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Catalytic asymmetric synthesis of *N*-substituted tetrahydroquinoxalines *via* regioselective Heyns rearrangement and stereoselective transfer hydrogenation in one pot†

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N-Substituted tetrahydroquinoxalines (37 examples) were step-economically obtained in good yield (<97%) and ee (<99%) with readily available substrates. The reaction proceeds through an interesting regioselective Heyns rearrangement/enantioselective transfer hydrogenation in one pot. The substrate scope and the reaction mechanism were systematically investigated.

Introduction

N-Substituted tetrahydroquinoxalines (THQ) represent an important class of *N*-heterocycles, which are present in numerous biologically active substances,¹ including the prostaglandin D2 receptor antagonist **I**,² the cholesteryl ester transfer protein (CETP) inhibitor **II**,³ and the selective bromodomain protein inhibitor **III**⁴ (Fig. 1). Therefore, extensive efforts have been devoted to the enantioselective synthesis of this class of heterocycles. Among the different strategies, asymmetric hydrogenation⁵ or transfer hydrogenation⁶ of quinoxalines represents one of the most straightforward choices (Scheme 1a). Many elegant catalytic systems have been reported using transition-metal catalysis or organocatalysis. However, despite these advances, synthesis of multi-substituted THQ, especially *N*-substituted THQ is still difficult,⁷ owing to the prior preparation and purification of the quinoxaline substrate, the limited regioselectivity, or multi-step procedures. Consequently, the step-economic synthesis of THQ *via* the *in situ* generation of quinoxalines from readily available starting materials in a regioselective,^{5g,6d} diastereoselective, and enantioselective way is both challenging and meaningful.

Amadori and Heyns rearrangements have been famous among carbohydrate chemists over the decades.⁸ Both reactions suffer from a variety of preparative shortcomings such as separation drawbacks, side reactions, further degradation

entering into the Maillard reaction cascade, *etc.* Therefore, this rearrangement appears to be highly underrated as a useful method for synthetic chemists.⁹ Due to the significance of the reaction as well as the importance of the corresponding products, our group has paid much attention to its application.¹⁰ Recently, we investigated the production and application of the *in situ* formed α -amino aldehyde intermediate and synthesized different *N*-heterocycles by using different types of nucleophiles.^{10a}

For example, symmetric *o*-phenylenediamine (*o*-PDA) reacted smoothly with α -hydroxyl ketones to afford the corresponding quinoxaline (Scheme 1b). Due to the important application of *N*-substituted THQ as well as our interest in Heyns rearrangement, we proposed that the substituted unsymmetric *o*-PDA could react with α -hydroxyl ketone *via* Heyns rearrangement to afford the corresponding α -amino ketone **A** or **A'** (Scheme 1c). Then the reaction continues to form the iminium ion **B** or imine **B'** by cyclization. Next, the reaction could proceed in three possible pathways: (1) **B** could isomerize to enamine **C** which would be isomerized again to stable imine **D**. Then **D** would be reduced to afford *N*-substituted THQ. (2) Iminium ion **B** might be reduced directly to afford the

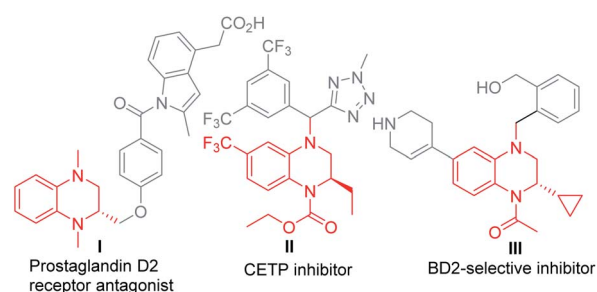


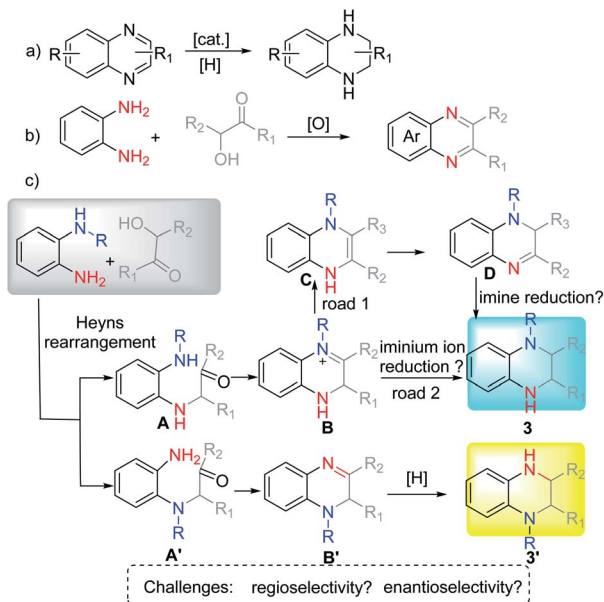
Fig. 1 *N*-Substituted THQ with biological activities.

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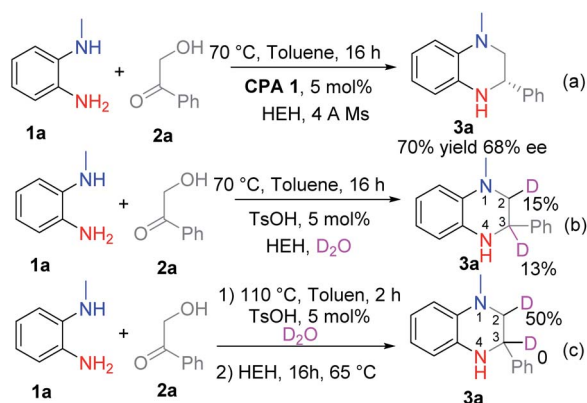


Scheme 1 The background and the proposal of this research: (a) Previous works *via* catalytic reduction of quinoxalines. (b) Previous work for preparation of quinoxalines *via* Heyns rearrangement. (c) Our proposal for obtaining chiral THQ *via* regioselective Heyns rearrangement and stereoselective reduction in one pot.

corresponding product. (3) Imine **B'** might be reduced to get product **3'**. According to the possible reaction process, the regioselectivity of the reaction might be controlled by the Heyns rearrangement, while the enantioselectivity might be controlled in different ways: enantioselective protonation and enantioselective reduction of iminium ions or imine. These properties pose great challenges for us to obtain *N*-substituted THQ in one pot.

Results and discussion

Luckily, THQ **3a** was obtained exclusively in 70% yield and 68% ee using Hantzsch ester (HEH) and chiral phosphoric acid **CPA**



Scheme 2 Investigation of the reaction process: (a) moderate ee was obtained if HEH was added to the reaction at the very beginning. (b) D_2O and HEH were added to the reaction at the beginning. (c) D_2O was added at the beginning while HEH was added after 2 hours.

Table 1 Investigation of the scope of the *N*-substituent of *o*-PDA

 92% yield ee: 80%	 95% yield ee: 94%
 92% yield ee: 90%	 94% yield ee: 90%
 95% yield ee: 82%	 97% yield ee: 98%
 96% yield ee: 92%	 R = 9-phenanthryl

1 at 70 °C after optimizing the reaction conditions (Scheme 2a, for the optimization experiments, see Table S1 in the ESI†). However, further improvement of the reaction yield and the ee value was very hard. We therefore investigated the reaction process *via* the addition of D_2O into the reaction (Scheme 2b and c). When the reaction was run with the addition of HEH at the beginning, the corresponding product **3a** was deuterated at C2–H and C3–H (Scheme 2b). This means that **3a** might be formed by the reduction of intermediates **B** and **D**. In contrast, only the C2–H was deuterated when the reaction was run in two steps (Scheme 2c). This means that only the intermediate **D** was reduced.

According to this result, we changed the addition sequence of HEH to ensure that the THQ **3** was formed from the transfer hydrogenation of imine **D**. To our delight, both the reaction yield and the ee value could be improved in this way (Table S1, see ESI†). The optimal reaction conditions were obtained as follows: equal equiv. of **1a** and **2a** reacted under a nitrogen atmosphere with 5 mol% **CPA 1** in toluene for 2 h, then HEH was added and the reaction continued to proceed at 65 °C for 16 h in one pot. The corresponding product **3a** was obtained in 92% yield and 80% ee (Table 1).

Then the substituent of the nitrogen was investigated under the optimal conditions. The results revealed that the reaction proceeded smoothly with good yields (92–97%) and high regioselectivities. Moreover, the ee value of **3** increased greatly for substituents with better steric hindrance (**3b** and **3f**). Meanwhile, the long alkyl substituents (**3c** and **3d**) and aromatic ring substituent (**3g**) are proved to be feasible substrates with good ee values. Substrates with allyl afforded the corresponding product **3e** with a moderate ee value due to the small steric hindrance.

Next, we investigated the substituents of the aromatic ring of *o*-PDA (Table 2). Generally, the reaction proceeded smoothly with good regioselectivity. Firstly, symmetric *o*-PDAs were investigated, which smoothly reacted and afforded the corresponding products **3h–3j** in high yield (91–95%) and ee (84–94%). Then unsymmetric *o*-PDAs were evaluated. The results



Reaction scheme showing the synthesis of various 1*i*-propyl-2-substituted-1,2,3,4-tetrahydroquinolines (**3**) from 1 (1*i*-propyl-2-aminobenzene) and 2 (R-CH₂-COOH) under two sets of conditions:

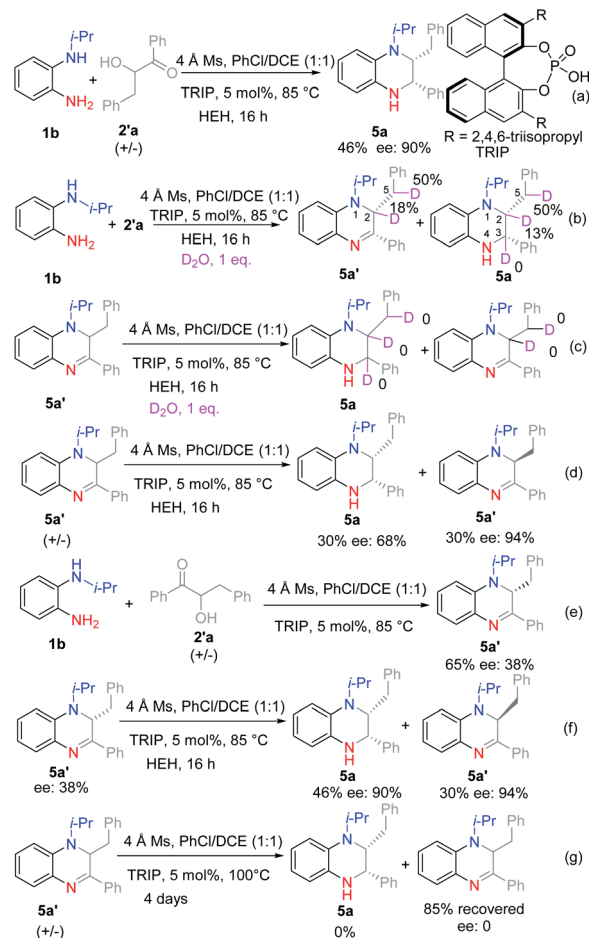
1) CPA **1**, 5 mol%, 110 °C, 4 Å Ms, toluene, 2 h
2) HEH, 65 °C, 16 h, one pot

Yields and enantiomeric excesses (ee) for the products are listed below:

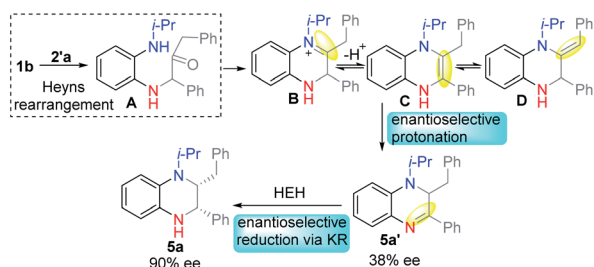
ID	R	yield	ee
3h	F	93%	ee: 84%
3i	Cl	95%	ee: 94%
3j	Ph	91%	ee: 94%
3k	Ph F	85%	ee: 86%
3l	Ph Br	92%	ee: 94%
3m	Ph I	87%	ee: 92%
3n	Ph OMe	90%	ee: 88%
3o	Ph	85%	ee: 92%
3p	Br, Cl	95%	ee: 92%
3q	furan	98%	ee: 90%
3r	thiophene	96%	ee: 92%
3w	CH ₃	80%	ee: 64%
3s	F	89%	96%
3t	Cl	93%	98%
3u	Br	88%	99%
3v	OCH ₃	93%	98%
3x	Ts		

3D molecular model of a product is shown on the right.

Firstly, 1 equiv. D₂O was added to the reaction mixture under the optimal reaction conditions (Scheme 3b). According to the result, the C2-H at the α -position of the tertiary amine was deuterated, while C3-H at the α -position of the secondary amine was not deuterated. Moreover, the benzylic hydrogen was



deuterated. Based on this result, we guess that the reaction proceeded selectively by the reduction of ketone imine rather than the iminium ion. Then dihydroquinoxaline (DHQ) **5a'** was used as a substrate with D₂O to check if the ketone imine would isomerize into enamine or iminium ions (Scheme 3c). According to the result, no deuterated product was found, which proved that the ketone imine was stable and could not isomerize into enamine under the reaction conditions. Finally, the racemic DHQ **5a'** was reduced under the optimal reaction conditions, and the corresponding product **5a** was obtained in 30% yield and 68% ee (Scheme 3d). To our surprise, the recovered substrate was obtained in 94% ee. Therefore, we could conclude that the reaction proceeded through a kinetic resolution process. To figure out the source of the enantioselectivities we also investigated the reaction without the addition of reduction reagents (Scheme 3e). According to the result, **5a'** was obtained with moderate yield and low ee (38%). Moreover, **5a'** with 38% ee could be reduced under the optimal reaction

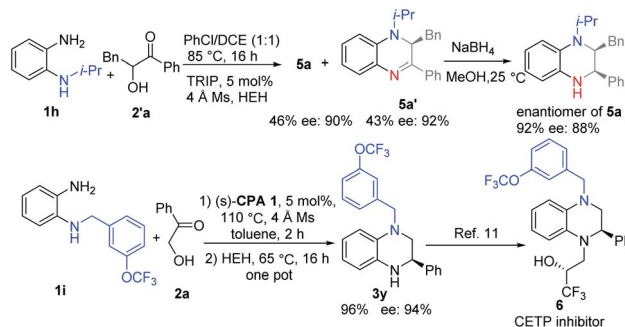
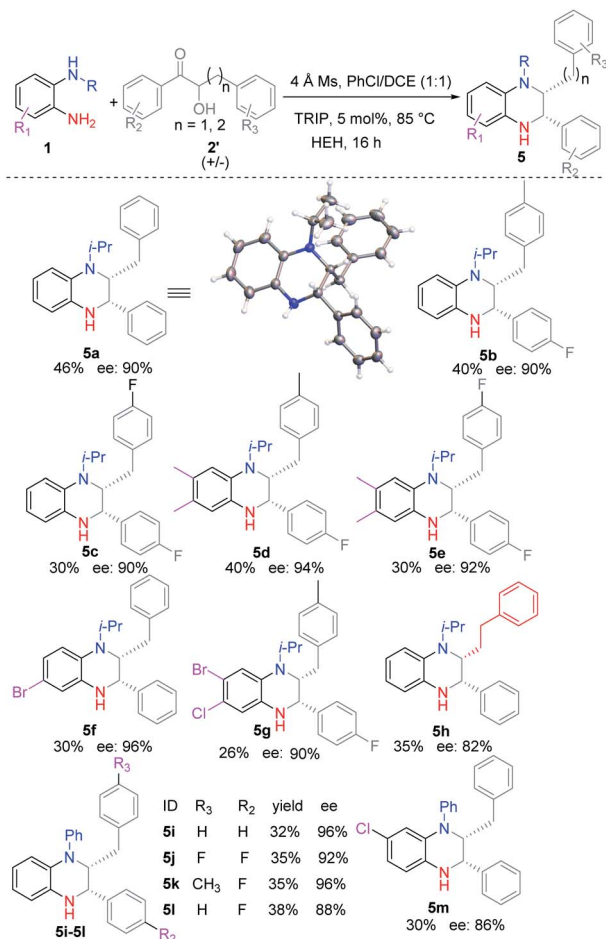


Scheme 4 Plausible reaction process for obtaining disubstituted THQ.

conditions to afford **5a** with similar ee (Scheme 3f). When racemic **5a'** was stirred under the optimal reaction conditions without adding HEH, no product was found even after raising the reaction temperature to 100 °C for 4 days (Scheme 3g). Therefore, we could preclude that **5a'** might act as a reductant.¹¹

Based on the above results, we proposed a reasonable reaction mechanism (Scheme 4). Firstly, the reaction selectively proceeded *via* Heyns rearrangement to form α -amino ketone **A**. Then the iminium ion **B** was formed by cyclization. Meanwhile, enamine intermediates **C** and **D** might be formed by

Table 3 Investigation of the substrate scope for obtaining disubstituted THQ



Scheme 5 Application of the method in the synthesis of useful compounds.

isomerization. Next, the enantioselective protonation occurred to form the stable DHQ **5a'** in low ee. Finally, **5a** was formed by enantioselective reduction *via* kinetic resolution.

Then we turned to investigate the substrate scope for obtaining disubstituted THQ (Table 3). Generally, racemic α -hydroxyl ketones could easily react with substituted *o*-PDAs to afford the corresponding THQ (**5a–5m**) in moderate yields (25–46%) and good ees (86–96%). Compared with symmetric *o*-PDAs as substrates, the use of unsymmetric *o*-PDAs as substrates afforded the corresponding THQ (**5f–5g**, **5m**) in slightly lower yields. Interestingly, increasing the carbon chain also afforded the corresponding product **5h** in moderate yield (35%) and ee (82%). The absolute configuration of the products was confirmed according to the single crystal diffraction result of **5a**.

Then we tried to show the advantages of the method. DHQ **5'a** could be obtained from the reaction mixture in moderate yield and high ee, which might explain the slightly low yield of the reaction for obtaining 2,3-disubstituted THQ **5**. Interestingly the other enantiomer of **5a** could be easily obtained by reducing DHQ **5'a** with NaBH₄ (Scheme 5). Meanwhile, *o*-PDA **1i** was synthesized and used under the optimal reaction conditions to provide the *N*-substituted product **3y** in good yield and ee, which could be used for the preparation of useful CETP inhibitor **6**.¹¹

Conclusions

In summary, we have developed an interesting tandem reaction for conveniently obtaining *N*-substituted THQ with readily available *o*-PDA and α -hydroxyl ketones as starting materials. A series of monosubstituted and disubstituted THQ (37 examples) were obtained in good yields (up to 97%) and high ees (up to 99%). Moreover, good regioselectivity was achieved for reactions with unsymmetric *o*-PDA as the substrate, which was seldom used as a substrate due to its low regioselectivity. The substituents of the amino group of *o*-PDA were investigated, and it was demonstrated that the reaction could tolerate alkyl, allyl, and aromatic substituents for high yield and ee. Meanwhile, different types of primary α -hydroxyl ketones and racemic α -hydroxyl ketones could be efficiently reacted to afford the corresponding monosubstituted and disubstituted THQ. Generally, high regioselectivities of the reaction were realized *via*



selective Heyns rearrangement. The high enantioselectivities of the reactions were investigated. For reactions with primary α -hydroxyl ketones as substrates, the high enantioselectivities were obtained from enantioselective transfer hydrogenation, while for reactions with racemic secondary α -hydroxyl ketones, the enantioselectivities came from the combination of enantioselective protonation and kinetic resolution.

Conflicts of interest

There are no conflicts to declare.

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Notes and references

- (a) M. Patel, R. J. McHugh, B. C. Cordova, R. M. Klabe, S. Erickson-Viitanen, G. L. Trainor and J. D. Rodgers, *Bioorg. Med. Chem. Lett.*, 2000, **10**, 1729–1731; (b) S. Li, X. Tian, D. M. Hartley and L. A. Feig, *J. Neurosci.*, 2006, **26**, 1721–1729; (c) M. Fantin, M. Marti, Y. P. Auberson and M. Morari, *J. Neurosci.*, 2007, **103**, 2200–2211.
- K. Torisu, K. Kobayashi, M. Iwahashi, Y. Nakai, T. Onoda, T. Nagase, I. Sugimoto, Y. Okada, R. Matsumoto, F. Nanbu, S. Ohuchida, H. Nakai and M. Toda, *Bioorg. Med. Chem.*, 2004, **12**, 5361–5378.
- (a) J. A. Sikorski, *J. Med. Chem.*, 2006, **49**, 1–22; (b) C. T. Eary, Z. S. Jones, R. D. Groneberg, L. E. Burgess, D. A. Mareska, M. D. Drew, J. F. Blake, E. R. Laird, D. Balachari, M. O'Sullivan, A. Allen and V. Marsh, *Bioorg. Med. Chem. Lett.*, 2007, **17**, 2608–2613; (c) J. E. Wilson, R. Kurukulasuriya, M. Reibarkh, M. Reiter, A. Zwicker, K. Zhao, F. Zhang, R. Anand, V. J. Colandrea, A.-M. Cumiskey, A. Crespo, R. A. Duffy, B. A. Murphy, K. Mitra, D. G. Johns, J. L. Duffy and P. Vachal, *ACS Med. Chem. Lett.*, 2016, **7**, 261–265.
- R. P. Law, S. J. Atkinson, P. Bamborough, C.-w. Chung, E. H. Demont, L. J. Gordon, M. Lindon, R. K. Prinjha, A. J. B. Watson and D. J. Hirst, *J. Med. Chem.*, 2018, **61**, 4317–4334.
- (a) C. Bianchini, P. Barbaro, G. Scapacci, E. Farnetti and M. Graziani, *Organometallics*, 1998, **17**, 3308–3310; (b) N. Mršić, T. Jerphagnon, A. J. Minnaard, B. L. Feringa and J. G. de Vries, *Adv. Synth. Catal.*, 2009, **351**, 2549–2552; (c) W. Tang, L. Xu, Q.-H. Fan, J. Wang, B. Fan, Z. Zhou, K.-h. Lam and A. S. C. Chan, *Angew. Chem., Int. Ed.*, 2009, **48**, 9135–9138; (d) D. Cartigny, T. Nagano, T. Ayad, J.-P. Genêt, T. Ohshima, K. Mashima and V. Ratovelomanana-Vidal, *Adv. Synth. Catal.*, 2010, **352**, 1886–1891; (e) S. Urban, N. Ortega and F. Glorius, *Angew. Chem., Int. Ed.*, 2011, **50**, 3803–3806; (f) T. Nagano, A. Iimuro, R. Schwenk, T. Ohshima, Y. Kita, A. Togni and K. Mashima, *Chem.-Eur. J.*, 2012, **18**, 11578–11592; (g) D. Cartigny, F. Berhal, T. Nagano, P. Phansavath, T. Ayad, J.-P. Genêt, T. Ohshima, K. Mashima and V. Ratovelomanana-Vidal, *J. Org. Chem.*, 2012, **77**, 4544–4556; (h) S. Fleischer, S. Zhou, S. Werkmeister, K. Junge and M. Beller, *Chem.-Eur. J.*, 2013, **19**, 4997–5003; (i) N. Arai, Y. Saruwatari, K. Isobe and T. Ohkuma, *Adv. Synth. Catal.*, 2013, **355**, 2769–2774; (j) Z. Zhang and H. Du, *Angew. Chem., Int. Ed.*, 2015, **127**, 633–636; (k) S. Sun and P. Nagorny, *Chem. Commun.*, 2020, **56**, 8432–8435.
- (a) M. Rueping, F. Tato and F. R. Schoepke, The First General, Efficient and Highly Enantioselective Reduction of Quinoxalines and Quinoxalinones, *Chem.-Eur. J.*, 2010, **16**, 2688–2691; (b) D.-W. Wang, D.-S. Wang, Q.-A. Chen and Y.-G. Zhou, *Chem.-Eur. J.*, 2010, **16**, 1133–1136; (c) Q.-A. Chen, D.-S. Wang, Y.-G. Zhou, Y. Duan, H.-J. Fan, Y. Yang and Z. Zhang, *J. Am. Chem. Soc.*, 2011, **133**, 6126–6129; (d) F. Shi, W. Tan, H.-H. Zhang, M. Li, Q. Ye, G.-H. Ma, S.-J. Tu and G. Li, *Adv. Synth. Catal.*, 2013, **355**, 3715–3726.
- (a) C. J. Abraham, D. H. Paull, M. T. Scerba, J. W. Grebinski and T. Lectka, *J. Am. Chem. Soc.*, 2006, **128**, 13370–13371; (b) C. L. Hamblett, J. L. Methot, D. M. Mampreian, D. L. Sloman, M. G. Stanton, A. M. Kral, J. C. Fleming, J. C. Cruz, M. Chenard, N. Ozerova, A. M. Hitz, H. Wang, S. V. Deshmukh, N. Nazef, A. Harsch, B. Hughes, W. K. Dahlberg, A. A. Szewczak, R. E. Middleton, R. T. Mosley, J. P. Secrist and T. A. Miller, *Bioorg. Med. Chem. Lett.*, 2007, **17**, 5300–5309; (c) M. K. Ghorai, A. K. Sahoo and S. Kumar, *Org. Lett.*, 2011, **13**, 5972–5975; (d) L. Gavara, E. Saugues, F. Anizon and P. Moreau, *Tetrahedron*, 2011, **67**, 1633–1639; (e) B. A. Hopkins and J. P. Wolfe, *Chem. Sci.*, 2014, **5**, 4840–4844; (f) A.-G. A. El-Helby, R. R. A. Ayyad, K. El-Adl and A. Elwan, *Med. Chem. Res.*, 2017, **26**, 2967–2984; (g) R. Huang, X. Chen, C. Mou, G. Luo, Y. Li, X. Li, W. Xue, Z. Jin and Y. R. Chi, *Org. Lett.*, 2019, **21**, 4340–4344.
- Z. Wang, Heyns Rearrangement, in *Comprehensive Organic Name Reactions and Reagents*, ed. Z. Wang, 2010, pp. 1403–1407.
- (a) T. J. Guzi and T. L. Macdonald, *Tetrahedron Lett.*, 1996, **37**, 2939–2942; (b) A. Frongia, F. Secci, F. Capitta, P. P. Piras and M. L. Sanna, *Chem. Commun.*, 2013, **49**, 8812–8814; (c) A. Frongia, N. Melis, I. Serra, F. Secci, P. P. Piras and P. Caboni, *Asian J. Org. Chem.*, 2014, **3**, 378–381; (d) D. J. Aitken, P. Caboni, H. Eijlsberg, A. Frongia, R. Guillot, J. Ollivier, P. P. Piras and F. Secci, *Adv. Synth. Catal.*, 2014, **356**, 941–945; (e) N. Melis, L. Ghisu, R. Guillot, P. Caboni, F. Secci, D. J. Aitken and A. Frongia, *Eur. J. Org. Chem.*, 2015, **2015**, 4358–4366.
- (a) G. Li, L. Tang, H. Liu, Y. Wang, G. Zhao and Z. Tang, *Org. Lett.*, 2016, **18**, 4526–4529; (b) L.-y. Li, Q.-l. Zeng, G.-x. Li and Z. Tang, *Synlett*, 2019, **30**, 694–698; (c) J.-x. Liang, G.-b. Yang, Y.-p. Zhang, D.-d. Guo, J.-z. Zhao, G.-x. Li and Z. Tang, *Org. Chem. Front.*, 2020, **7**, 3242–3246.
- R. Anand, V. J. Colandrea, M. Reiter, P. Vachal, A. Zwicker, J. E. Wilson, F. Zhang and R. Zhao, Benzopiperazine Derivatives as CETP Inhibitors, Patent application WO2013/028382, Feb 28, 2013.

