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Catalytic asymmetric oxidative carbonylation-induced kinetic resolution of sterically hindered benzylamines to chiral isoindolinones†

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A highly enantioselective kinetic resolution of sterically hindered benzylamines has been achieved for the first time through transition-metal-catalyzed oxidative carbonylation, in which the new KR strategy offered a new approach to afford chiral isoindolinones (er up to 97 : 3) and the origin of chemoselectivity and stereoselectivity was confirmed by density functional theory (DFT) calculations.

The chiral isoindolinone core serves as a privileged structure, and is widely present in many medicine candidates.[1] Typical examples are the dopamine D_4 receptor PD-172938,[1a] pagoclone (an anxiolytic drug)[1b] and 9*b*-phenyl-2,3-dihydrothiazolo[2,3-*a*]-isoindol-5(9*b*H)-one, which was used as an HIV-1 reverse transcriptase inhibitor (Fig. 1).[1c] The chiral isoindolinone skeleton is also an integral part of biologically significant natrual products such as the isoindolobenzazepine alkaloid (+)-lennoxamine (Fig. 1).[1d] Thus, devising novel and facile methods to access the chiral isoindolinone motif is of great interest.[1a,2] During our studies, we became interested in the synthesis of chiral isoindolinones based on the desymmetric amine carbonylation strategy.[3] It should be noted that, our reported method for desymmetrization C–H bond activation/amine carbonylation was only suitable for the prochiral sulfonamides, which contain two prochiral C–H bonds, thus limiting the chiral isoindolinone diversity. Therefore, exploring new methods for preparing chiral isoindolinone from readily available substrates is highly desirable.

In recent years, kinetic resolution has emerged as an attractive and efficient method to generate different types of chiral compounds from racemic starting substrates.[4] In this context, List demonstrated chiral phosphoric acid (STRIP) catalyzed enantioselective kinetic resolution of homoaldol acetals to obtain cyclic acetals *via* asymmetric transacetalization reaction in 2010.[4a] In 2015, Yu firstly reported the palladium-catalyzed enantioselective C–H olefination of alfa-aminophenylacetic acids and alfa-hydroxy *via* kinetic resolution, which provided a general protocol for the synthesis of olefinated mandelic acids and phenylglycines.[4b] The Oestreich group disclosed Cu–H species catalyzed enantioselective silylation to give chiral tertiary propargylic alcohols for the first time in 2018.[4c] Subsequently in 2019, Dong described Rh-catalyzed kinetic resolution of cyclobutanones *via* a "cut-and sew" reaction to afford trans 5,6-fused bicycles and C2-substituted cyclobutanones with excellent ee at room temperature.[4d] Recently, Zhang reported the kinetic resolution strategy to synthesized chiral piperidines and chiral

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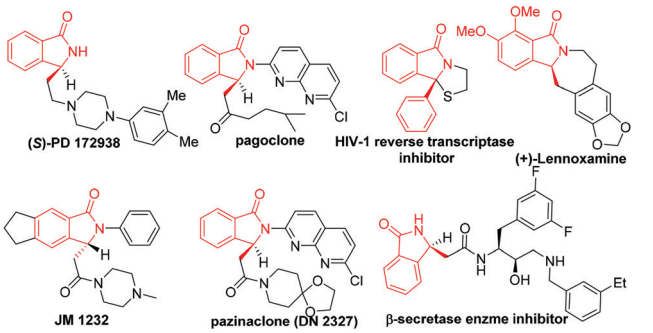
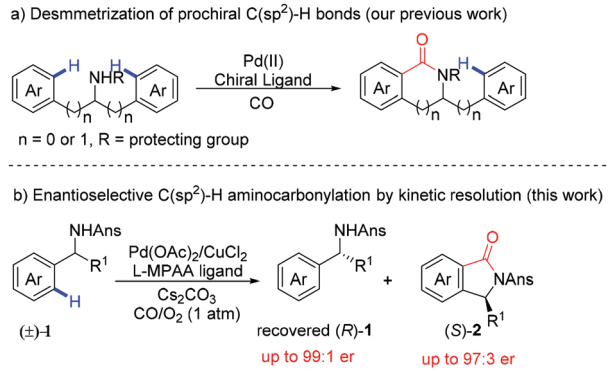


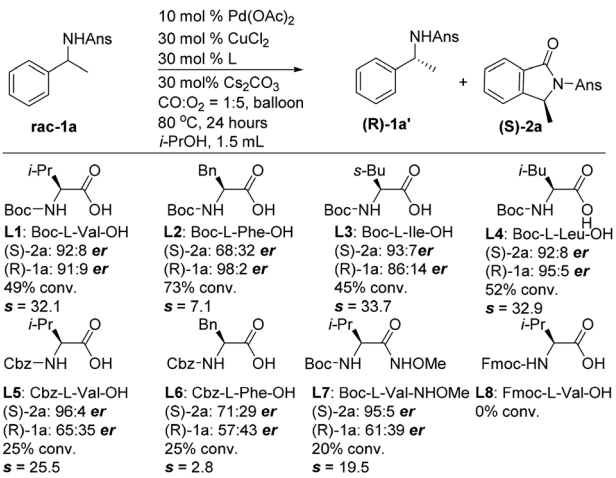
Fig. 1 Biological active compounds containing a chiral isoindolinone motif.



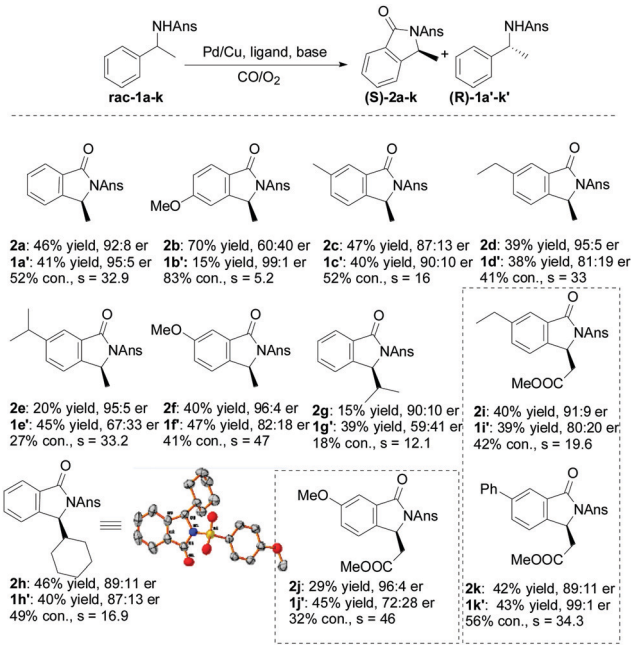
Scheme 1 Kinetic resolution of racemic sterically hindered benzylamines.

1,4,5,6-tetrahydropyridines using racemic 1,4-dihydropyridines and 3,4-disubstituted 1,4,5,6-tetrahydropyridines through Rhodium-catalyzed asymmetric hydrogenation.[4e] Although many kinetic resolution strategis have been widely recognized and extensively investigated in catalytic asymmetric reaction, catalytic asymmetric carbonylation is still not easily accessible. To the best of our knowledge, no reports on the construction of chiral isoindolinone through the kinetic resolution strategy exist. Since racemic sterically hindered benzylamines are readily accessible, kinetic resolution can be an attractive alternative method for the preparation of chiral isoindolinones based on a C–H activation/carbonylation strategy. Herein, we firstly report an efficient protocol of kinetic resolution for the synthesis of chiral isoindolinones through Pd/Cu-cocatalysis C–H functionalization/amine carbonylation, which would fill a gap in synthetic chemistry (Scheme 1).

Considering our previous work on the C–H desymmetrization aminocarbonylation of prochiral sulfonamides by Pd/Cu-cocatalysis,[3] the study commenced with a survey of ***rac*-1** with different N-protecting groups using our previously

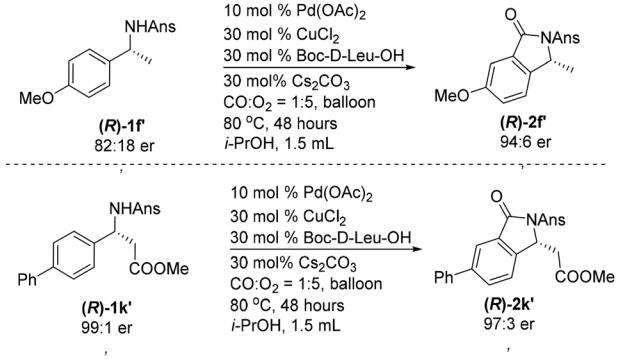


Scheme 2 Catalytic asymmetric oxidative carbonylation-induced kinetic resolution of racemic **1a**. Enantiomeric excess (ee) was determined by chiral HPLC analysis, where ee_1 is the enantiomeric excess of the recovered **1a'** and ee_2 is the enantiomeric excess of **2a**. *S* = selectivity factor, and $S = \ln[(1-C)(1-ee)]/\ln[(1-C)(1+ee)]$, where $ee = ee_1/100$ and C = conversion/100.

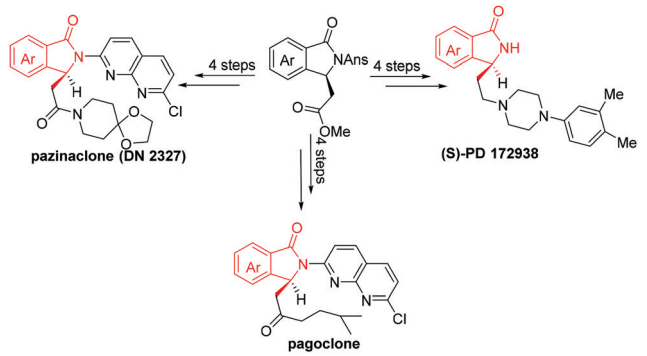


Scheme 3 Substrate scope of catalytic asymmetric oxidative carbonylation-induced kinetic resolution of sterically hindered benzylamines **1**.

established catalyst system (ESI,† Table S1). Variation of the N-protecting groups of ***rac*-1** showed that different sulfinates, such as methanesulfinate (Ms-), 4-methoxylbenzenesulfinate (Ans-), 4-nitrobenzenesulfinate (Ns-), trifluoromethanesulfinate (Tf-), and 4-methylbenzenesulfinate (Ts-), all worked well for the reaction to give the corresponding chiral isoindolinones in good conversion (33–55%) and good selectivity (*S* = 13.5–32.1). Among them, 4-methoxylbenzenesulfinate (Ans-) was eventually identified as the optimal N-protecting group of ***rac*-1**, achieving high conversion (49%) and featuring the best selectivity (*S* = 32.1). In analogy to the sulfinates, when using Boc- as the protecting group, there was no reaction. To further explore the effect of ligand structure on conversion and selectivity, a wide range of chiral amino acid ligands was screened using ***rac*-1a** as the model substrate (Scheme 2). After an extensive survey of readily available Boc-N-protected amino acids, we found that Boc-L-Leu-OH proved to be the optimal ligand for this kinetic resolution protocol. In addition, when the acid



Scheme 4 Enantioselective C–H activation/amine carbonylation of the recovered starting material.



Scheme 5 Potential application of the core segment.

moiety of the ligand was substituted with *N*-methoxyamide, no reaction was observed. Based on the previous studies, the N-protecting group on the MPAA ligand exerts a significant influence on the enatioselectivity, and we then explored other protecting groups on the amino group, such as Cbz-, Fmoc, and Ac-groups. Unfortunately, no significant improvement was observed with these ligands. Extensive experimentation using Boc-L-Leu-OH as the chiral ligand revealed a series of critical reaction parameters (ESI,† Tables S3–S6). In particular, no reaction occurred when $PdCl_2$ or $Pd(TFA)_2$ was utilized as a palladium catalyst (Table S3, ESI†). And low levels of reactivity and selectivity were obtained using $Pd(CH_3CN)_2Cl_2$ instead of $Pd(OAc)_2$. Other Cu salts could be used as the oxidant in this reaction, including $Cu(OAc)_2$, $Cu(TFA)_2{\cdot}XH_2O$, and $Cu(OTf)_2$, which could also reoxidized the Pd(0) species to active center Pd(II) with the aid of O_2 to complete the entire catalyzed cycle, albeit an inferior result was obtained (Tabel S4, ESI†). The use of other bases allowed for no improvement, and even led to no reaction (Table S5, ESI†). Attemps to further improve the reactivity and selectivity by investigating various solvents were not fruitful (Table S6, ESI†).

After establishing the optimized conditions, we began to explore the substrate scope of the sterically hindered benzylamines (Scheme 3). In most cases, both isoindolinone **2** and benzylamines **1** were obtained with excellent enantioselectivity. For example, the substrate bearing no substituent on the aromatic ring (***rac*-1a**) was resolved with high selectivity factors (S = 32.9) and **2a** was obtained in excellent optical purity (92 : 8 er). The nature of the aromatic substituents did not exhibit a significant effect on the reaction, and ***rac*-1b-1f** underwent superb kinetic resolutions, with selectivity factors (S) up to 47.

Notably, high enantiomeric purity of the recovered starting material **(*R*)-1f′** and **(*R*)-1k′**, could be used to synthesize chiral isoindolinones **(*R*)-2f′** and **(*R*)-2k′** in 94 : 6 er and 97 : 3 er using a mono-N-protected amino acid ligand (Boc-D-Leu-OH) with the opposite configuration, which demonstrated the feasibility of affording both enantiomers of chiral isoindolinones through this approach (Scheme 4). Similarly, **2g** and **2h** were also produced in 90 : 10 er and 89 : 11 er, respectively, demonstrating that steric hindrance did not dramatically hamper the kinetic resolution. Gratifyingly, ***rac*-1i** and ***rac*-1j** proved to be excellent substrates. Both **2i** and **2j**, the key intermediates for synthesis of the bioactive compound derivatives ((S)-PD 172938, pazinaclone and pagoclone) (Scheme 5),[5] were obtained with 91 : 9 er and 96 : 4 er respectively. These results demonstrated that the current protocol could provide a versatile entry point for the asymmetric synthesis of bioactive isoindolinones.

The absolute configuration of **2h** was confirmed by X-ray crystallography analysis to be S, which prompted us to propose a stereomodel to investigate the origin of the stereoselectivity.

Inspired by previous reports on the reasonable transient state model for Pd-catalyzed and mono-N-protected amino acid promoted asymmetric C(sp^2)–H functionalization,[6] we performed DFT calculations to elucidate the origin of the chemoselectivity and stereoselectivity (Fig. 2). Notably, both our group and Xia's group have developed the Pd-catalyzed enantioselective C–H activation/amine carbonylation by a desymmetrization strategy, and the DFT calculations have been conducted to clarify the possible reaction pathways.[3,7] Based on the previous theoretical

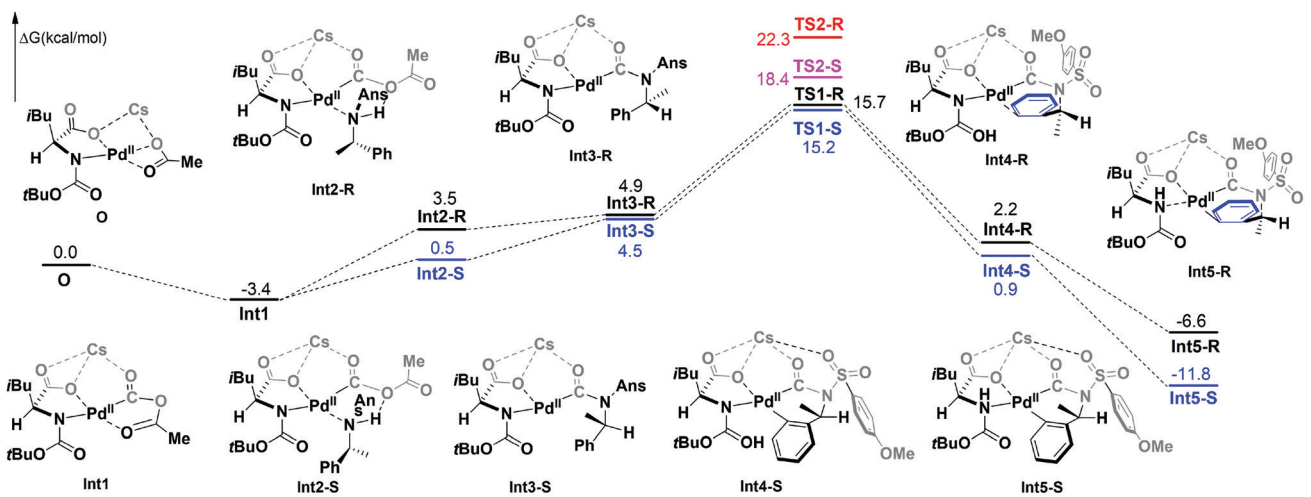


Fig. 2 The free energy profiles for the Pd/Cu-cocatalyzed C–H functionalization/carbonylation. The free energies (in kcal mol^{-1}) are calculated at the B3lyp and BS (BS = 6-31g(d,p) for main group elements and LanL2DZ for Pd) level of theory.

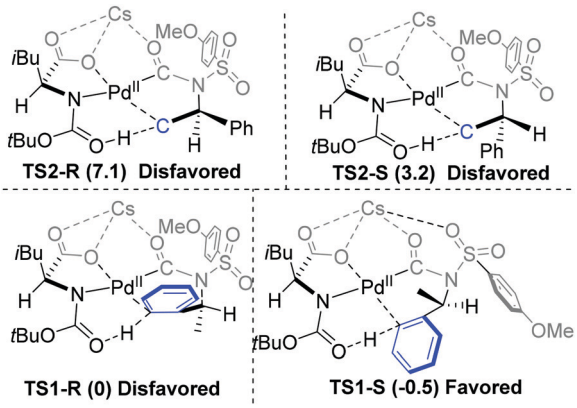


Fig. 3 Optimized geometries of the transition states.

studies, Pd(II)-amino acid salt was usually set to the relative zero value. As shown in Fig. 2, four different transition states (**TS1-S**, **TS1-R**, **TS2-S**, **TS2-R** of Fig. 3) were simulated from **int3** to **int4**. The lowest activation energy of the C(sp^2)–H bond activation was calculated to be 15.2 kcal mol^{-1} (**TS1-S**), while the C(sp^3)–H bond activation was calculated to be 18.4 kcal mol^{-1} (**TS2-S**), that is 3.2 kcal mol^{-1} higher than **TS1-S**, which was in agreement with the experimental results of Scheme 3. In the transition state **TS1-S** and **TS1-R** of C(sp^2)–H bond activation, the higher energy state for the R-enantiomer (**TS1-R**) was calculated to be 15.7 kcal mol^{-1}, which is 0.5 kcal mol^{-1} higher than **TS1-S**. The energy difference between **TS1-S** and **TS1-R** indicated that the S-configuration of chiral isoindolinone **2a** was formed preferentially.

In conclusion, Pd/Cu-cocatalyzed enantioselective C–H activation/amine carbonylation of sterically hindered benzylamines by kinetic resolution has been developed first, which will fill an important gap in the synthesis of bioactive compounds containing an isoindolinone motif. Elucidated by density functional theory (DFT) calculations, the origin of the chemoselectivity and stereoselectivity could have implications for other kinetic resolution reactions. The further development of the synthetic strategy is ongoing in our laboratory.

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Conflicts of interest

There are no conflicts to declare.

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