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Enantioconvergent synthesis of chiral fluorenols from racemic secondary alcohols *via* Pd(II)/chiral norbornene cooperative catalysis†

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An efficient protocol for the asymmetric synthesis of fluorenols has been developed through an enantioconvergent process enabled by Pd(II)/chiral norbornene cooperative catalysis. This approach allows facile access to diverse functionalized chiral fluorenols with constantly excellent enantioselectivities, applying readily available racemic secondary *ortho*-bromobenzyl alcohols and aryl iodides as the starting materials.

Introduction

Racemic secondary alcohols have been recognized as one of the most useful feedstocks for organic transformations owing to their generally stable, nontoxic, and readily available properties.[1,2] Therefore, the transformation of racemic secondary alcohols into value-added chiral compounds is an attractive approach in asymmetric synthesis.[1a,2–6] Considerable progress has been made in this area so far, culminating in the development of several elegant strategies, including deracemization,[3,4] enantioconvergent transformation,[1a,2,5] and kinetic resolution (KR).[6] For example, two common reaction modes, linear and cyclic redox deracemizations, have been established to prepare enantioenriched secondary alcohols from the corresponding racemates (Fig. 1a).[4c–h] In particular, Zuo and co-workers reported a photoinduced deracemization of secondary alcohols enabled by asymmetric ligand-to-metal charge transfer (LMCT) catalysis.[4i] In 2021, Shi and co-workers disclosed the nickel/N-heterocyclic carbene-catalyzed enantioconvergent arylation of racemic secondary alcohols to synthesize enantioenriched tertiary alcohols (Fig. 1b).[2a] Moreover, enantioconvergent transformations of racemic secondary alcohols into enantioenriched chiral higher-order alcohols, amines, N-

heterocycles and ketones through asymmetric borrowing hydrogen catalysis have also been developed (Fig. 1c).[1a,2b,5]

Palladium/norbornene (Pd/NBE) cooperative catalysis, firstly reported by Catellani and co-workers in 1997,[7] has become a powerful strategy for expeditious synthesis of polysubstituted arenes.[8] For instance, the synthesis of racemic fluorenols (FOLs)
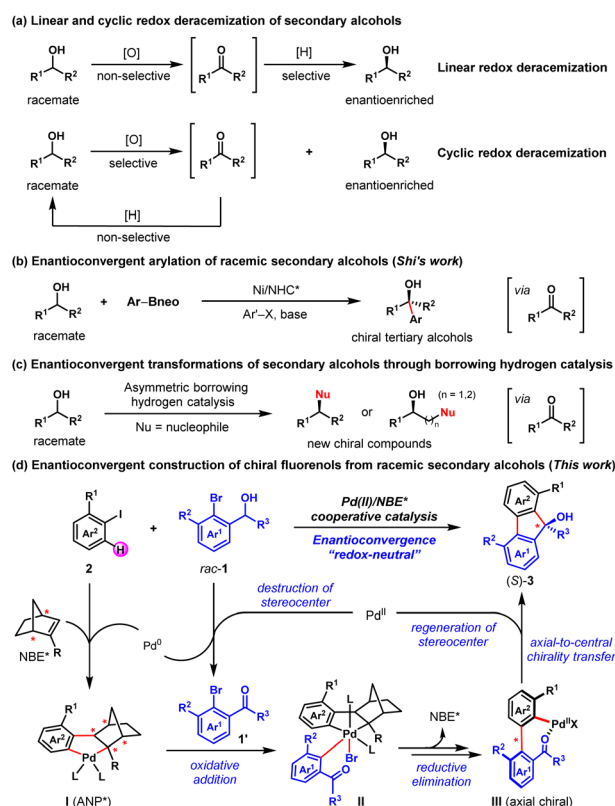

Fig. 1 Typical strategies for transforming racemic secondary alcohols into enantioenriched compounds.

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† Electronic supplementary information (ESI) available. CCDC 2222332 and 2323314. For ESI and crystallographic data in CIF or other electronic format see DOI: https://doi.org/10.1039/d4sc01004c

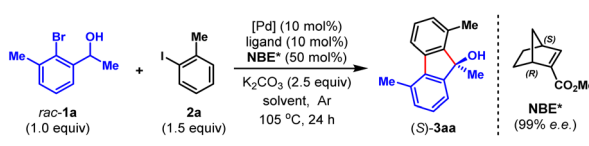‡ These authors contributed equally: Han Wei and Jiangwei Chen.

via Pd/NBE cooperative catalysis has been successfully developed by Lautens[9a] and Della Ca',[9b] respectively. Asymmetric palladium/chiral norbornene (Pd/NBE*) cooperative catalysis has been theoretically expected as a potential strategy for asymmetric synthesis. However, exploitation of this asymmetric tactic has rarely been initiated for a long time, due to the associated formidable challenges of this complex process.[10] It is only until recently that remarkable breakthroughs have been achieved in this field, owing to the efforts of Yu,[11] Dong,[12] Song,[13] Liang[14] and us.[15]

Inspired by these elegant works, we envisioned an asymmetric method to access enantioenriched FOLs through an enantioconvergent process enabled by Pd/NBE* cooperative catalysis, with widely available racemic secondary benzyl alcohols and aryl iodides as the reactants. As depicted in Fig. 1d, this method includes two sequential steps. Firstly, a Pd(II)-initiated oxidation of the racemic secondary *ortho*-bromobenzyl alcohol (**1**) will afford the achiral *ortho*-bromoacetophenone (**1′**) and the corresponding Pd(0) species.[9b,16] Secondly, the Pd(0)/NBE* co-catalyzed asymmetric Catellani-type reaction between the *in situ* generated *ortho*-bromoacetophenone (**1′**) and aryl iodide (**2**) will lead to enantioenriched FOL (**3**) *via* Pd(IV) intermediate (**II**) and axial chiral Pd(II) intermediate (**III**), and meanwhile regenerating the Pd(II) species[9,15a] (see Fig. S5 in ESI† for more details of the proposed catalytic cycle). The potential features of this protocol include readily available starting materials, redox-neutral process (no external redox reagent is needed), the intriguing asymmetric strategy for destruction/reconstruction of stereoelement and the unique axial-to-central chirality transfer mode. From a practical perspective, the FOL products are known for their biological activity and applications in material.[17] Until now, extensive efforts have been devoted to the synthesis of racemic FOLs and a number of effective strategies have been developed.[9,18] However, only three examples of the asymmetric synthesis of FOLs have been reported,[15a,19] to the best of our knowledge. Thus, the development of new strategies for their asymmetric synthesis is highly desirable. Nevertheless, there are three foreseeable main challenges regarding this proposal: (1) the identification of an appropriate catalyst combination of Pd(II) species, ligand and NBE* to ensure that the oxidation of racemic benzyl alcohol and the Catellani-type reaction connect well to each other and progress in an overall redox-neutral manner; (2) since NBE* is the only chiral source of this complex asymmetric transformation, the employment of a versatile NBE* cocatalyst is pivotal to achieve both good reactivity and enantioselectivity of this method; (3) multiple competitive side reactions, for example, the direct annulation of racemic secondary benzyl alcohol with aryl iodide to afford the benzo[c]chromene product,[15d,20] premature *ipso*-protonation of the transient ary-Pd(II) species (*e.g.*, **III**)[21] and *etc.* (see Table 1).
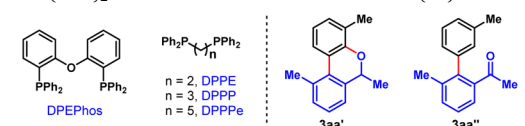
Results and discussion

To validate our hypothesis, we performed a model reaction using racemic secondary *ortho*-bromobenzyl alcohol (*rac*-**1a**) and 2-iodotoluene (**2a**) as the reactants (Table 1). To our delight, under

Table 1 Optimization of reaction conditions[a]

Entry	[Pd]	Ligand	Solvent	Yield[b] (%)	E.e.[c] (%)
1	Pd(OAc)₂	TFP[d]	Toluene	24	98
2	Pd(OAc)₂	DPEPhos	Toluene	65	—
3	Pd(OAc)₂	DPPE	Toluene	66	—
4	Pd(OAc)₂	DPPP	Toluene	78	98
5	Pd(OAc)₂	DPPPe	Toluene	73	—
6	PdI₂	DPPP	Toluene	23	—
7	Pd(PPh₃)₄	DPPP	Toluene	Trace	—
8[e]	Pd(OAc)₂	DPPP	Toluene	83	—
9[e]	Pd(OAc)₂	DPPP	DCE	89	—
10[e,f]	Pd(OAc)₂	DPPP	DCE	88	98
11[e,f,g]	Pd(OAc)₂	DPPP	DCE	88 (82)	98

[a] All reactions were performed on a 0.1 mmol scale. [b] GC yield with biphenyl as an internal standard and isolated yield shown in parentheses. [c] Determined by HPLC analysis on a chiral stationary phase. [d] 20 mol% TFP. [e] 110 °C instead of 105 °C. [f] 25 mol% NBE* was applied. [g] 1.5 equiv. of K₂CO₃ was applied. —: not detected. TFP: tri(2-furyl)phosphine. DCE: 1,2-dichloroethane.

our previously reported reaction conditions (Pd(OAc)₂ (10 mol%), tri(2-furyl)phosphine (TFP) (20 mol%), (1*R*,4*S*)-2-methyl ester-substituted NBE (NBE*, 99% e.e., 50 mol%) and heating at 105 °C),[15d] the desired chiral FOL **3aa** was obtained with excellent enantioselectivity (98% e.e.), albeit in only 24% yield (entry 1). Meanwhile, two main expected side products were isolated, which were the benzo[c]chromene **3aa′** (12% isolated yield) formed through intramolecular *ipso*-etherification and the *ipso*-hydrogen-terminated one **3aa″** (8% isolated yield). Encouraged by these preliminary results, we next focused on optimization of the reaction parameters to increase the reaction efficiency and chemical selectivity. Gratifyingly, the phosphine ligand proved to take a critical role for increasing the yield and chemical selectivity. The unique bidentate phosphine ligands with a flexible backbone,[22] such as DPEPhos, DPPE, DPPP and DPPPe, are generally superior to monodentate phosphine ligands, to deliver **3aa** in significantly improved yields (65–78%, entries 2–5). DPPP is identified as the optimal one (entry 4). Further screening of palladium catalyst, solvent, and reaction temperature indicated that Pd(OAc)₂, 1,2-dichloroethane (DCE) and 110 °C was the optimal combination (entries 6–9), which provided **3aa** in a substantially improved yield (89%, entry 9). It is worth mentioning that the use of DCE can reduce the production of side product **3aa″**. Importantly, the loading of NBE* could be reduced to a truly catalytic amount (25 mol%) without any erosion of the yield and enantiopurity of **3aa** (entry 10). Moreover,

the amount of K_2CO_3 could also be reduced to 1.5 equiv. without any deleterious effects on the reaction (entry 11). Additional optimization of other reaction parameters (*e.g.*, base, concentration and *etc.*) did not improve the efficiency further (see Tables S1–S5 in ESI† for more details). Thus, the optimal reaction conditions were identified to be entry 11 of Table 1, which delivered **3aa** in 82% isolated yield and 98% e.e.

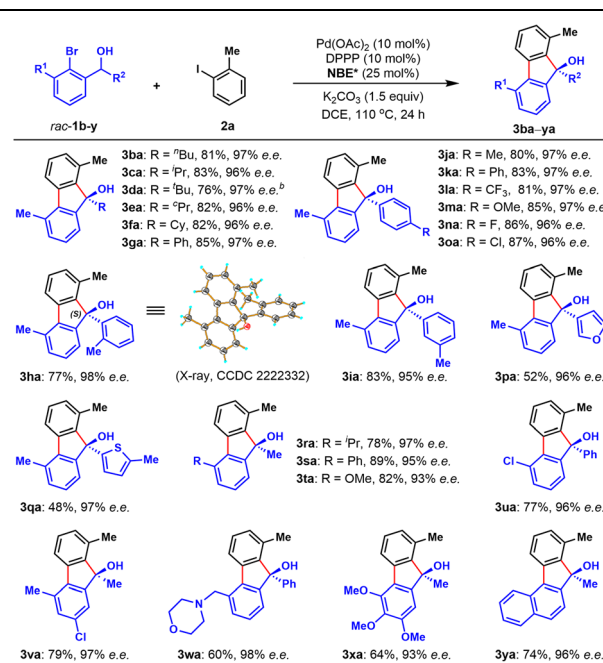With the optimal reaction conditions on hand, we first examined the scope of aryl iodides (**2**), using *rac*-**1a** as the reaction partner. As shown in Table 2, a wide variety of *ortho*-substituted aryl iodides were suitable substrates, including sterically hindered isopropyl (**3ab**), functionalized alkyl (**3ac** and **3ad**), electron-withdrawing trifluoromethyl (**3ae**), electron donating methoxy and benzyloxy (**3af** and **3ag**), fluoro (**3ah**) and chloro (**3as**) groups, and the corresponding products were produced in 46–82% yields. In addition, the substituents at either the 3-, 4- or 5-positions of aryl iodides were well tolerated, which included alkyl (**3ai**), halogen (**3aj**, **3ak**, **3am**, **3an** and **3ar**), methoxy (**3al**), amide (**3ao**), ester (**3ap**), and nitro (**3aq**) groups. Moreover, 1-iodonaphtalene derivatives with extended π system were also suitable substrates for this reaction and afforded the benzo[*a*]fluorenol products in good yields (**3at** and **3au**). More importantly, this method could be extended to heteroaryl iodides (**2v–x**) and 4-iodo-2-quinolone (**2y**), delivering the enantioenriched heterocyclic FOLs in 50–75% yields (**3av–ay**).
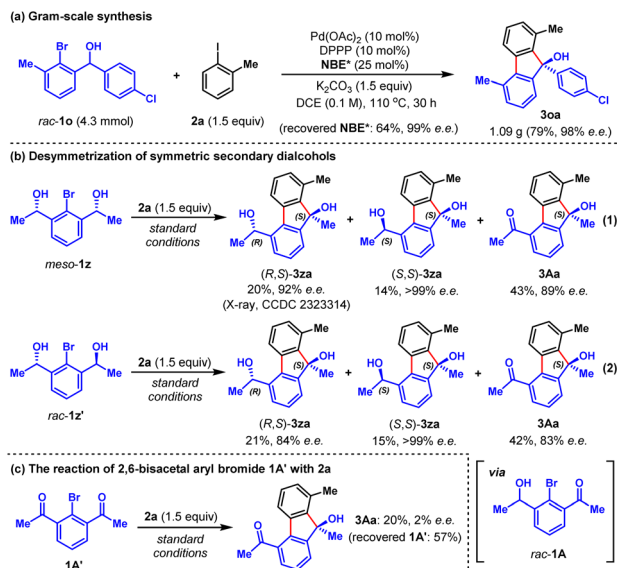
These heterocyclic chiral FOLs may have potential applications in the development of new antimycobacterial and antiprotozoal agents.[17d,g,18d] Remarkably, all the products (**3aa–ay**) were obtained with excellent enantioselectivities (90–99% e.e.s), and those compatible functional groups would provide handles for further manipulation of the obtained FOLs.

Next, the scope of racemic secondary *ortho*-bromobenzyl alcohols (**1**) was investigated, with 2-iodotoluene (**2a**) as the reaction partner (Table 3). Various alkyl substituents other than methyl group at the R^2 position were applicable for this protocol, including butyl (**3ba**), branched alkyl (**3ca** and **3da**), and cycloalkyl (**3ea** and **3fa**). It is worth mentioning that the alcohol substrate with a sterically very hindered *tert*-butyl substitution was able to provide the corresponding FOL in 76% yield after extending the reaction time to 36 h (**3da**). Additionally, the scope of R^2 substitution of racemic alcohols could be extended to a wide range of aryl groups, and the corresponding enantioenriched FOLs (**3ga–oa**) were obtained in 77–87% yields. For example, besides the simple phenyl group (**3ga**), other functionalized aryl groups with various substitution including methyl (**3ha–ja**), electron-withdrawing trifluoromethyl (**3la**), electron-donating methoxy (**3ma**), fluoro (**3na**) and chloro (**3oa**) groups were tolerated. Notably, secondary benzyl alcohols with a heteroaryl motif were also suitable substrates to deliver corresponding products in moderate yields (**3pa** and **3qa**). Finally, we probed the scope of *ortho*-substituent of the aryl bromide moiety of racemic alcohols, and found sterically hindered isopropyl (**3ra**), phenyl (**3sa**), methoxy (**3ta** and **3xa**), chloro (**3ua**), morpholino-methyl (**3wa**) and naphthyl (**3ya**) were well tolerated

Table 2 Substrate scope of aryl iodides[a]

3aa: R¹ = Me, 82%, 98% *e.e.*
3ab: R¹ = *i*Pr, 80%, 96% *e.e.*
3ac: R¹ = CH₂CN, 51%, 90% *e.e.*
3ad: R¹ = CH₂CO₂Me, 50%, 97% *e.e.*
3ae: R¹ = CF₃, 65%, 98% *e.e.*[b]
3af: R¹ = OMe, 50%, 98% *e.e.*
3ag: R¹ = OBn, 61%, 98% *e.e.*
3ah: R¹ = F, 46%, 99% *e.e.*

3ai: R = 3-Me, 73%, 98% *e.e.*
3aj: R = 3-F, 78%, 98% *e.e.*
3ak: R = 3-Cl, 66%, 98% *e.e.*
3al: R = 4-OMe, 78%, 97% *e.e*
3am: R = 4-F, 66%, 98% *e.e.*
3an: R = 4-Br, 72%, 97% *e.e.*

3ao: 73%, 98% *e.e.*

3ap: 56%, 97% *e.e.*

3aq: 48%, 98% *e.e.*

3ar: 64%, 97% *e.e.*

3as: 48%, 98% *e.e.*

3at: 81%, 97% *e.e.*

3au: 73%, 97% *e.e.*

3av: 75%, 98% *e.e.*

3aw: 50%, 97% *e.e.*

3ax: 56%, 98% *e.e.*

3ay: 61%, 99% *e.e.*

Table 3 Substrate scope of racemic brominated benzyl alcohols[a]

3ba: R = *n*Bu, 81%, 97% *e.e.*
3ca: R = *i*Pr, 83%, 96% *e.e.*
3da: R = *t*Bu, 76%, 97% *e.e.*[b]
3ea: R = *c*Pr, 82%, 96% *e.e.*
3fa: R = Cy, 82%, 96% *e.e.*
3ga: R = Ph, 85%, 97% *e.e.*

3ja: R = Me, 80%, 97% *e.e.*
3ka: R = *i*Pr, 83%, 97% *e.e.*
3la: R = CF₃, 81%, 97% *e.e.*
3ma: R = OMe, 85%, 97% *e.e.*
3na: R = F, 86%, 96% *e.e.*
3oa: R = Cl, 87%, 96% *e.e.*

3ha: 77%, 98% *e.e.* (X-ray, CCDC 2222332)

3ia: 83%, 95% *e.e.*

3pa: 52%, 96% *e.e.*

3qa: 48%, 97% *e.e.*

3ra: R = *i*Pr, 78%, 97% *e.e.*
3sa: R = Ph, 89%, 95% *e.e.*
3ta: R = OMe, 82%, 93% *e.e.*

3ua: 77%, 96% *e.e.*

3va: 79%, 97% *e.e.*

3wa: 60%, 98% *e.e.*

3xa: 64%, 93% *e.e.*

3ya: 74%, 96% *e.e.*

[a] All reactions were performed on a 0.1 mmol scale, and isolated yields were reported. [b] 2.0 equiv. of aryl iodide **2e** and 4 Å MS (40 mg) were applied, toluene as the solvent, 36 h.

[a] All reactions were performed on a 0.1 mmol scale, and isolated yields were reported. [b] 36 h.

Scheme 1 (a) Gram-scale synthesis; (b) desymmetrization of symmetric secondary dialcohols; (c) the reaction of 2,6-bisacetal aryl bromide with **2a**.

(**3ra–ya**), delivering the desired products in good yields (60–89%). In particular, the protocol was applicable for densely functionalized secondary *ortho*-bromobenzyl alcohol, providing polysubstituted chiral FOL **3xa** in 64% yield. Similar to Table 2, all the products in Table 3 were obtained with constantly excellent enantioselectivities (93–98% e.e.s). The absolute configuration of **3ha** was unambiguously confirmed to be (*S*) by X-ray crystallographic analysis and those of other products were assigned by analogy.

To demonstrate the synthetic practicality of this method, a larger scale (4.3 mmol) reaction was performed, which proceeded smoothly to give 1.09 gram of the desired product **3oa** in 79% yield and 98% e.e. (Scheme 1a), alongside the recovery of 64% of NBE* (99% e.e.) after work-up. Furthermore, based on this method, we developed an intriguing desymmetrization strategy possessing the ability to generate three chiral products in just one operation (Scheme 1b). For instance, by using readily available symmetric secondary dialcohols *meso*-**1z** as the reactant, the reaction with **2a** under standard conditions delivered three separable chiral products (*R*,*S*)-**3za** (20%, 92% e.e.), (*S*,*S*)-**3za** (14%, >99% e.e.) and **3Aa** (43%, 89% e.e.) (Scheme 1b, eqn (1)). The structure of (*R*,*S*)-**3za** was unambiguously confirmed by X-ray crystallographic analysis. The ratio of (*R*,*S*)-**3za**, (*S*,*S*)-**3za**
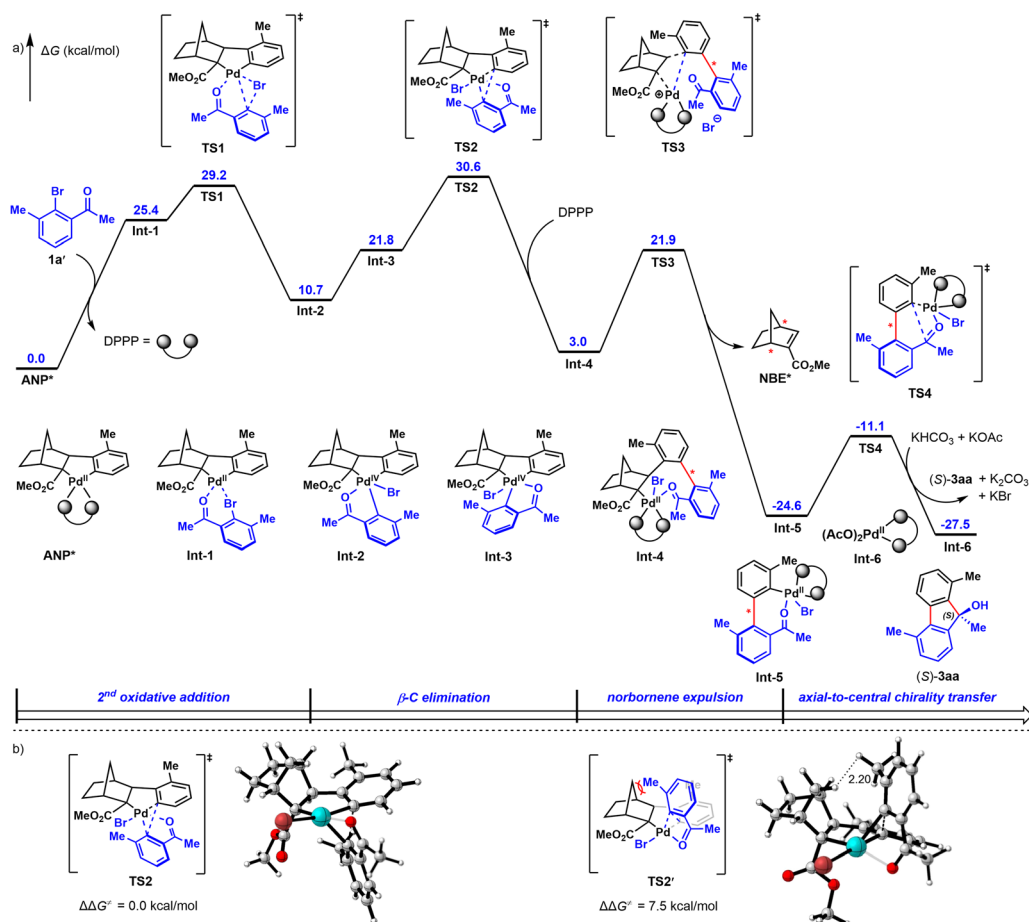

Fig. 2 (a) DFT-computed free energy profile for the formations of (*S*)-**3aa** *via* the computational method of M06L/6-311+G(d,p)-SDD/SMD(DCE)//B3LYP-D3(BJ)/6-31G(d)-LANL2DZ. (b) The optimized structures and relative free energies of the transition states of the stereo-selectivity-determining reductive elimination step.

and **3Aa** can be simply tuned by the reaction time (see Fig. S1b in ESI† for details). Similar results were obtained from the reaction of racemic secondary dialcohols *rac*-**1z′** with **2a** under standard conditions (Scheme 1b, eqn (2)). We reasoned that both *meso*-**1z** and *rac*-**1z′** could be partially oxidized to generate the same intermediate *rac*-**1A**, which was the real arylating reagent to react with **2a**. Interestingly, a control experiment involving the reaction of fully oxidized symmetric diketone intermediate **1A′** with **2a** resulted in almost racemic product **3Aa** in a poor yield (Scheme 1c), which indicated that product **3Aa** of Scheme 1b was mainly formed through *in situ* oxidation of the preformed products (*R*,*S*)-**3za** and (*S*,*S*)-**3za**.

Lastly, to probe the reaction mechanism[9b,23] and the origin of enantioselectivity, density functional theory (DFT) calculations were performed. As revealed in Fig. 2a (the detailed free energy profiles of the generation of both (*S*)- and (*R*)-**3aa** are included in Fig. S3 and S4†), the reductive elimination step for *ortho*-C–H arylation is the stereoselectivity-determining step of this reaction. The corresponding transition state **TS2′** leading to (*R*)-**3aa** is disfavored because of the steric repulsions between the methyl substituent and the NBE* fragment (Fig. 2b). In contrast, such steric repulsions are absent in the favored transition state **TS2**, which leads to (*S*)-**3aa** *via* a stereospecific axial-to-central chirality transfer process. The free energy difference between the two competing reductive elimination processes is calculated to be 7.5 kcal mol⁻¹. These DFT calculations are in good agreement with the observed experimental results and the determined absolute configuration of **3ha** by X-ray crystallographic analysis. Based on these experimental and calculated results, a possible catalytic cycle for this reaction was proposed in Fig. S5.†

Conclusions

In summary, we have developed an enantioconvergent strategy for the synthesis of enantioenriched fluorenols from racemic secondary benzyl alcohols and aryl iodides *via* Pd(ɪɪ)/chiral norbornene cooperative catalysis. This is an overall redox-neutral transformation involving sequential steps of destroying and regenerating stereoelements. A wide range of readily available aryl iodides and racemic secondary benzyl alcohols are compatible with this protocol, affording a diverse of chiral fluorenols bearing various functional groups with constantly excellent enantioselectivities (49 examples, 90–99% e.e.s). Based on this method, an intriguing desymmetrization strategy possessing the ability to generate three chiral fluorenols in one operation is developed. This work provides a valuable addition to the toolbox of enantioconvergent transformations. Preliminary DFT calculations were carried out to elucidate the reaction mechanism and the origin of enantioselectivity. Lastly, we believe this work will also promote the research and application of chiral fluorenols.

Data availability

All experimental procedures, characterisation data, mechanistic investigations, NMR spectra and HPLC spectra can be found in the ESI.†

Author contributions

Q. Z. conceived the idea and directed the project. B. D., Q. X., H. W., J. C., Z.-S. L. and J. T. performed the experiments under the supervision of H.-G. C. and Q. Z. Q. X. performed the density functional theory calculations. H. C. performed the X-ray crystallographic analysis. B. D. and Q. Z. co-wrote the manuscript.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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