VIP Cooperative Catalysis Very Important Paper

How to cite:
International Edition: doi.org/10.1002/anie.202103428
German Edition: doi.org/10.1002/ange.202103428

Kinetic Resolution of Tertiary Benzyl Alcohols via Palladium/Chiral Norbornene Cooperative Catalysis

Yu Hua[+], Ze-Shui Liu[+], Pei-Pei Xie, Bo Ding, Hong-Gang Cheng, Xin Hong, and Qianghui Zhou**

Abstract: *Herein we report a highly enantioselective kinetic resolution of tertiary benzyl alcohols via palladium/chiral norbornene cooperative catalysis. With simple aryl iodides as the resolution reagent, a wide range of readily available racemic tertiary benzyl alcohols are applicable to this method. Both chiral tertiary benzyl alcohols and benzo[c]chromene products are obtained in good to excellent enantioselectivities (selectivity factor up to 544). The appealing synthetic utility of the obtained enantioenriched tertiary alcohols is demonstrated by the facile preparation of several valuable chiral heterocycles. Preliminary mechanism studies include DFT calculations to explain the origin of enantiodiscrimination and control experiments to uncover the formation of a transient axial chirality during the kinetic resolution step.*

Catalytic kinetic resolution (KR) is a practical strategy to access enantioenriched chiral alcohols because the corresponding racemates are usually readily available.[1] Although KR of secondary alcohols has been well-developed, KR of tertiary alcohols remains a challenging task and has been rarely explored, which is mainly attributed to the innate low reactivity of sterically congested tertiary alcohols and difficulties in precise differentiation of three non-hydrogen substituents.[2–4] Since chiral tertiary benzyl alcohols are important structural motifs prevalent in pharmaceuticals (Figure 1 A), considerable efforts have been devoted to the challenging KR of these tertiary alcohols so far, culminating in the development of a few elegant strategies (Figure 1 B).[2–13] Pioneered by Miller[2] and later on by Zhao,[3] Smith[4] and Suga,[5] the nonenzymatic[6] acylative KRs using pentapeptide or chiral Lewis base catalyst were developed. List and Yang successively developed efficient KR strategies based on chiral phosphoric acid-catalyzed (trans)acetalization,[7] transesterification[8] or condensation.[9] Additionally, efficient KR strategies based on transition metal catalysis were also developed by Hayashi,[10] Ma,[11] Oestreich[12] and Zhou.[13] Despite these stunning progresses, there is still room for improvement with regard to KR efficiency, substrate generality and so on. Therefore, the development of more versatile KR methods using readily available reagents are highly desirable.

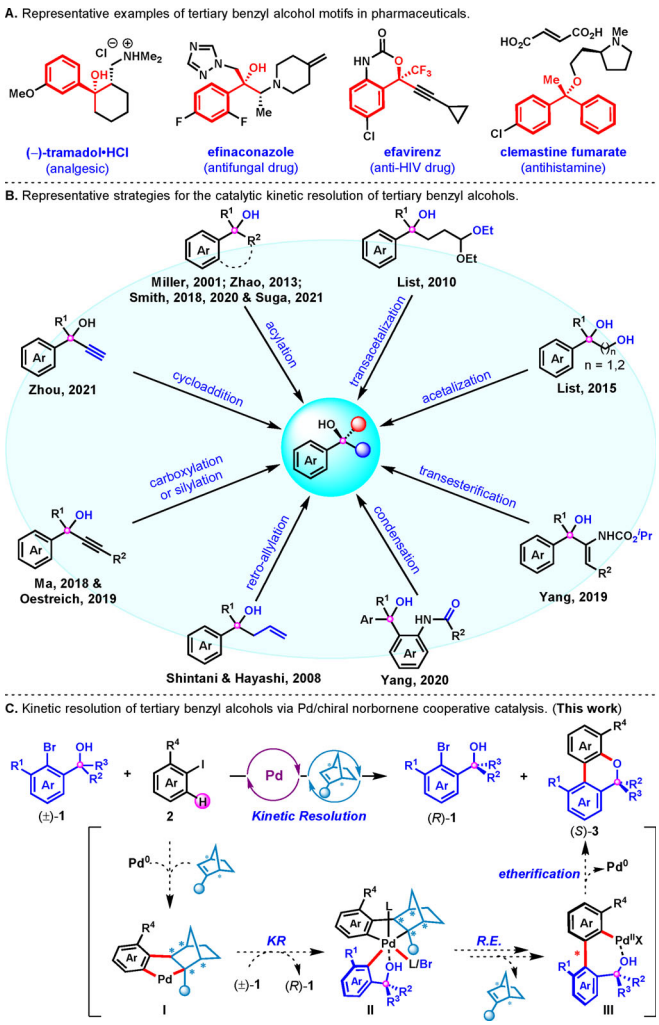

Figure 1. Approaches to access chiral tertiary alcohols via KRs.

The palladium/norbornene (Pd/NBE) cooperative catalysis, firstly reported by Catellani and co-workers,[14] has become a powerful tool for expeditious synthesis of polysubstituted arenes.[15] Pd/chiral NBE* cooperative catalysis is

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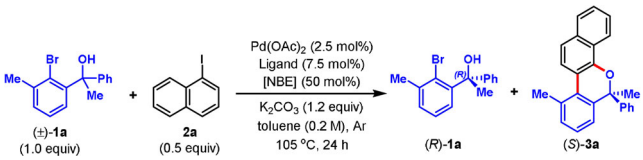
Supporting information and the ORCID identification number(s) for the author(s) of this article can be found under: https://doi.org/10.1002/anie.202103428.

treated as a potential strategy for asymmetric synthesis. However, owing to multiple formidable challenges,[16] it has rarely been realized so far.[17] Recently, we developed an efficient method to access axially chiral biaryls via Pd^0/chiral NBE* cooperative catalysis.[17c] Inspired by this chemistry, we envisioned a strategy for KR of tertiary benzyl alcohols. As shown in Figure 1C, aryl iodide **2** undergoes sequential oxidative addition, chiral NBE* insertion and *ortho*-C–H activation to generate the chiral aryl-NBE palladacycle (ANP) species **I**, which is then selectively oxidized by one enantiomer of the racemic tertiary benzyl alcohol bearing an aryl bromide motif (eg. (*S*)-**1**) to produce the Pd^{IV} intermediate **II**, leaving the other enantiomer (eg. (*R*)-**1**) unreacted. Intermediate **II** subsequently undergoes reductive elimination and β-carbon elimination to form axially chiral complex **III** and replenish the chiral NBE*. Finally, an intramolecular etherification occurs via complex **III** to give the central chiral benzo[*c*]chromene product (*S*)-**3**,[18] alongside disappearance of the transient axial chirality. Potential features of this KR method included the unprecedented resolution mode, the use of simple aryl iodides as the resolution reagent and providing two valuable chiral molecules in one operation. Nevertheless, multiple challanges are foreseeable. For example, the identification of a suitable chiral NBE* co-catalyst to ensure both good reactivity and enantiodiscrimination,[16] the innate low reactivity of 2,6-disubstituted arylbromide motif of the tertiary alcohols,[17c] and the dichotomy between required high reaction temperature and expected good KR effciency.

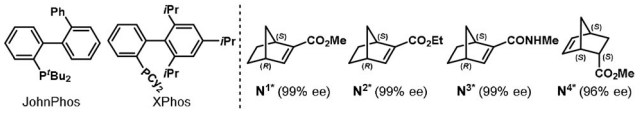
To probe this challenging process, we initiated our studies with a model reaction between racemic tertiary benzyl alcohol **1a** (1.0 equiv) and 1-iodonaphthalene **2a** (0.5 equiv) in the presence of $Pd(OAc)_2$ (2.5 mol%), tri(2-furyl)phosphine (TFP) (7.5 mol%), and (1*S*,4*R*)-2-methyl ester-substituted NBE ($\mathbf{N^{1*}}$, 99% *ee*, 50 mol%)[17a] (Table 1). Gratifyingly, KR of racemic tertiary benzyl alcohol (±)-**1a** was indeed achieved with good efficiency (the selectivity factor (*S*) is 104), providing the desired benzo[*c*]chromene product **3a** with 96% *ee* and recovered **1a** with 71% *ee* (entry 1). Subsequently, the KR effect of other chiral NBEs* was investigated. The C2-ethyl ester substituted chiral NBE* ($\mathbf{N^{2*}}$)[17b–c] behaved similarly to $\mathbf{N^{1*}}$ (entry 2), and the C2-amide substituted chiral NBE* ($\mathbf{N^{3*}}$)[16] led to erosion of the *S* factor (entry 3). In sharp contrast, the C5-methyl ester substituted chiral NBE* ($\mathbf{N^{4*}}$) resulted in almost a complete loss of KR selectivity (entry 4). Then we investigated the effect of phosphine ligand on KR efficiency (entries 5–8). The use of PPh_3 as the ligand led to a lower conversion (entry 5), while other ligands such as JohnPhos, XPhos or PCy_3, resulted in low efficiency or even no reaction (entries 6–8). Notably, the loading of $\mathbf{N^{1*}}$ could be reduced to 30 mol% with a slightly lower conversion (entry 9). Lastly, increasing the amount of **2a** (to 0.8 equiv) and TFP (to 10 mol%) gave the best results (51% conversion, $S = 127$), which was determined as the optimal reaction conditions (entry 10).

With the optimal reaction conditions established, we first set out to explore the reaction scope of aryl iodide **2**, with (±)-**1a** as the reaction partner (Table 2). To our delight, a wide range of aryl iodides containing electron-donating or electron-withdrawing groups all proved to be suitable substrates,

Table 1: Optimization of reaction conditions.[a]



Entry	Ligand	[NBE]	*ee* [%][b] 1a	*ee* [%][b] 3a	*C* [%][c]	*S* [%][d]
1	TFP	$\mathbf{N^{1*}}$	71	96	43	104
2	TFP	$\mathbf{N^{2*}}$	68	96	41	100
3	TFP	$\mathbf{N^{3*}}$	89	92	49	72
4	TFP	$\mathbf{N^{4*}}$	21	18	54	2
5[e]	PPh_3	$\mathbf{N^{1*}}$	44	95	31	60
6[e]	JohnPhos	$\mathbf{N^{1*}}$	10	94	10	36
7[e]	XPhos	$\mathbf{N^{1*}}$	0	–	0	–
8[e]	PCy_3	$\mathbf{N^{1*}}$	0	–	0	–
9[f]	TFP	$\mathbf{N^{1*}}$	53	96	36	83
10[f,g]	TFP	$\mathbf{N^{1*}}$	96	94	51	127

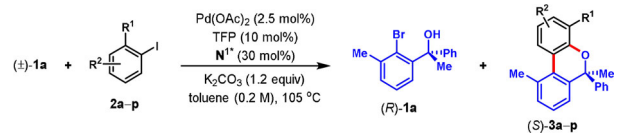


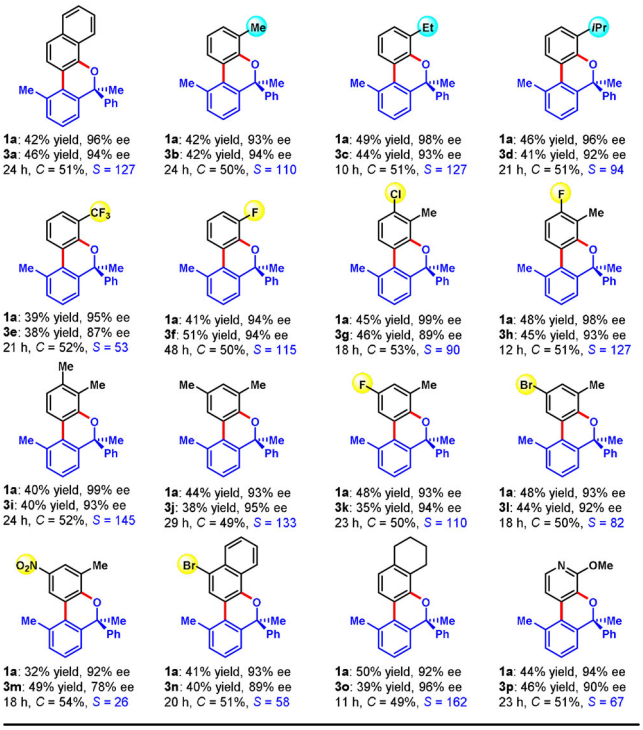
[a] All reactions were performed on a 0.2 mmol scale. [b] Determined by chiral HPLC analysis. [c] Conversion ($C = ee_s/(ee_s + ee_p)$). [d] $S = \ln[(1-C)\ (1-ee_p)]/\ln[(1-C)\ (1+ee_p)]$. [e] $\mathbf{N^{1*}}$ (97% *ee*) was applied. [f] 30 mol% of $\mathbf{N^{1*}}$ was applied. [g] 10 mol% of TFP and 0.8 equiv of **2a** were applied.

providing the desired chiral benzo[*c*]chromene products as well as the recovered **1a** with good to excellent enantiopurity (78–99% *ee*s). In general, electron-withdrawing aryl iodides were inferior to the reaction (**2e** and **2m**) and provided smaller *S* factors. Besides the alkyl substituents (**2b–d**), various functional groups of aryl iodides, including fluoro (**2f**, **2h** and **2k**), chloro (**2g**), bromo (**2l** and **2n**), trifluoromethyl (**2e**) and nitro (**2m**) groups were tolerated. In addition, bicyclic aryl iodides (**2n** and **2o**) and heteroaryl iodide (**2p**) were competent to afford excellent KR results.

Subsequently, the reaction scope of racemic tertiary benzyl alcohols (**1**) were evaluated, with 1-iodonaphthalene **2a** as the resolution reagent (Table 3). Firstly, we investigated the aryl/Me-type tertiary benzyl alcohols, and found that good KR results could be obtained with various groups (eg. methyl, fluoro and methoxy) at different positions of the phenyl motif (**1b–g**). The *S* factor reached 544 for the alcohol with an *ortho*-methyl phenyl group (**1d**), although longer reaction time was required (probably due to the increased steric hindrance). Notably, tertiary alcohols with a heteroaryl motif (**1h** and **1i**) were also smoothly resolved with good efficiency. Next, the more challenging alkyl/Me-type tertiary alcohols were investigated. After screening, we found only the ones with a proper steric differentiation of the two alkyl groups (**1j** and **1k**) gave good *S* factors. We also explored the reaction scope of Ph/alkyl-type tertiary alcohols. Both the Ph/Et- and Ph/CF_3-substituted ones (**1l** and **1m**) afforded good *S* factors. Finally, we probed the scope of *ortho* substituent of the aryl bromide moiety of tertiary alcohols, and found ethyl (**1n**), cyanomethyl (**1o**), TBS-protected hydroxymethyl (**1p**), *N*,*N*-dimethylaminomethyl (**1q**), pyrrolidin-1-ylmethyl (**1r**), mor-

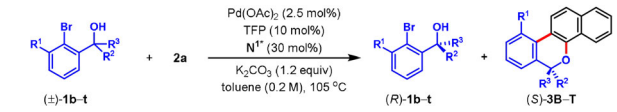
Table 2: Reaction scope of aryl iodide.[a]

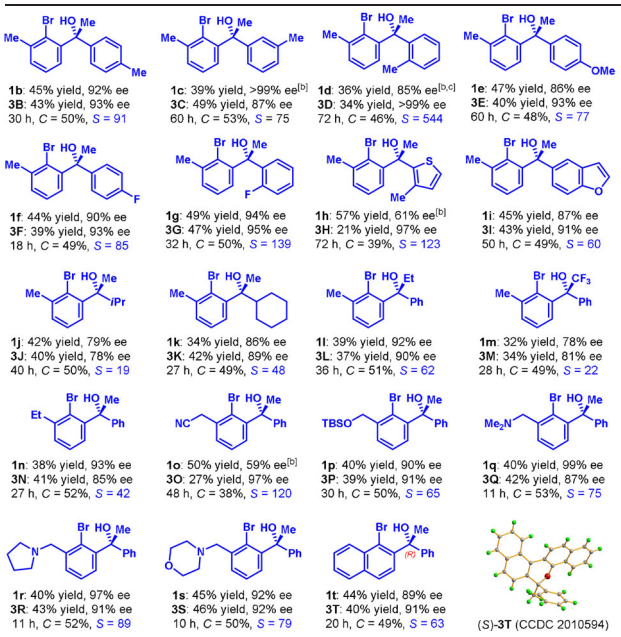




[a] All reactions were performed on a 0.2 mmol scale. The reactions were monitored by chiral HPLC analysis. Reported yields are for the isolated products. The *ee* values were determined by chiral HPLC analysis.

Table 3: Reaction scope of tertiary alcohol.[a]

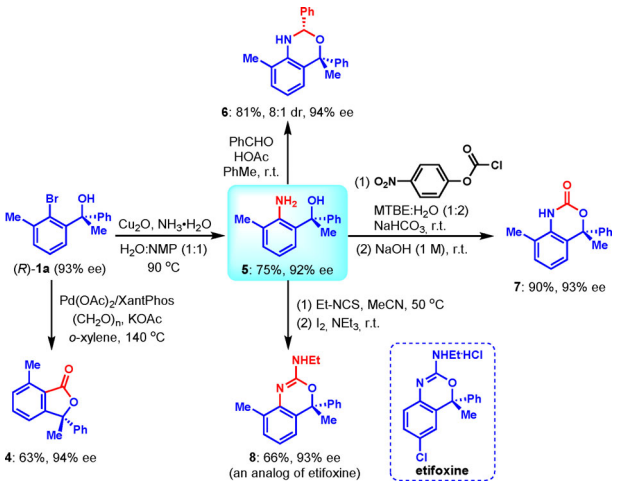




[a] All reactions were performed on a 0.2 mmol scale. The reactions were monitored by chiral HPLC analysis. Reported yields are for the isolated products. The *ee* values were determined by chiral HPLC analysis. [b] 5 mol% of $Pd(OAc)_2$ and 20 mol% of TFP were applied. [c] 110 °C.

pholino-methyl (**1s**) and naphthyl (**1t**) were well tolerated. The absolute configuration of **3T** was unambiguously determined to be (*S*) by X-ray crystallographic analysis[19] and those of other products and recovered enantioenriched tertiary alcohols were assigned by analogy. Notably, the *ortho*-bromo substitution in the recovered enatioenriched tertiary benzyl alcohols (*R*)-**1b–t** could act as a good synthetic handle for further manipulations (see Scheme 1).

Since the obtained enantioenriched tertiary benzyl alcohols are valuable intermediates, eg. assembling biorelevant heterocycles, a series of follow-up transformations were demonstrated (Scheme 1). For instance, isobenzofuranone **4** was synthesized from (*R*)-**1a** in just one step by palladium-catalyzed carbonylation (63% yield, 94% *ee*).[20] In addition, a versatile chiral amino alcohol **5** was readily obtained from (*R*)-**1a** and ammonia by Ullmann-type amination in 75% yield and 92% *ee*.[21] To our delight, **5** could be further transformed into a variety of chiral heterocycles. For example, condensation of **5** with benzaldehyde under acidic conditions afforded the benzoxazine **6** in good yield and diastereoselectivity (81%, 8:1 dr, 94% *ee*).[9a] The reaction of **5** with 4-nitrophenyl chloroformate and a following base treatment afforded benzoxazinone **7** in 90% yield and 93% *ee*.[22] Moreover, subjecting **5** to ethyl isothiocyanate then iodine provided benzofused heterocycle **8**,[23] an analogue of the



Scheme 1. Application of enantioenriched tertiary benzyl alcohol in heterocycles synthesis.

anticonvulsant drug etifoxine. It is worth mentioning that all these transformations proceeded without any erosion of the enantiopurity.

Lastly, a possible catalytic cycle of the reaction was proposed in Figure 2A, based on the obtained data and previous mechanistic studies on Catellani-type reactions.[24] To shed light on this catalytic cycle, some mechanistic studies

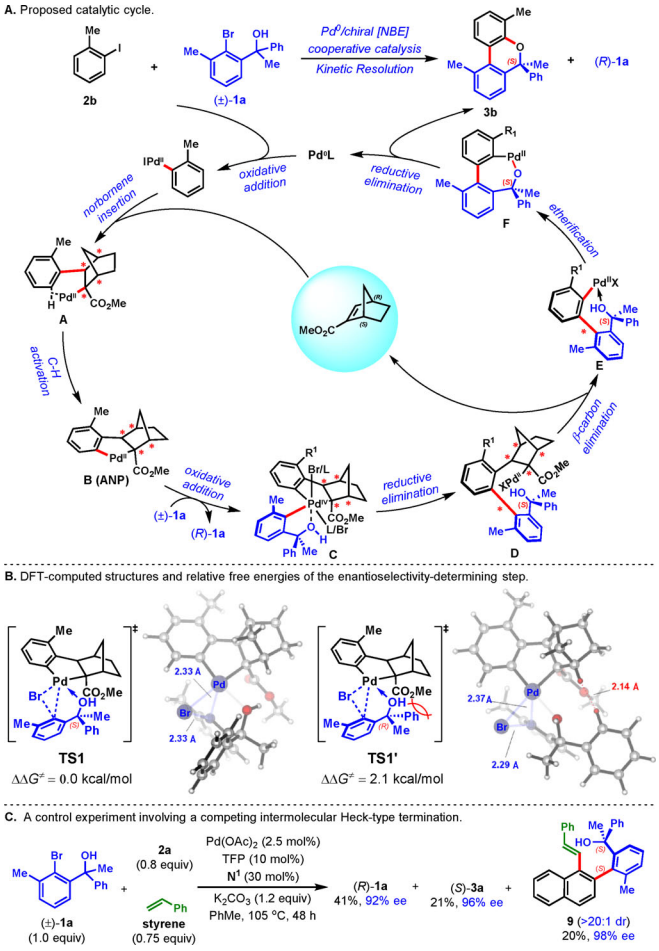


Figure 2. Proposed catalytic cycle and related reaction mechanism studies.

were performed. First, density functional theory (DFT) calculations were carried out to rationalize the enantiodiscrimination process, the sequential oxidative addition and reductive elimination from **B** to **D**. The detailed free energy profiles of the generation of both (*S*)- and (*R*)-C–C axial chirality intermediates are included in the Supporting Information (Figure S1). We found that the oxidative addition of aryl bromide (±)-**1a** to chiral ANP **B** is the enantiodiscrimination step that differentiates the two diastereomer intermediates **C** with (*S*)-C–C axial chirality. The optimized structures and relative free energies of the enantioselective oxidative addition transition states **TS1** and **TS1′** are shown in Figure 2B. Transition state **TS1′** ((*R*)-**1a** with **B**) is disfavored because of steric repulsions arising from the proximal placement of the bulky phenyl substituent and the chiral NBE* fragment. Such steric repulsions are not present in the favored transition state **TS1** ((*S*)-**1a** with **B**), which leads to the 2.1 kcal mol^{-1} free energy difference between the two competing oxidative addition processes and eventually results in an excellent KR efficiency ($S = 110$). The DFT results well explained the origin of enantiodiscrimination which was consistent with the experimental results. Additionally, a control experiment introducing styrene as a competitive terminating reagent was conducted under the standard reaction conditions. Besides the recovered enantioenriched (*R*)-**1a** and normal product (*S*)-**3a**, the intermolecular Heck-type terminating product **9** containing both axial and central chirality was also isolated in a comparable 20% yield with excellent enantioselectivity and diastereoselectivity (98% *ee*, >20:1 dr). The formation of **9** is a solid evidence of the transient axial chirality generated during the KR step, which provides a strong experimental support for the mechanism proposed in Figure 2A.

In summary, we have developed a highly efficient method for the KR of tertiary benzyl alcohols, based on palladium/chiral norbornene cooperative catalysis. With simple aryl iodides as the resolution reagent, a wide range of readily available racemic tertiary benzyl alcohols are applicable to this method, providing both chiral tertiary benzyl alcohols and benzo[*c*]chromene products with excellent enantioselectivities. The synthetic utility is demonstrated by the facile synthesis of diversified biorelevant heterocycles. Preliminary mechanism studies are performed to elucidate the origin of enantiodiscrimination and the formation of a transient axial chirality during the KR step.

Acknowledgements

We are grateful to the National Natural Science Foundation of China (grant nos. 21871213, 22071189 for Q.Z., and 21873081 for X.H.), Fundamental Research Funds for the Central Universities (2020XZZX002-02 for X.H.), and the State Key Laboratory of Clean Energy Utilization (ZJUCEU2020007 for X.H.) for financial support. We thank Dr. Liming Cao and Mr Tao Yang for technical assistance.

Conflict of interest

Q.Z., Y.H. and Z.-S.L. have filed a provisional patent application (2021103260547). All other authors declare no conflict of interest.

Keywords: chiral norbornene · cooperative catalysis · kinetic resolution · tertiary benzyl alcohol · transient axial chirality

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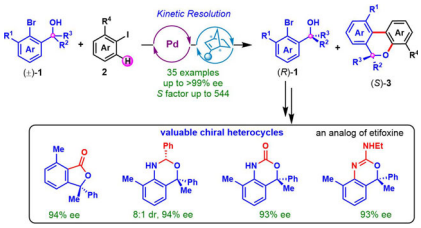
Manuscript received: March 9, 2021
Accepted manuscript online: March 30, 2021
Version of record online: ■■ ■■, ■■■■

Communications

Cooperative Catalysis

Y. Hua, Z.-S. Liu, P.-P. Xie, B. Ding, H.-G. Cheng, X. Hong,* Q. Zhou* ——— ■■■■–■■■■

Kinetic Resolution of Tertiary Benzyl Alcohols via Palladium/Chiral Norbornene Cooperative Catalysis



A highly enantioselective kinetic resolution of tertiary benzyl alcohols via palladium/chiral norbornene cooperative catalysis is developed. Simple aryl iodides is used as the resolution reagent. Both enantioenriched tertiary benzyl alcohols and benzo[*c*]chromene products are obtained in good to excellent enantioselectivities. The synthetic applications are demonstrated by the facile synthesis of diversified biorelevant heterocycles.