[d,f]	H	20	40	**2a**, 1.28g	81	96
3[d,g]	H	10	20	**2a**, 1.26g	80	97
4[d,h]	H	5	10	**2a**, 1.50g	95	98
5[d,i]	H	2.5	5	**2a**, 1.35g	86	97
6[e,j]	H	2	5	**2a**, 1.28g	82	99.5
7[e,j]	4-F	2	5	**2b**, 1.23g	75	93
8[e,i]	3-Cl	2	5	**2d**, 1.49g	87	91
9[e,k]	3-Me	2	5	**2i**, 1.43g	88	99.5

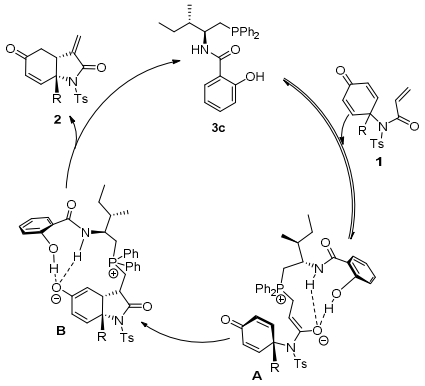
[a]Yields of isolated products. [b]Determined by HPLC analysis using a chiral stationary phase. [c]Reaction was carried out with **1** (0.1 mmol), **3c** (20 mol%) in toluene at 0 °C. [d]Reaction was carried out with **1** (4 mmol), **3c** (x mol%) in toluene at 0 °C. [e]Reaction was carried out with **1** (4 mmol), **3c** (2 mol%) in toluene at 25 °C. [f]Reaction with 30 min. [g]Reaction with 60 min. [h]Reaction with 120 min. [i]Reaction with 150 min. [j]Reaction with 180 min. [k]Reaction with 40 min.

And then two transformations were performed to demonstrate the synthetic utility of the highly functionalized RC product. The Michael addition of dimethyl malonate to **2a** produced **4a** (d.r.>20:1) in good yields without decreasing in the enantioselectivity (Scheme 3, Eq. (1)). Furthermore, the Lu's [3+2] annulation process could be easily achieved in the presence of allenic esters and a new spirocyclo skeleton **4b** was obtained with satisfactory yield and enantioselectivity results (Scheme 3, Eq. (2)).[13]



Scheme 3. Further transformation of products.

The proposed mechanism of the RC reaction using the chiral catalyst **3c** bearing both Brønsted acid (-NHBz and -OH) and Lewis base (-PPh_2) moieties is shown (Scheme 4). First the Michael addition of the LB moiety to the acrylate unit generates the phosphonium enolate **A**. Then the enolate **A** reacts with one of the olefins on the dienone. This second Michael addition results in the formation of the intermediate **B**. Finally, a proton transfer process results in the formation of the chiral nitrogen-containing hydro-2*H*-indole core skeleton **2**, along with regeneration of the catalyst through a retro-Michael reaction. According to our experiment results and previous research reports,[14] we found that the Brønsted acid unit plays an important role in controlling steric configuration of the product by intramolecular hydrogen bond interaction, and the proton transfer step is a crucial process.[15]



Scheme 4. Proposed mechanism of the RC process.

In summary, we have developed a highly enantioselective intramolecular Rauhut-Currier reaction of cyclohexadienones catalyzed by a multifunctional chiral aminophosphine catalyst. This present approach could be used to construct nitrogen-containing hydro-2*H*-indole core skeletons that bear an all-carbon quaternary center rapidly (reaction completion within 30 min). Excellent stereoselectivity and yields could be obtained in most cases (up to 20:1 d.r. and >99% ee and up to 94% yield) under mild conditions. It should be noted that the reaction undergo smoothly on a gram scale using 2 mol% catalyst loading. Further investigation of the reaction mechanism and the application of this method to natural

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product synthesis are underway and will be reported in due course.

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Notes and references

1 (a) D. Kakuta, Y. Hitotsuyanagi, N. Matsuura, H. Fukaya and K. Takeya, *Tetrahedron* 2003, **59**, 7779; (b) S. Nimgirawath and P. Udomputtimekakul, *Molecules* 2009, **14**, 917; (c) B. Liu, L. Jian, G. Chen, X. Song, C. Han and J. Wang, *Chem. Nat. Compd.* 2014, **49**, 1172; (d) M.-K. Lu, Y.-W. Shih, T.-T. C. Chien, L.-H. Fang, H.-C. Huang and P.-S. Chen, *Biol. Pharm. Bull*. 2010, **33**, 1685; (e) Z.-D. Zhang, Y. Shi, J.-J. Wu, J.-R. Lin and W.-S. Tian, *Org. Lett.* 2016, **18**, 3038.

2 (a) J. H. Rigby, A. Cavezza and G. Ahmed, *J. Am. Chem. Soc.* 1996, **118**, 12848; (b) L. E. Overman and M. Kakimoto, *J. Am. Chem. Soc.* 1979, **101**, 1310; (c) S. J. Danishefsky and J. S. Panek, *J. Am. Chem. Soc.* 1987, **109**, 917; (d) G. Stork and R. Mah, *Heterocycle* 1989, **28**, 723; (e) H. Nagashima, N. Ozaki, M. Ishii, K. Seki, M. Washiyama and K. Itoh, *J. Org. Chem.* 1993, **58**, 464; (f) J. Cassayre, D. Dauge and S. Z. Zard, *Synlett* 2000, 471; (g) D. P. Curran, D. B. Guthrie and S. J. Geib, *J. Am. Chem. Soc.* 2008, **130**, 8437.

3 For reviews, see: (a) L.-W. Ye, J. Zhou and Y. Tang, *Chem. Soc. Rev.* 2008, **37**, 1140; (b) B. J. Cowen and S. J. Miller, *Chem. Soc. Rev.* 2009, **38**, 3102; (c) A. Marinetti and A. Voituriez, *Synlett* 2010, 174; (d) Y. Wei and M. Shi, *Acc. Chem. Res.* 2010, **43**, 1005; (e) S.-X. Wang, X. Han, F. Zhong and Y. Lu, *Synlett* 2011, 2766; (f) Q.-Y. Zhao, Z. Lian, Y. Wei and M. Shi, *Chem. Commun.* 2012, **48**, 1724; (g) L.-W.Xu, *ChemCatChem* 2013, **5**, 2775; (h) Y. Wei and M. Shi, *Chem. Rev*. 2013, **113**, 6659; (i) Y. C. Fan and O. Kwon, *Chem. Commun.* 2013, **49**, 11588; (j) Z. Wang, X. Xu and O. Kwon, *Chem. Soc. Rev.* 2014, **43**, 2927; (k) Y. Xiao, H. Guo and O. Kwon, *Aldrichimica Acta* 2016, **49**, 3; (l) W. Li and J. Zhang, *Chem. Soc. Rev.* 2016, **45**, 1657; (m) T. Wang, X. Han, F. Zhong, W. Yao and Y. Lu, *Acc. Chem. Res.* 2016, **49**, 1369.

4 M. M. Rauhut and H. Currier, U. S. Patent, 1963, 3074999; [*Chem. Abstr.* 1963, **58**, 11224a].

5 For reviews on the RC reaction, see: (a) J. L. Methot and W. R. Roush, *Adv. Synth. Catal.* 2004, **346**, 1035; (b) C. E. Aroyan, A. Dermenci and S. J. Miller, *Tetrahedron* 2009, **65**, 4069; (c) P. Xie and Y. Huang, *Eur. J. Org. Chem.* 2013, 6213.

6 (a) L.-C. Wang, A. L. Luis, K. Agapiou, H.-Y. Jang and M. J. Krische, *J. Am. Chem. Soc.* 2002, **124**, 2402; (b) S. A. Frank, D. J. Mergott and W. R. Roush, *J. Am. Chem. Soc.* 2002, **124**, 2404.

7 (a) D. J. Mergott, S. A. Frank and W. R. Roush, *Org. Lett.* 2002, **4**, 3157; (b) J. L. Methot and W. R. Roush, *Org. Lett.* 2003, **5**, 4223; (c) F. O. Seidel and J. A. Gladysz, *Adv. Synth. Catal.* 2008, **350**, 2443; (d) W. Yao, Y. Wu, G. Wang, Y. Zhang and C. Ma, *Angew. Chem. Int. Ed.* 2009, **48**, 9713; (e) Y. Qiao, S. Kumar and W. P. Malachowski, *Tetrahedron Lett.* 2010, **51**, 2636; (f) W. Liu, J. Zhou, C. Zheng, X. Chen, H. Xiao, Y. Yang, Y. Guo and G. Zhao, *Tetrahedron* 2011, **67**, 1768; (g) P. Xie, Y. Huang, W. Lai, X. Meng and R. Chen, *Org. Biomol. Chem.* 2011, **9**, 6707; (h) J. Ma, P. Xie, C. Hu, Y. Huang and R. Chen, *Chem. Eur. J.* 2011, **17**, 7418; (i) C. Hu, Z. Geng, J. Ma, Y. Huang and R. Chen, *Chem. Asian J.* 2012, **7**, 2032; (j) J. A. Mackay, Z. C. Landis, S. E. Motika and M. H. Kench, *J. Org. Chem.* 2012, **77**, 7768; (k) C. Hu, Q. Zhang and Y. Huang, *Chem. Asian J.* 2013, **8**, 1981.

8 (a) C. E. Aroyan and S. J. Miller, *J. Am. Chem. Soc.* 2007, **129**, 256; (b) C. E. Aroyan, A. Dermenci and S. J. Miller, *J. Org. Chem.* 2010, **75**, 5784; (c) P. S. Selig and S. J. Miller, *Tetrahedron Lett*. 2011, **52**, 2148.

9 (a) F. Seidel and J. A. Gladysz, *Synlett* 2007, 986; (b) E.; Herrera, R. P. Marqués-López, T. Marks, W. C. Jacobs, D. Donning, R. M. de Figueiredo and M. Christmann, *Org. Lett*. 2009, **11**, 4116; (c) J.-J. Gong, T.-Z. Li, K. Pan and X.-Y. Wu, *Chem. Commun.* 2011, **47**, 1491; (d) Q.-Y. Zhao, C.-K. Pei, X.-Y. Guan and M. Shi, *Adv. Synth. Catal.* 2011, **353**, 1973; (e) X.-F. Wang, L. Peng, J. An, C. Li, Q.-Q. Yang, L.-Q. Lu, F.-L. Gu and W.-J. Xiao, *Chem. Eur. J.* 2011, **17**, 6484; (f) S. Takizawa, T. M. N. Nguyen, A. Grossmann, D. Enders and H. Sasai, *Angew. Chem. Int. Ed.* 2012, **51**, 5423; (g) X.-N. Zhang and M. Shi, *Eur. J. Org. Chem.* 2012, 6271; (h) S. Takizawa, T. M. N. Nguyen, A. Grossmann, M. Suzuki, D. Enders and H. Sasai, *Tetrahedron* 2013, **69**, 1202; (i) X. Dong, L. Liang, E. Li and Y. Huang, *Angew. Chem. Int. Ed.* 2015, **54**, 1621; (j) X. Su, W. Zhou, Y. Li and J. Zhang, *Angew. Chem. Int. Ed.* 2015, **54**, 6874; (k) W. Zhou, X. Su, M. Tao, C. Zhu, Q. Zhao and J. Zhang, *Angew. Chem. Int. Ed.* 2015, **54,** 14853; (l) R. J. H. Scanes, O. Grossmann, A. Grossmann and D. R. Spring, *Org. Lett.* 2015, **17**, 2462; (m) A. Albrecht, A. Skrzyńska, A. Przydacz and Ł. Albrecht, *Synlett* 2015, 2679; (n) W. Zhou, P. Chen, M. Tao, X. Su, Q. Zhao and J. Zhang, *Chem. Commun.* 2016, **52**, 7612; (o) W. Yao, X. Dou, S. Wen, J. Wu, J. J. Vittal and Y. Lu, *Nat. Commun.* 2016, **7**, 13024; (p) S. Li, Y. Liu, B. Huang, T. Zhou, H. Tao, Y. Xiao, L. Liu and J. Zhang, *ACS Catal.* 2017, **7**, 2805; (q) X.-Z. Zhang, K.-J. Gan, X.-X. Liu, Y.-H. Deng, F.-X. Wang, K.-Y. Yu, J. Zhang and C.-A. Fan, *Org. Lett.* 2017, **19**, 3207.

10 (a) D. J. Mergott, S. A. Frank and W. R. Roush, *Org. Lett.* 2002, **4**, 3157; (b) K. Agapiou and M. J. Krische, *Org. Lett.* 2003, **5**, 1737; (c) D. J. Mergott, S. A. Frank and W. R. Roush, *Proc. Natl. Acad. Sci.* USA 2004, **101**, 11955; (d) L. M. Stark, K. Pekari and E. J. Sorensen, *Proc. Natl. Acad. Sci.* USA 2004, **101**, 12064; (e) S. M. Winbush, D. J. Mergott and W. R. Roush, *J. Org. Chem*. 2008, **73**, 1818; (f) A. Dermenci, P. S. Selig, R. A. Domaoal, K. A. Spasov, K. S. Anderson and S. J. Miller, *Chem. Sci.* 2011, **2**, 1568.

11 K. Kishi, F. A. Arteaga, S. Takizawa and H. Sasai, *Chem. Commun.* 2017, **53**, 7724.

12 CCDC 1524100 (**2b**) 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. And the configurations of the products are consistent with the configurations in Sasai's system (ref. 11) according to the value of specific rotation.

13 C. Zhang and X. Lu, *J. Org. Chem.* 1995, **60**, 2906.

14 (a) L. S. Santos, C. H. Pavam, W. P. Almeida, F. Coelho and M. N. Eberlin, *Angew. Chem. Int. Ed.* 2004, **43**, 4330; (b) V. K. Aggarwal, S. Y. Fulford and G. C. Lloyd-Jones, *Angew. Chem. Int. Ed.* 2005, **44**, 1706; (c) I. T. Raheem and E. N. Jacobsen, *Adv. Synth. Catal.* 2005, **347**, 1701; (d) K. E. Price, S. J.; Jung, H. M. Broadwater and D. T. McQuade, *Org. Lett.* 2005, **7**, 147; (e) L. Dong, S. Qin, Z. Su, H. Yang and C. Hu, *Org. Biomol. Chem.* 2010, **8**, 3985.

15 (a) T. Dudding, O. Kwon and E. Mercier, *Org. Lett.* 2006, **8**, 3643; (b) E. Mercier, B. Fonovic, C. Henry, O. Kwon and T. Dudding, *Tetrahedron Lett.* 2007, **48**, 3617; (c) Y. Xia, Y. Liang, Y. Chen, M. Wang, L. Jiao, F. Huang, S. Liu, Y. Li and Z.-X. Yu, *J. Am. Chem. Soc.* 2007, **129**, 3470; (d) Y. Liang, S. Liu, Y. Xia, Y. Li and Z.-X. Yu, *Chem. Eur. J.* 2008, **14**, 4361; (e) P. Buskens, J. Klankermayer and W. Leitner, *J. Am. Chem. Soc.* 2005, **127**, 16762; (f) R. Robiette, V. K. Aggarwal and J. N. Harvey, *J. Am. Chem. Soc.* 2007, **129**, 15513; (g) D. Roy, C. Patel and R. B. Sunoj, *J. Org. Chem.* 2009, **74**, 6936.