



Cite this: *Chem. Sci.*, 2017, 8, 4558

Kinetic resolution of racemic 2-substituted 1,2-dihydroquinolines *via* asymmetric Cu-catalyzed borylation†

Duanyang Kong, Suna Han, Rui Wang, Meina Li, Guofu Zi and Guohua Hou *

A highly efficient kinetic resolution of racemic 2-substituted 1,2-dihydroquinolines *via* asymmetric Cu-catalyzed borylation has been realized for the first time. Under mild conditions, a variety of chiral 3-boryl-1,2,3,4-tetrahydroquinolines containing two vicinal stereogenic centers as well as the recovered 2-substituted 1,2-dihydroquinolines were afforded after 30 minutes in high yields with up to 99% ee (dr > 99 : 1) and over 98% ee values, respectively, corresponding to kinetic selectivity factors of up to 569. Moreover, this protocol was successfully applied to the asymmetric synthesis of a selective estrogen receptor modulator.

Received 18th February 2017
Accepted 11th April 2017

DOI: 10.1039/c7sc01556a

rsc.li/chemical-science

Introduction

The optically active 1,2,3,4-tetrahydroquinoline framework constitutes a key synthetic intermediate in organic synthesis and is a privileged structural motif in a broad range of natural products, biologically active compounds,¹ and pharmaceuticals such as benzastatin D, angustureine and the anti-hypercholesterolemia drug torcetrapib (Fig. 1).² Therefore, optically active tetrahydroquinolines have elicited much interest, and a great deal of effort has been devoted to the development of convenient and general synthetic approaches,^{1,3} including intramolecular cyclization by Friedel–Crafts reactions, hydroamination, allylic amination or aza-Michael addition,⁴ asymmetric hydrogenation of 2-substituted quinolines,^{5–8} and enantioselective transition metal-catalyzed nucleophilic addition of quinolinium salts.^{9–11}

On the other hand, chiral organoboron compounds, because of their utility in C–C and C–heteroatom bond formation, have greatly expanded the potential applications in organic chemistry, specifically as key intermediates in asymmetric synthesis. The direct catalytic enantioselective synthesis of organoboron compounds can be achieved by a number of reported methods,¹² such as hydroboration,¹³ diboration,¹⁴ arylborylation,¹⁵ conjugate boron addition,¹⁶ and allylic substitution.¹⁷ Among these approaches, transition metal-catalyzed borylation of prochiral C–C multiple bonds has recently attracted much

interest in chemistry.^{12c,18} For instance, Ito and coworkers made an outstanding contribution to the Cu-catalyzed asymmetric hydroboration reaction and recently reported the stepwise dearomatization and enantioselective borylation of pyridines and quinolines with excellent enantioselectivities.^{18b,c}

Kinetic resolution, which provides a simple and efficient way to access both the chiral products and recover the starting materials, has attracted considerable attention from academy and industry.¹⁹ Most recently, several exciting developments in kinetic resolution have been reported.²⁰ Transition metal-catalyzed allylic substitution, C–H iodination, C–H olefination, C–H cross-coupling and C–P coupling reactions have been successfully applied to kinetic resolution.²¹ In addition, tremendous efforts have also been made for the development of organocatalysts, such as phase-transfer catalysts, *N*-heterocyclic carbenes and Brønsted acids, for kinetic resolution.²² Despite this significant progress, to date, the number of reactions, catalysts and substrates suitable for kinetic resolution is still limited and a higher resolution efficiency is highly required. To

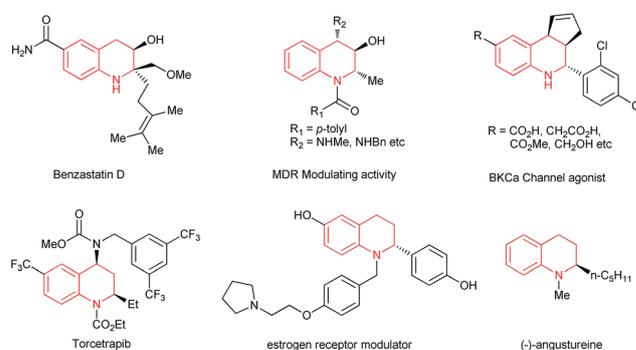
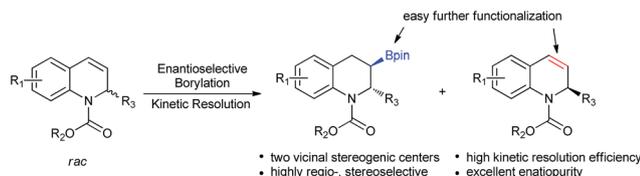


Fig. 1 Selected bioactive compounds containing tetrahydroquinolines.

Key Laboratory of Radiopharmaceuticals, College of Chemistry, Beijing Normal University, No. 19 Xijiekouwai St., Beijing 100875, China. E-mail: ghhou@bnu.edu.cn

† Electronic supplementary information (ESI) available: General experimental procedures. Compound characterization data, analysis of enantioselectivities of products and crystal parameters. CCDC 1542782–1542784. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c7sc01556a





Scheme 1 Kinetic resolution of 1,2-dihydroquinolines via Cu-catalyzed borylation.

the best of our knowledge, thus far, kinetic resolution *via* asymmetric borylation has not been explored. Therefore, we hypothesized the kinetic resolution of 2-substituted 1,2-dihydroquinolines *via* Cu-catalyzed borylation (Scheme 1), which can simultaneously afford both chiral organoboron compounds bearing two vicinal stereogenic centers and the enantiomerically enriched recovered 2-substituted 1,2-dihydroquinolines,²³ which can be transformed to the corresponding tetrahydroquinolines by simple methods. Herein, we present the kinetic resolution of 2-substituted 1,2-dihydroquinolines *via* Cu-catalyzed borylation for the first time. With kinetic resolution selectivity factors of up to 569, the chiral organoboron compounds were obtained with excellent diastereoselectivity and enantioselectivities (*dr* > 99 : 1 and up to 99% *ee*), while the unreacted 2-substituted 1,2-dihydroquinolines were recovered with extremely high enantiopurities (98–99.9% *ee*) and in high yields.

Results and discussion

The asymmetric borylation/kinetic resolution of racemic methyl 2-(naphthalene-1-yl)quinoline-1(2*H*)-carboxylate (*rac*-**1a**) was initially evaluated with B₂pin₂ in THF at 0 °C, catalyzed by a complex formed from CuCl and (*S,R*)-DuanPhos in the presence of MeOK and MeOH as additives (Table 1, entry 1). We were pleased to find that the borylation product **2a** as a single diastereomer (*dr* > 99 : 1) and the recovered **1a** were obtained with 60% *ee* and 98% *ee*, respectively, corresponding to a selectivity factor (*s*) of 17.^{19a} Although the determination of the conversion-independent selectivity factor ($s = \ln[(1 - C)(1 - ee_{1a})] / \ln[(1 - C)(1 + ee_{1a})]$) was not straightforward due to the product containing two stereogenic centers, the extraordinary diastereoselectivity (*dr* > 99 : 1) allowed for the calculation of the true selectivity factor.^{22b} Then, we examined the effect of solvents including toluene, DME and DCE (entries 2–4). According to the enantioselectivity and efficiency of the kinetic resolution, THF was a better choice albeit slightly higher *ee* values of the recovered **1a** and borylation product **2a** were observed in toluene and DME, respectively. The screening of various chiral ligands, shown in Fig. 2, which are often used in Cu-catalyzed asymmetric borylation reactions of C–C double bonds was subsequently carried out (entries 5–12). The use of (*S*)-Binap could provide good enantioselectivities for both the borylation product and the recovered starting material (entry 5), whereas (*R*)-DM-SEGPHOS, (*R,R*)-Me-Duphos and (*R,R*)-QuinoxP* afforded the recovered **1a** with very poor *ee* values, albeit with moderate to high enantioselectivities for the

Table 1 Optimization of reaction conditions^a

Entry	Ligand	Solvent	Conv ^b (%)	1a		2a	
				ee ^c (%)	ee ^{c,d} (%)	ee ^{c,d} (%)	<i>S</i> ^e
1	L1	THF	64	98	60	17	
2	L1	Toluene	71	99	42	11	
3	L1	DME	43	63	74	12	
4	L1	DCE	44	45	57	5	
5	L2	THF	53	92	83	29	
6	L3	THF	20	7	50	1	
7	L4	THF	21	24	88	25	
8	L5	THF	29	38	95	40	
9	L6	THF	51	99.4	97	251	
10	L7	THF	37	37	64	6	
11	L8	THF	39	23	36	3	
12	L9	THF	31	5	31	2	

^a Reaction conditions: CuCl (0.025 mmol), ligand (0.025 mmol), *rac*-**1a** (0.5 mmol), B₂pin₂ (0.6 mmol), MeOK (0.1 mmol), solvent (1.5 mL) MeOH (1.0 mmol), 0 °C, 2 h. ^b Calculated conversion, $C = ee_{1a} / (ee_{1a} + ee_{2a})$. ^c Determined by chiral HPLC and SFC analysis. ^d Diastereomeric ratio (*dr*) > 99 : 1 (determined by ¹H NMR). ^e Selectivity factor (*s*) = $\ln[(1 - C)(1 - ee_{1a})] / \ln[(1 - C)(1 + ee_{1a})]$.

borylation product **2a** (entries 6–8). To our delight, in addition to a satisfactory conversion, (*R,S*_p)-JosiPhos-1 dramatically increased the enantioselectivity of both product **2a** and recovered **1a** to 97% *ee* and 99.4% *ee*, respectively with an outstanding selectivity factor (*s*) of 251 (entry 9). Some other similar ligands proved to be inefficient for this kinetic resolution, with very poor enantioselectivity and selectivity factors (entries 10–12). In the end, the optimal reaction conditions were selected as CuCl/(*R,S*_p)-JosiPhos-1/MeOK/THF.

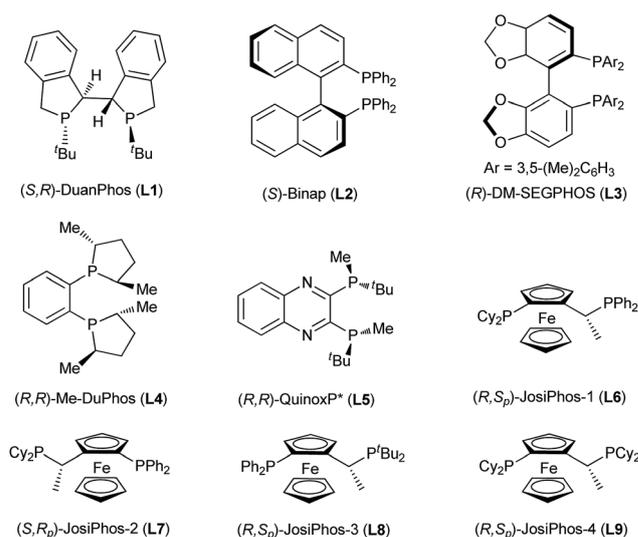


Fig. 2 Structures of the phosphine ligands screened.



In the ideal kinetic resolution of a racemate, only one of the two enantiomers reacts, and the other one is recovered (*i.e.*, $C = 50\%$). To explore the kinetic resolution of *rac*-**1a** in more detail, the ee values of product **2a** and recovered **1a**, and the conversion of *rac*-**1a** were monitored from the start of the reaction (Fig. 3). Remarkably, the enantiomeric excess of recovered **1a** increased from 0 to 99.4% after 30 minutes and remained constant thereafter. Moreover, the borylation product **2a** was afforded with an almost unaltered excellent enantioselectivity of 97% ee, even if the kinetic resolution lasted for 2 hours. These results revealed that the kinetic resolution of *rac*-**1a** via Cu-catalyzed borylation was highly effective and almost perfect. In order to confirm that only one enantiomer reacts, we performed the borylation of recovered **1a** (99.4% ee) under identical reaction conditions and, as expected, almost no borylated product was observed.

Under the optimized reaction conditions, the kinetic resolution of various racemic 2-substituted 1,2-dihydroquinolines (*rac*-**1**) via asymmetric Cu-catalyzed borylation was investigated (Table 2). All of the racemic 1,2-dihydroquinolines **1** were resolved smoothly with selectivity factors of up to 569 to afford the corresponding chiral borylated tetrahydroquinolines **2** as the single diastereomer with up to 99% ee and the recovered 2-substituted 1,2-dihydroquinolines **1** in high yields with excellent enantioselectivities (98–99.9% ee). It is notable that various carbamate moieties of 1,2-dihydroquinolines have no obvious effect on the kinetic resolution, affording the borylation products **2a–2e** with 91–97% ee and the recovered products **1a–1e** with 98–99.9% ee, corresponding to selectivity factors (*s*) of 111 to 251. The racemic 1,2-dihydroquinolines bearing a Me or MeO group at the 6- or 7-position were also tolerated, furnishing the chiral products **2f–2h** in high yields, with excellent enantioselectivities (95–96% ee) and selectivity factors ($s = 229–251$). In addition, replacing 1-naphthyl with 2-naphthyl led to a similar result, producing the borylation product **2i** with 94% ee and recovered product **1i** with 98% ee, with a selectivity factor (*s*) of 211. Gratifyingly, substituted phenyl groups at the 2-position of 1,2-dihydroquinoline proved to have no effect on kinetic resolution. Thus, excellent ee values for both borylation products and recovered materials were achieved with high selectivity

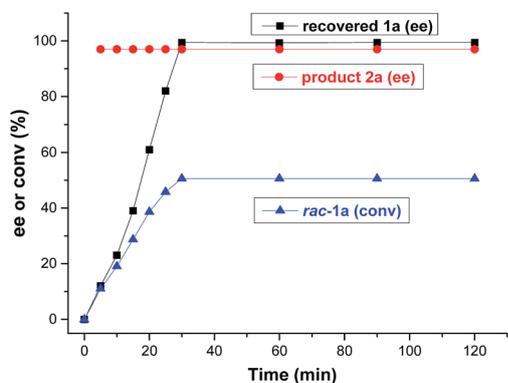


Fig. 3 Plot of the enantioselectivity of product **2a** and recovered **1a**, and the conversion of *rac*-**1a** against reaction time.

Table 2 Substrate scope^{a,b}

 2a : 45% yield, 97% ee 1a : 47% yield, 99.4% ee <i>C</i> = 51%, <i>s</i> = 251	 2b : 44% yield, 97% ee 1b : 45% yield, 98% ee <i>C</i> = 51%, <i>s</i> = 230	 2c : 46% yield, 94% ee 1c : 42% yield, 99% ee <i>C</i> = 51%, <i>s</i> = 211
 2d : 47% yield, 91% ee 1d : 41% yield, 99% ee <i>C</i> = 52%, <i>s</i> = 111	 2e : 43% yield, 93% ee 1e : 45% yield, 99.9% ee <i>C</i> = 52%, <i>s</i> = 185	 2f : 45% yield, 96% ee 1f : 47% yield, 99.3% ee <i>C</i> = 51%, <i>s</i> = 239
 2g : 46% yield, 96% ee 1g : 43% yield, 99.2% ee <i>C</i> = 51%, <i>s</i> = 229	 2h : 47% yield, 95% ee 1h : 44% yield, 99.4% ee <i>C</i> = 51%, <i>s</i> = 251	 2i : 45% yield, 94% ee 1i : 46% yield, 99% ee <i>C</i> = 51%, <i>s</i> = 211
 2j : 47% yield, 94% ee 1j : 43% yield, 99% ee <i>C</i> = 51%, <i>s</i> = 211	 2k : 45% yield, 99% ee 1k : 47% yield, 99.5% ee <i>C</i> = 50%, <i>s</i> = 569	 2l : 46% yield, 93% ee 1l : 43% yield, 99% ee <i>C</i> = 52%, <i>s</i> = 145
 2m : 47% yield, 92% ee 1m : 44% yield, 99% ee <i>C</i> = 52%, <i>s</i> = 128	 2n : 44% yield, 92% ee 1n : 43% yield, 99.9% ee <i>C</i> = 52%, <i>s</i> = 184	 2o : 43% yield, 90% ee 1o : 40% yield, 99% ee <i>C</i> = 52%, <i>s</i> = 99
 2p : 46% yield, 93% ee 1p : 45% yield, 99% ee <i>C</i> = 52%, <i>s</i> = 145	 2q : 48% yield, 90% ee 1q : 41% yield, 99% ee <i>C</i> = 52%, <i>s</i> = 99	 2r : 47% yield, 93% ee 1r : 40% yield, 99% ee <i>C</i> = 52%, <i>s</i> = 145

^a Unless otherwise mentioned, all reactions were performed with CuCl (0.025 mmol), (*R,S*)-JosiPhos-1 (0.025 mmol), *rac*-**1** (0.5 mmol), B₂Pin₂ (0.6 mmol), MeOK (0.1 mmol), THF (1.5 mL), MeOH (1.0 mmol), 0 °C, 30 min. ^b Isolated yield; calculated conversion, $C = ee_1/(ee_1 + ee_2)$; enantiomeric excess (ee) was determined by chiral HPLC or SFC analysis using a chiral stationary phase; diastereomeric ratio (*dr*) > 99 : 1 (determined by ¹H NMR). Selectivity factor (*s*) = $\ln[(1 - C)(1 - ee_1)]/\ln[(1 - C)(1 + ee_1)]$. ^c THF/toluene/DME = 2 : 1 : 1 (1.5 mL), 2 h. ^d BuOK (0.1 mmol), THF/toluene/DME = 1 : 1 : 1 (1.5 mL), 2 h. ^e THF/toluene/DME = 1 : 1 : 1 (1.5 mL), 2 h.

factors ($s = 99–569$) irrespective of the electronic properties or position of the substituents in the 2-phenyl group, affording **2j–2p** with 90–99% ee and recovered product **1j–1p** with over 99% ee. Remarkably, the *o*-tolyl substituted substrate *rac*-**1k** provided the product **2k** with both the highest enantioselectivity (99% ee) and a selectivity factor of 569. It is noteworthy that the



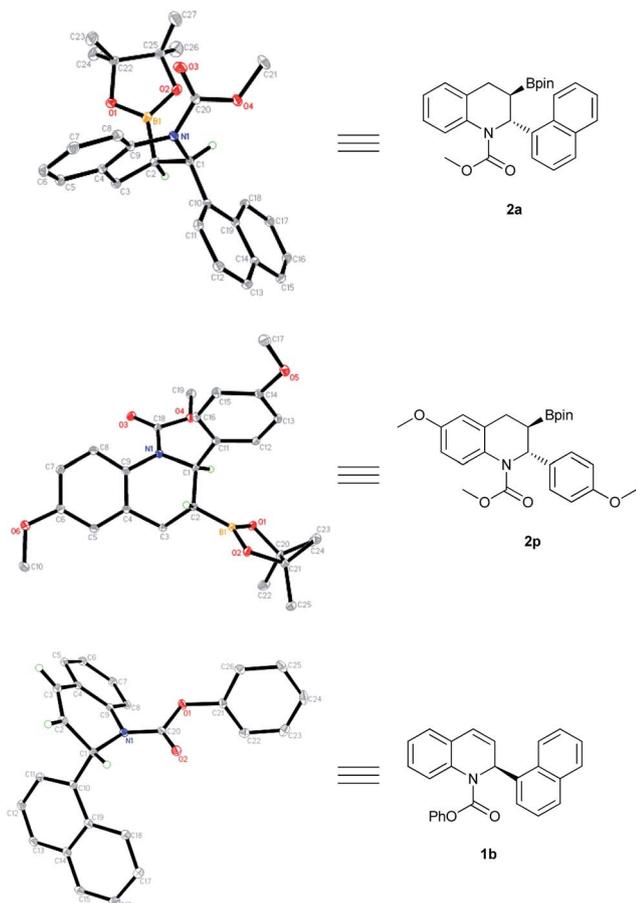
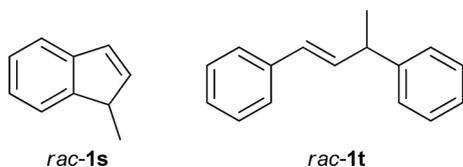


Fig. 4 X-ray crystallographic analysis of products **2a**, **2p** and recovered **1b**.

2-alkyl substituted substrates **1q** and **1r** could also be resolved with high selectivity factors (99 and 145, respectively), giving the corresponding borylation products **2q** and **2r** with comparable enantioselectivities (90% ee and 93% ee), and recovered products **1q** and **1r** with an identical ee of 99%.

The generated borylation products **2a** and **2p** were the trans isomers, with an absolute configuration of (2*R*,3*R*), determined by X-ray crystallography. Likewise, recovered product **1b** was assigned the (*S*) configuration according to the corresponding single-crystal structure (Fig. 4).

However, this strategy was not effective for the kinetic resolution of simple olefins. Thus, under the optimized reaction conditions, the borylation of substrates **1s** and **1t** did not proceed at all. The *rac*-**1s** and **1t** were completely recovered.



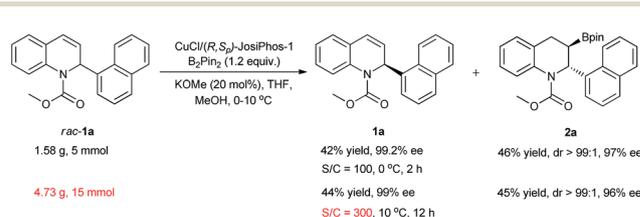
To demonstrate the potential of the kinetic resolution, turnover number (TON) experiments were conducted on a gram-scale. With a lower catalyst loading of 1.0 mol% (TON =

100), the kinetic resolution of *rac*-**1a** was completed, providing the desired product **2a** in 46% yield with 97% ee and the recovered product **1a** in 42% yield with 99.2% ee. With a much lower catalyst loading of 0.33 mol% (TON = 300), *rac*-**1a** (15 mmol, 4.73 g) was smoothly resolved at 10 °C to produce the corresponding product **2a** in 45% yield with 96% ee and the recovered product **1a** in 44% yield with 99% ee (Scheme 2), which represents the highest activity achieved in Cu-catalyzed borylation reactions to date.

The chiral 3-boryl-tetrahydroquinolines **2** are versatile synthetic intermediates that can be easily converted to various derivatives (Scheme 3(a)).^{18e,24} For example, product **2f** could be converted to the chiral 3-hydroxyl tetrahydroquinoline **3** bearing two vicinal stereogenic centers by oxidation with NaBO₃, in high yields and without any loss of enantioselectivity. The oxidation of **2a**, followed by the hydrolysis of the carbamate afforded the chiral 3-hydroxyl tetrahydroquinoline **4** with maintained enantioselectivity, 97% ee. Compound **2a** could also be successfully transformed into both the corresponding boronic acid **5** and the trifluoroborate salt **6** in good yields. Moreover, **2a** could also be converted to the primary alcohol **7** and compound **8** with high enantioselectivities by homologation and Suzuki–Miyaura coupling, respectively.^{12b,25} In addition, a simple Pd/C-catalyzed hydrogenation of the chiral recovered compound **1p** with 99% ee afforded the tetrahydroquinoline **9** with retention of configuration, which was subsequently applied to the enantioselective synthesis of selective estrogen receptor modulators (Scheme 3(b)).²⁶

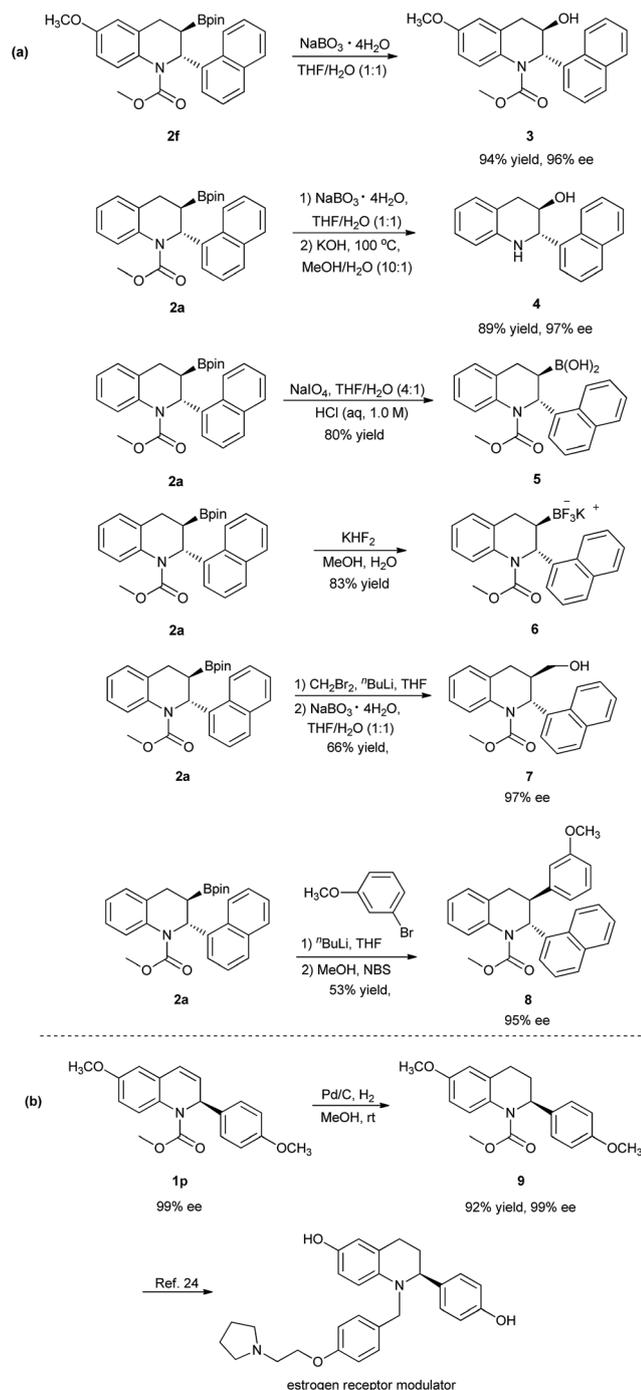
In order to elucidate the reaction mechanism, a labeling experiment with deuterium was performed (see the ESI†). The borylation of *rac*-**1a** under the optimized conditions using CD₃OD instead of CH₃OH gave the product **2a** labelled with deuterium at the 4-position (>95% D), with excellent enantioselectivity, 97% ee (Scheme 4). The *syn* configuration between the deuterium atom at the 4-position and the boryl group at the 3-position indicated that the addition of the Cu–B complex to the C–C double bond of *rac*-**1a** occurred in a *syn* fashion.

Based on previous reports and our experiment,^{18c,27} a feasible mechanism for the kinetic resolution of 2-substituted 1,2-dihydroquinolines *via* Cu-catalyzed borylation was proposed, as shown in Fig. 5. The initial exchange of CuCl with the ligand and MeOK resulted in the formation of the Cu–OMe complex **A**, followed by a σ -bond metathesis with B₂pin₂ to generate the borylcopper species **B**. Subsequently, the coordination of the racemic 2-substituted 1,2-dihydroquinoline **1** to copper gave complex **C**. The *syn*-addition furnished the borylated

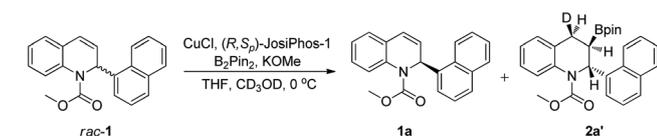


Scheme 2 Kinetic resolution of *rac*-**1a** on a gram scale with a lower catalyst loading.





Scheme 3 Representative transformations of products 2 and enantiomerically enriched recovered starting material 1.



Scheme 4 Deuterium labeling experiment.

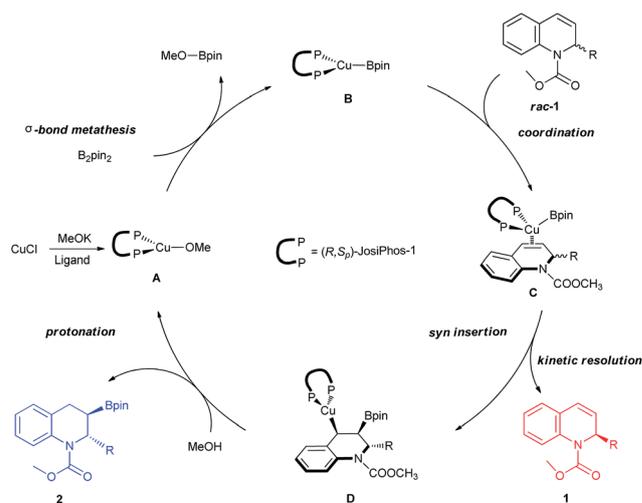


Fig. 5 Proposed catalytic cycle for the kinetic resolution via Cu-catalyzed borylation.

alkylcopper intermediate **D** along with the chiral recovered starting material **1**. Finally, the protonation of **D** by MeOH formed the corresponding borylation product **2** and regenerated the Cu-OMe complex **A**.

Conclusions

In conclusion, we have presented the first kinetic resolution of 2-substituted 1,2-dihydroquinolines by asymmetric Cu-catalyzed borylation under mild reaction conditions, achieving excellent enantiodiscrimination and kinetic resolution. A wide range of chiral 3-boryl-1,2,3,4-tetrahydroquinolines containing two vicinal stereogenic centers and recovered 2-substituted 1,2-dihydroquinolines were obtained after 30 minutes in high yields with 90–99% ee (dr > 99 : 1) and over 98% ee, respectively, corresponding to kinetic selectivity factors of up to 569. Finally, this protocol was successfully applied to the asymmetric synthesis of selective estrogen receptor modulators.

Acknowledgements

We thank for their generous financial support the National Natural Science Foundation of China (Grant No. 21672024, 21272026, and 21472013), the Fundamental Research Funds for the Central Universities, the Program for Changjiang Scholars and the Innovative Research Team in University, and the Beijing Municipal Commission of Education. Guohua Hou dedicates this work to Professor Qi-Lin Zhou on the occasion of his 60th birthday.

Notes and references

- V. Sridharan, P. A. Suryavanshi and J. C. Menéndez, *Chem. Rev.*, 2011, **111**, 7157.
- (a) W.-G. Kim, J.-P. Kim, C.-J. Kim, K.-H. Lee and I.-D. Yoo, *J. Antibiot.*, 1996, **49**, 20; (b) R. Hiessböck, C. Wolf, E. Richter,



- M. Hitzler, P. Chiba, M. Kratzel and G. Ecker, *J. Med. Chem.*, 1999, **42**, 1921; (c) V. K. Gore, V. V. Ma, R. Yin, J. Ligutti, D. Immke, E. M. Doherty and M. H. Norman, *Bioorg. Med. Chem. Lett.*, 2010, **20**, 3573; (d) J. A. Sikorski, *J. Med. Chem.*, 2006, **49**, 1.
- 3 L. Mengozzi, A. Gualandi and P. G. Cozzi, *Eur. J. Org. Chem.*, 2016, **2016**, 3200.
- 4 (a) D. Ma, C. Xia, J. Jiang and J. Zhang, *Org. Lett.*, 2001, **3**, 2189; (b) O. Hara, T. Koshizawa, K. Makino, I. Kunimune, A. Namiki and Y. Hamada, *Tetrahedron*, 2007, **63**, 6170; (c) N. T. Patil, H. Wu and Y. J. Yamamoto, *Org. Chem.*, 2007, **72**, 6577.
- 5 (a) J. Wu and A. S. C. Chan, *Acc. Chem. Res.*, 2006, **39**, 711; (b) Y.-G. Zhou, *Acc. Chem. Res.*, 2007, **40**, 1357; (c) D.-S. Wang, Q.-A. Chen, S.-M. Lu and Y.-G. Zhou, *Chem. Rev.*, 2012, **112**, 2557.
- 6 (a) S.-M. Lu, Y.-Q. Wang, X.-W. Han and Y.-G. Zhou, *Angew. Chem., Int. Ed.*, 2006, **45**, 2260; (b) D.-W. Wang, X.-B. Wang, D.-S. Wang, S.-M. Lu, Y.-G. Zhou and Y.-X. Li, *J. Org. Chem.*, 2009, **74**, 2780; (c) T. Wang, L.-G. Zhuo, Z. Li, F. Chen, Z. Ding, Y. He, Q.-H. Fan, J. Xiang, Z.-X. Yu and A. S. C. Chan, *J. Am. Chem. Soc.*, 2011, **133**, 9878; (d) Z.-P. Chen, Z.-S. Ye, M.-W. Chen and Y.-G. Zhou, *Synthesis*, 2013, **45**, 3239; (e) J. Zhou, Q.-F. Zhang, W.-H. Zhao and G.-F. Jiang, *Org. Biomol. Chem.*, 2016, **14**, 6937; (f) H. Zhou, Z. Li, Z. Wang, T. Wang, L. Xu, Y. He, Q.-H. Fan, J. Pan, L. Gu and A. S. C. Chan, *Angew. Chem., Int. Ed.*, 2008, **47**, 8464.
- 7 (a) Q.-S. Guo, D.-M. Du and J. Xu, *Angew. Chem., Int. Ed.*, 2008, **47**, 759; (b) C. Wang, C. Li, X. Wu, A. Pettman and J. Xiao, *Angew. Chem., Int. Ed.*, 2009, **48**, 6524; (c) M. Rueping, A. P. Antonchick and T. Theissmann, *Angew. Chem., Int. Ed.*, 2006, **45**, 3683.
- 8 (a) Z. Zhang and H. Du, *Org. Lett.*, 2015, **17**, 6266; (b) Z. Zhang and H. Du, *Org. Lett.*, 2015, **17**, 2816.
- 9 (a) M. Pappoppula, F. S. P. Cardoso, B. O. Garrett and A. Aponick, *Angew. Chem., Int. Ed.*, 2015, **54**, 15202; (b) D. A. Black, R. E. Beveridge and B. A. Arndtsen, *J. Org. Chem.*, 2008, **73**, 1906.
- 10 (a) K. T. Sylvester, K. Wu and A. G. Doyle, *J. Am. Chem. Soc.*, 2012, **134**, 16967; (b) J. D. Shields, D. T. Ahneman, T. J. A. Graham and A. G. Doyle, *Org. Lett.*, 2014, **16**, 142.
- 11 Y. Wang, Y. Liu, D. Zhang, H. Wei, M. Shi and F. Wang, *Angew. Chem., Int. Ed.*, 2016, **55**, 3776.
- 12 (a) K. Semba, T. Fujihara, J. Terao and Y. Tsuji, *Tetrahedron*, 2015, **71**, 2183; (b) M. V. Joannou, B. S. Moyer and S. J. Meek, *J. Am. Chem. Soc.*, 2015, **137**, 6176; (c) Y. Xi and J. F. Hartwig, *J. Am. Chem. Soc.*, 2016, **138**, 6703; (d) H. Lee, J. T. Han and J. Yun, *ACS Catal.*, 2016, **6**, 6487.
- 13 For reviews on catalytic enantioselective hydroboration, see: (a) C. M. Crudden and D. Edwards, *Eur. J. Org. Chem.*, 2003, **2003**, 4695; (b) A.-M. Carroll, T. P. O'Sullivan and P. J. Guiry, *Adv. Synth. Catal.*, 2005, **347**, 609; for selected examples, see: (c) D. Noh, H. Chea, J. Ju and J. Yun, *Angew. Chem., Int. Ed.*, 2009, **48**, 6062; (d) S. M. Smith and J. M. Takacs, *J. Am. Chem. Soc.*, 2010, **132**, 1740; (e) Y. Lee and A. H. Hoveyda, *J. Am. Chem. Soc.*, 2009, **131**, 3160; (f) X. Feng, H. Jeon and J. Yun, *Angew. Chem., Int. Ed.*, 2013, **52**, 3989; (g) H. Lee, B. Y. Lee and J. Yun, *Org. Lett.*, 2015, **17**, 764; (h) Y. Sasaki, C. Zhong, M. Sawamura and H. Ito, *J. Am. Chem. Soc.*, 2010, **132**, 1226; (i) R. Corberan, N. W. Mszar and A. H. Hoveyda, *Angew. Chem., Int. Ed.*, 2011, **50**, 7079.
- 14 For selected examples on catalytic enantioselective diboration, see: (a) H. E. Burks and J. P. Morken, *Chem. Commun.*, 2007, **2007**, 4717; (b) S. N. Mlynarski, C. H. Schuster and J. P. Morken, *Nature*, 2014, **505**, 386; (c) Y. Lee, H. Jang and A. H. Hoveyda, *J. Am. Chem. Soc.*, 2009, **131**, 18234; (d) H. E. Burks, L. T. Kliman and J. P. Morken, *J. Am. Chem. Soc.*, 2009, **131**, 9134; (e) J. R. Coombs, F. Haeffner, L. T. Kliman and J. P. Morken, *J. Am. Chem. Soc.*, 2013, **135**, 11222; (f) K. Toribatake and H. Nishiyama, *Angew. Chem., Int. Ed.*, 2013, **52**, 11011; (g) J. R. Coombs, L. Zhang and J. P. Morken, *J. Am. Chem. Soc.*, 2014, **136**, 16140; (h) L. T. Kliman, S. N. Mlynarski and J. P. Morken, *J. Am. Chem. Soc.*, 2009, **131**, 13210.
- 15 For selected examples on catalytic enantioselective arylborylation, see: (a) H. M. Nelson, B. D. Williams, J. Miró and F. D. Toste, *J. Am. Chem. Soc.*, 2015, **137**, 3213; (b) W. Su, T. J. Gong, X. Lu, M. Y. Xu, C. G. Yu, Z. Y. Xu, H. Z. Yu, B. Xiao and Y. Fu, *Angew. Chem., Int. Ed.*, 2015, **54**, 12957.
- 16 For selected examples of metal-catalyzed enantioselective conjugate boron additions, see: (a) J.-E. Lee and J. Yun, *Angew. Chem., Int. Ed.*, 2008, **47**, 145; (b) I. H. Chen, L. Yin, W. Itano, M. Kanai and M. Shibasaki, *J. Am. Chem. Soc.*, 2009, **131**, 11664; (c) I.-H. Chen, M. Kanai and M. Shibasaki, *Org. Lett.*, 2010, **12**, 4098; (d) J. C. H. Lee, R. Hall and D. G. McDonald, *Nat. Chem.*, 2011, **3**, 894; (e) Y. Lou, P. Cao, T. Jia, Y. Zhang, M. Wang and J. Liao, *Angew. Chem., Int. Ed.*, 2015, **54**, 12134. For selected examples of metal-free enantioselective conjugate boron additions, see: (f) J. M. O'Brien, K.-S. Lee and A. H. Hoveyda, *J. Am. Chem. Soc.*, 2010, **132**, 10630; (g) H. Wu, S. Radomkit, J. M. O'Brien and A. H. Hoveyda, *J. Am. Chem. Soc.*, 2012, **134**, 8277; (h) S. Radomkit and A. H. Hoveyda, *Angew. Chem., Int. Ed.*, 2014, **53**, 3387.
- 17 For selected examples on catalytic allylic boration, see: (a) H. Ito, S. Ito, Y. Sasaki, K. Matsuura and M. Sawamura, *J. Am. Chem. Soc.*, 2007, **129**, 14856; (b) A. Guzman-Martinez and A. H. Hoveyda, *J. Am. Chem. Soc.*, 2010, **132**, 10634; (c) H. Ito, S. Kunii and M. Sawamura, *Nat. Chem.*, 2010, **2**, 972; (d) J. K. Park, H. H. Lackey, B. A. Ondrusek and D. T. McQuade, *J. Am. Chem. Soc.*, 2011, **133**, 2410; (e) K. Semba, T. Fujihara, J. Terao and Y. Tsuji, *Tetrahedron*, 2015, **71**, 2183.
- 18 For selected examples on boration of heterocyclic compounds, see: (a) K. Kubota, K. Hayama, H. Iwamoto and H. Ito, *Angew. Chem., Int. Ed.*, 2015, **54**, 8809; (b) K. Kubota, Y. Watanabe, K. Hayama and H. Ito, *J. Am. Chem. Soc.*, 2016, **138**, 4338; (c) K. Kubota, Y. Watanabe and H. Ito, *Adv. Synth. Catal.*, 2016, **358**, 2379; (d) D. Nishikawa, K. Hirano and M. Miura, *Org. Lett.*, 2016, **18**, 4856; (e) M. Guisan-Ceinos, A. Parra, V. Martin-Heras and M. Tortosa, *Angew. Chem., Int. Ed.*, 2016, **55**, 6969.



- 19 (a) The selectivity factor (s) = (rate of fast-reacting enantiomer)/(rate of slow-reacting enantiomer) = $\ln[(1 - C)(1 - ee)]/\ln[(1 - C)(1 + ee)]$ where C is the conversion and ee is the enantiomeric excess of the remaining starting material. $C = ee/(ee + ee')$, which ee is the enantiomeric excess of the remaining starting material and ee' is the enantiomeric excess of the corresponding product. H. B. Kagan and J. C. Fiaud, *Top. Stereochem.*, 1988, **18**, 249; (b) E. Vedejs and M. Jure, *Angew. Chem., Int. Ed.*, 2005, **44**, 3974; (c) D. E. J. E. Robinson and S. D. Bull, *Tetrahedron: Asymmetry*, 2003, **14**, 1407; (d) J.-H. Xie and Q.-L. Zhou, *Acc. Chem. Res.*, 2008, **41**, 581.
- 20 For selected examples of kinetic resolution, see: (a) H. Hu, Y. Liu, L. Liu, Y. Zhang, X. Liu and X. Feng, *Angew. Chem., Int. Ed.*, 2016, **55**, 10098; (b) T. Shinozawa, S. Terasaki, S. Mizuno and M. Kawatsura, *J. Org. Chem.*, 2016, **81**, 5766; (c) T. Huang, L. Lin, X. Hu, J. Zheng, X. Liu and X. Feng, *Chem. Commun.*, 2015, **51**, 11374; (d) D. Grassi and A. Alexakis, *Chem. Sci.*, 2014, **5**, 3803.
- 21 For selected examples of kinetic resolution by cross-coupling, see: (a) B.-L. Lei, C.-H. Ding, X.-F. Yang, X.-L. Wan and X.-L. Hou, *J. Am. Chem. Soc.*, 2009, **131**, 18250; (b) K.-J. Xiao, L. Chu, G. Chen and J.-Q. Yu, *J. Am. Chem. Soc.*, 2016, **138**, 7796; (c) Y. K. Choi, J. H. Suh, D. Lee, I. T. Lim, J. Y. Jung and M.-J. Kim, *J. Org. Chem.*, 1999, **64**, 8423; (d) B. J. Lüssem and H.-J. Gais, *J. Am. Chem. Soc.*, 2003, **125**, 6066; (e) C. Fischer, C. Defieber, T. Suzuki and E. M. Carreira, *J. Am. Chem. Soc.*, 2004, **126**, 1628; (f) X. L. Hou and B. H. Zheng, *Org. Lett.*, 2009, **11**, 1789; (g) L. Chu, K.-J. Xiao and J.-Q. Yu, *Science*, 2014, **346**, 451; (h) D.-W. Gao, Q. Gu and S.-L. You, *ACS Catal.*, 2014, **4**, 2741; (i) K.-J. Xiao, L. Chu and J.-Q. Yu, *Angew. Chem., Int. Ed.*, 2016, **55**, 2856; (j) V. Bhat, S. Wang, B. M. Stoltz and S. C. Virgil, *J. Am. Chem. Soc.*, 2013, **135**, 16829.
- 22 For selected examples of kinetic resolution by organocatalysts, see: (a) Y. Kuroda, S. Harada, A. Oonishi, H. Kiyama, Y. Yamaoka, K.-i. Yamada and K. Takasu, *Angew. Chem., Int. Ed.*, 2016, **55**, 13137; (b) K. Saito and T. Akiyama, *Angew. Chem., Int. Ed.*, 2016, **55**, 3148; (c) D. An, X. Guan, R. Guan, L. Jin, G. Zhang and S. Zhang, *Chem. Commun.*, 2016, **52**, 11211; (d) S. Dong, M. Frings, H. Cheng, J. Wen, D. Zhang, G. Raabe and C. Bolm, *J. Am. Chem. Soc.*, 2016, **138**, 2166; (e) J. Wang, M.-W. Chen, Y. Ji, S.-B. Hu and Y.-G. Zhou, *J. Am. Chem. Soc.*, 2016, **138**, 10413; (f) B. Wanner, I. Kreituss, O. Gutierrez, M. C. Kozłowski and J. W. Bode, *J. Am. Chem. Soc.*, 2015, **137**, 11491; (g) X. Lin, S. Ruan, Q. Yao, C. Yin, L. Lin, X. Feng and X. Liu, *Org. Lett.*, 2016, **18**, 3602; (h) E. Sorrentino and S. J. Connon, *Org. Lett.*, 2016, **18**, 5204; (i) S. Shirakawa, X. Wu and K. Maruoka, *Angew. Chem., Int. Ed.*, 2013, **52**, 14200; (j) D.-J. Cheng, L. Yan, S.-K. Tian, M.-Y. Wu, L.-X. Wang, Z.-L. Fan, S.-C. Zheng, X.-Y. Liu and B. Tan, *Angew. Chem., Int. Ed.*, 2014, **53**, 3684.
- 23 F. Amiot, L. Cointeaux, E. J. Silve and A. Alexakis, *Tetrahedron*, 2004, **60**, 8221.
- 24 C. W. Liskey and J. F. Hartwig, *J. Am. Chem. Soc.*, 2013, **135**, 3375.
- 25 A. Bonet, M. Odachowski, D. Leonori, S. Essafi and V. K. Aggarwal, *Nat. Chem.*, 2014, **6**, 584.
- 26 (a) O. B. Wallace, K. S. Lauwers, S. A. Jones and J. A. Dodge, *Bioorg. Med. Chem. Lett.*, 2003, **13**, 1907; (b) H. Tadaoka, D. Cartigny, T. Nagano, T. Gosavi, T. Ayad, J.-P. Genêt, T. Ohshima, V. Ratovelomanana-Vidal and K. Mashima, *Chem.-Eur. J.*, 2009, **15**, 9990.
- 27 (a) N. Matsuda, K. Hirano, T. Satoh and M. Miura, *J. Am. Chem. Soc.*, 2013, **135**, 4934; (b) D. S. Laitar, P. Müller and J. P. Sadighi, *J. Am. Chem. Soc.*, 2005, **127**, 17196.

