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Enantioselective Remote *Meta*-C–H Arylation and Alkylation *via* a Chiral Transient Mediator

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Abstract

Asymmetric C–H metalation has recently emerged as a promising approach for developing enantioselective C–H activation reactions. However, this approach is typically limited to 5- and 6-membered cyclometalation, thereby preventing the asymmetric functionalization of C–H bonds at positions remote to existing functional groups. Herein, we report the realization of enantioselective remote *meta*-C–H arylation of benzylamines, as well as arylation and alkylation of homobenzylamines. The desymmetrization and kinetic resolution are achieved using an achiral ligand and a catalytic amount of chiral transient mediator that relays an initial *ortho*-C–H activation to the *meta* position. The same chiral transient mediator affords comparable enantioselectivities with different classes of substrates containing either neutral σ-donor or anionic coordinating groups. This relay strategy could provide an alternative means to remote chiral induction, one of the most challenging problems in asymmetric catalysis.

Enantioselective C–H activation reactions via asymmetric metalation have the potential to open a new avenue for constructing chiral molecules owing to the diverse reactivity of chiral carbon–metal bonds[1–2]. Efforts to achieve this goal have been met with tremendous difficulties due to the lack of appropriate catalytic redox manifolds and conceptual bases for effective chiral ligand design. Enantioselective activation of C(sp^2)–H bonds has played an important role in developing chiral ligands and understanding chiral induction in the metalation of C–H bonds. For example, an early example of Ru(0)-catalyzed atropselective alkylation of 2-arylpyridine afforded only 49% ee[3]. In the past decade, the extensive search for suitable metal catalysts, chiral ligands and catalytic cycles that can achieve highly enantioselective C–H activation reactions has led to the finding that a Pd(II) catalyst bound to a chiral mono-protected amino acid ligand (MPAA) enables highly enantioselective C–H coupling via a Pd(II)/Pd(0) catalytic cycle[4–6], as well as C–H iodination and oxidation

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Supplementary Information is available in the online version of the paper.

Author Contributions J.-Q. Y. and H. S. conceived the concept. H. S. developed the enantioselective remote C–H activation. H. S. and A. N. H. performed the mechanistic study. H. S., A. N. H., Y. S., and Q. S. prepared reaction substrates. J.-Q. Y. directed the project.

The authors declare no competing financial interests.

Readers are welcome to comment on the online version of this article.

Data Availability The data supporting the findings of this study are available within the article and its Supplementary Information files. Metrical parameters for the structure of **2ah**, **4m**, and **4n** (see Supplementary Information) are available free of charge from the Cambridge Crystallographic Data Centre (https://www.ccdc.cam.ac.uk/) under reference number CCDC-1586807, CCDC-1586808, and CCDC-1586809, respectively.

involving Pd(II)/Pd(IV) catalysis[7–8] (Figure 1a). In addition to point desymmetrizations, this class of chiral ligand is also competent in planar and axial desymmetrizations, as demonstrated by multiple research groups[9–12]. Pd(0)-catalyzed intramolecular vinylation and arylation of C(sp^2)–H bonds has also been rendered enantioselective by using chiral phosphine ligands[13–14]. Recently, chiral rhodium[15–18] and iridium[19] catalysts have been developed to enable enantioselective C(sp^2)–H activation; however, these reactions are largely limited to either intramolecular silylations or pyridine-directed C–H olefinations. Hitherto, transition metal-catalyzed enantioselective remote *meta*-C(sp^2)–H activation has not been reported.[20–23] Asymmetric metalation of remote sp^2-C–H bonds presents a distinct challenge: the metal insertion event occurs too far from the carbon that becomes the chiral center. Remote C–H functionalization directed by a nitrile-template has been developed recently;[22] however, the control of the stereochemistry through a conformationally flexible macro-cyclic transition state remains to be demonstrated (Figure 1b). In general, remote chiral induction remains one of the most challenging problems in asymmetric catalysis.[24–25]

Here we report a strategy using a catalytic amount of chiral norbornene as a transient mediator to achieve enantioselective remote C–H activation (Figure 1c). The norbornene plays a dual role: to relay C–H activation from the *ortho* position to the remote *meta* position[26–30]; and to achieve chiral differentiation of the racemic *ortho*-C–H palladation intermediates, generated by an achiral catalyst, to ensure the formation of the enantio-enriched product. This approach has been successfully implemented in enantioselective remote *meta*-C–H activation reactions of benzyl and homobenzylamines, both of which are prevalent motifs in bioactive natural products, drug compounds, and chiral organic catalysts (Figure 1d). The chiral norbornene methyl (1*S*,4*R*)-bicyclo[2.2.1]hept-2-ene-2-carboxylate ((+)-NBE-CO_2Me) serves as a versatile chiral transient mediator (CTM) for both X- and L-type substrates. Kinetic resolution of homobenzylamines was also achieved using the same CTM to broaden the scope of the substrates.

Our experimental design was based on a previous finding that norbornene can intercept the *ortho*-palladation intermediate via migratory insertion and subsequently effect *meta*-C–H functionalizations[26–28]. This reaction mechanism guided us to hypothesize that a chiral, enantioenriched norbornene might be able to differentiate the racemic *ortho*-palladate intermediate during the alkene insertion, or the subsequent alkene insertion intermediate (from the *meta*-C–H palladation step). We selected diarylmethylamine **1**[31], which contains a σ-donor coordinating group, as the model substrate to investigate the potential asymmetric arylation using chiral norbornene mediators (Figure 2a). While the chiral bicyclo[2.2.1]heptene derivatives **CTM1** and **CTM2** were effective mediators, both gave negligible enantioselectivity. Likewise, the lactam **CTM3** failed to display any degree of stereoinduction. The use of chiral (+)-NBE-CO_2Me as the transient mediator led to a dramatic improvement in enantioselectivity to 88:12 (see Supplementary Information for optimization). While neither inorganic base nor carboxylic acid additives were effective, the phosphoric acid $(PhO)_2PO_2H$ increased the er to 93:7. Pleasingly, (*R*)-BNDHP produced a 70% yield and an excellent enantioselectivity (97:3 er). Bulky substituents (like anthracenyl group) on the phosphoric acid proved detrimental to the reaction. To investigate the role of the chiral norbornene and phosphoric acid, we performed a number of control experiments.

The use of racemic NBE-CO_2Me and (*R*)-BNDHP gave poor enantioselectivity (57:43). The use of (*S*)-BNDHP, (*R*)-phosphorylimide or chiral camphorsulfonic acid in combination with (+)-NBE-CO_2Me led to a slight drop in yield and enantioselectivity. These combined experiments suggest that (+)-NBE-CO_2Me is responsible for the chiral induction and the chiral phosphoric acid has a minor beneficial effect.

Using the optimized conditions, we then tested the substrate scope with methyl 2-iodobenzoate (Figure 2b). Electron-neutral (**2a**, **2b**), electron-donating (**2c**) and electron-withdrawing (**2d** to **2f**) substituents were all well tolerated, providing enantioselectivities of up to 97:3. Substrate **1g** bearing an alkyne group afforded a lower yield due to the instability of the C–C triple bond under the standard conditions. Substituents at the *ortho*-position (**2h**) reduced the reactivity via a presumed steric effect, but high enantioselectivity (91:9 er) was preserved. Bis-substituted arenes **2i** and **2j**, which contain heterocycles, were also compatible and afford consistently high enantioselectivity. The 5-membered heterocycle **2k** gave lower selectivity, probably due to a coordinative effect.

We next surveyed the scope of aryl iodides (Figure 2b). The scope of *ortho*-substituted aryl iodides (**2m** to **2q**) is broad, providing enantioselectivity in up to 97:3 er. Electronically diverse *meta*-substituted aryl iodides (**2r** to **2w**) were tolerated, and produced enantiomeric ratios greater than 95:5 (**2s** to **2v**). The scope of *para*-substituted aryl iodides is also broad, and electronic factors do not affect the enantioselectivity (**2x** to **2ac**). Multi-substituted aryl iodides (**2ad** to **2ai**) were also tolerated under the conditions, and the enantiomeric ratios all exceeded 95:5. The above scope of various aryl iodides features either halogens (as in **2t** to **2v**) or reactive groups (NHAc in **2m** and **2r**, phosphonate moiety in **2x**, alkyl chloride **2z**, and aldehyde in **2aa**) that can serve as useful synthetic handles for subsequent chemical manipulation. Importantly, heterocyclic aryl iodides also proved successful in the reaction (**2aj** to **2au**). Pyridine, quinoline, quinazoline, furan, thiophene, and indole derivatives were all suitable coupling partners, providing good to high enantioselectivities. The simple removal of directing group was demonstrated with product **2ae** (see Supplementary Information for details).

We then investigated asymmetric *meta*-C–H activation of homobenzylamines[32]. Until now, no *ortho*-C–H activation method has achieved the construction of a homobenzylic chiral center. Considering that the challenge might be overcome by the CTM strategy, we tested different mediators and found that (+)-NBE-CO_2Me remained the most effective one, providing a 97:3 enantioselectivity with nosyl-protected homobenzylamine **3a**, which contains an anionic coordinating group (see Supplementary Information for details). Notably, the use of a nosyl-protected (Ns) amino moiety as the directing group represents a practical advantage in synthetic applications. Further investigation revealed that this method covers a broad range of symmetric homobenzylamines (Figure 3a). *Ortho*-, *meta*-, and *para*-substituents were all well-tolerated, and provided the desired products (**4a** to **4f**, **4h**) in good to high enantioselectivities. Moreover, both naphthalene (**4g**) and the bis-substituted arene (**4h**) were amenable to the standard conditions.

The reaction tolerated electronically diverse aryl iodides (**4i** to **4l**) and provided enantioselectivities in up to 99:1 er. Heterocyclic aryl iodides such as pyridine, furan, and

thiophene (**4m** to **4o**) were also successful. In addition to aryl iodides, 2-bromobenzoate was also tested and provided moderate yield and excellent enantioselectivity (**4a**, >99:1 er). Likewise, the aliphatic coupling partner iodoacetate gave product **4p** with 92:8 er.

In addition to desymmetrization, kinetic resolution of secondary amines was also realized (Figure 3b). (+)-NBE-CO_2Me successfully resolved a racemic mixture of amino esters providing *meta*-arylated products and recovered starting materials in good enantioselectivity with 2-bromo-benzoate (**6a**, **6b**). These *meta*-arylated phenylalanines are central motifs in a family of bioactive natural products[33]. Alkyl- and aryl-substituted homobenzylamines (**6c** to **6e**) were also compatible with this system. Moreover, simple arene (**6f**), heterocycle (**6g**) and alkyl groups (**6h**, **6i**) were all enantioselectively installed at the *meta*-position by this method. To showcase the synthetic utility of this reaction, a copper-catalyzed intramolecular amination of **6j** yielded chiral indoline **7** with the 5-position substituted, a core structure of chemotherapy medication Vincristine.

Mechanistic studies of our previous enantioselective C–H activation reactions have established the asymmetric C–H metalation step as the enantio-determining step[34–35]. Since the chiral mediator (+)-NBE-CO_2Me) is not involved in the *ortho*-C–H activation step, chiral differentiation should occur in one of the subsequent steps. A number of mechanistic experiments were thus carried out to provide further insights (see Supplementary Information for details). First, kinetic isotope effects (KIE) of 1.03 and 1.33 for the *ortho*- and *meta*-deuterated substrates respectively indicated that the C–H activation steps are likely not rate-limiting. First-order rate dependence observed for aryl iodide points to the oxidative addition of aryl iodide as rate-limiting (Figure 4a).[36] Second, substantial hydrogen/deuterium exchange at the *ortho*-position and the lack of such exchange at the *meta*-position suggests that the *ortho*-C–H activation step is fast and reversible while the *meta*-C–H activation is not readily reversible on the reaction time scale. These combined data suggest that the chiral differentiation by the chiral norbornene occurs at either the norbornene insertion into the *ortho*-palladation intermediate or subsequent *meta*-C–H activation step (Figure 4b).

In summary, remote enantioselective C–H activation reactions were realized by relaying *ortho*-C–H activation to remote *meta*-C–H activation using a chiral norbornene as the mediator. The chiral amplification is achieved by fast reversible non-asymmetric C–H activation followed by enantioselective norbornene insertion or *meta*-C–H activation. This approach is compatible with substrates containing either neutral σ-donor or anionic coordinating groups.

Methods Summary

General procedure for the Pd/(+)-NBE-CO_2Me catalyzed enantioselective *meta*-C–H activation

Arene (0.10 mmol, 1.0 equiv), $Pd(OAc)_2$ (2.2 mg, 10 μmol, 10 mol%), Ligand (15 mol% or 20 mol%), hydrogenphosphate (15 mol% for benzylamine substrate), aryl iodide (0.3 mmol, 3.0 equiv.), and AgOAc (50 mg, 0.30 mmol, 3.0 equiv.) were added into a 2-dram reaction vial. Solvent and (+)-NBE-CO_2Me (20 mol% or 50 mol%) were added to the mixture. The

vial was flushed with N_2, and capped. The reaction mixture was then stirred at the given temperature for 12 to 24 hours. After cooling to room temperature, the mixture was filtered through Celite and eluted with EtOAc. The filtrate was evaporated under reduced pressure. Purification by preparative TLC chromatography afforded the desired product. Full experimental details and characterization of new compounds can be found in the Supplementary Information.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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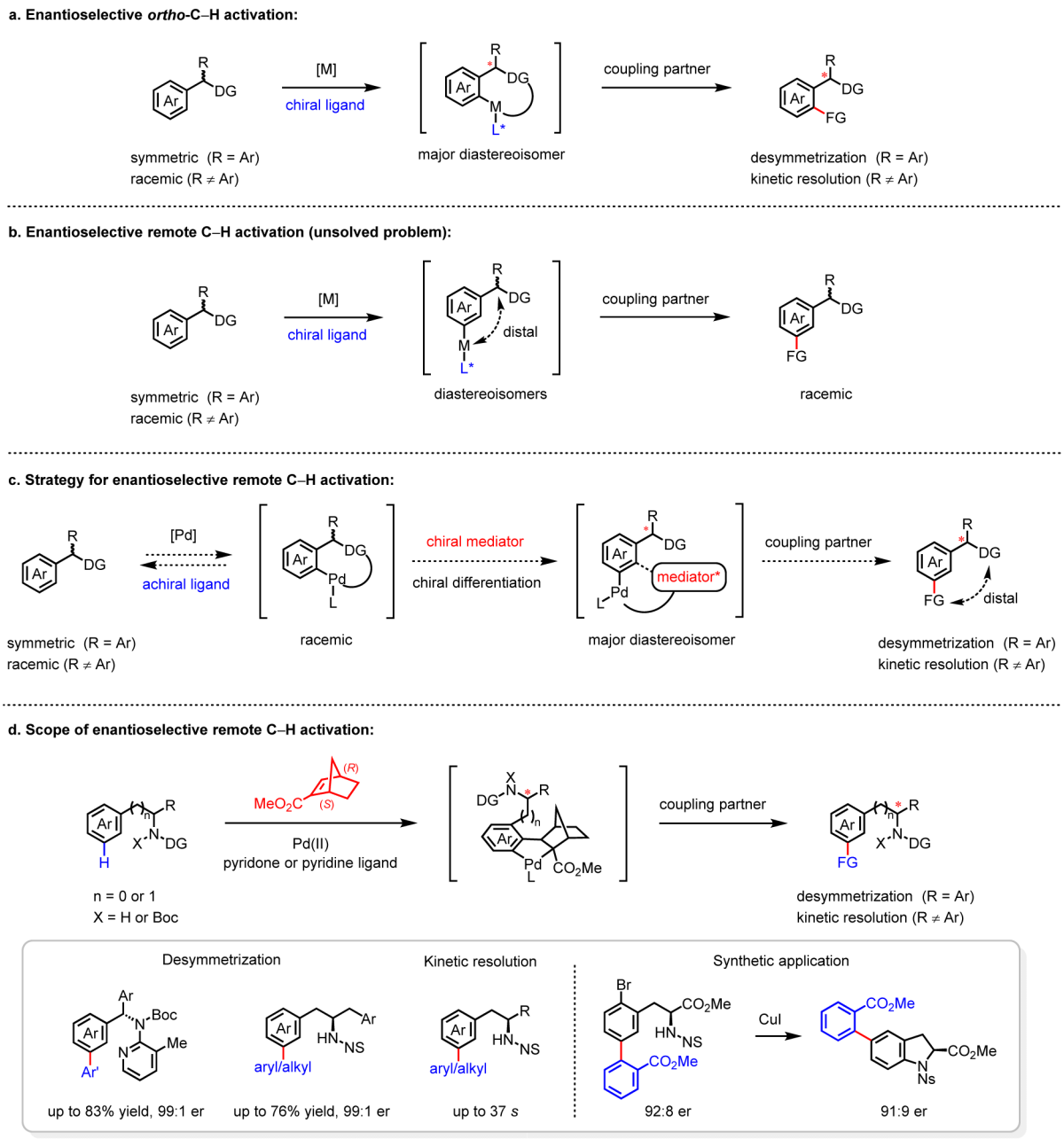

Figure 1. Enantioselective C(sp^2)–H activation

a, Enantioselective *ortho*-C–H activation. **b**, Enantioselective remote C–H activation (unsolved problem). **c**, Strategy for enantioselective remote C–H activation. **d**, Scope of enantioselective remote C–H activation.

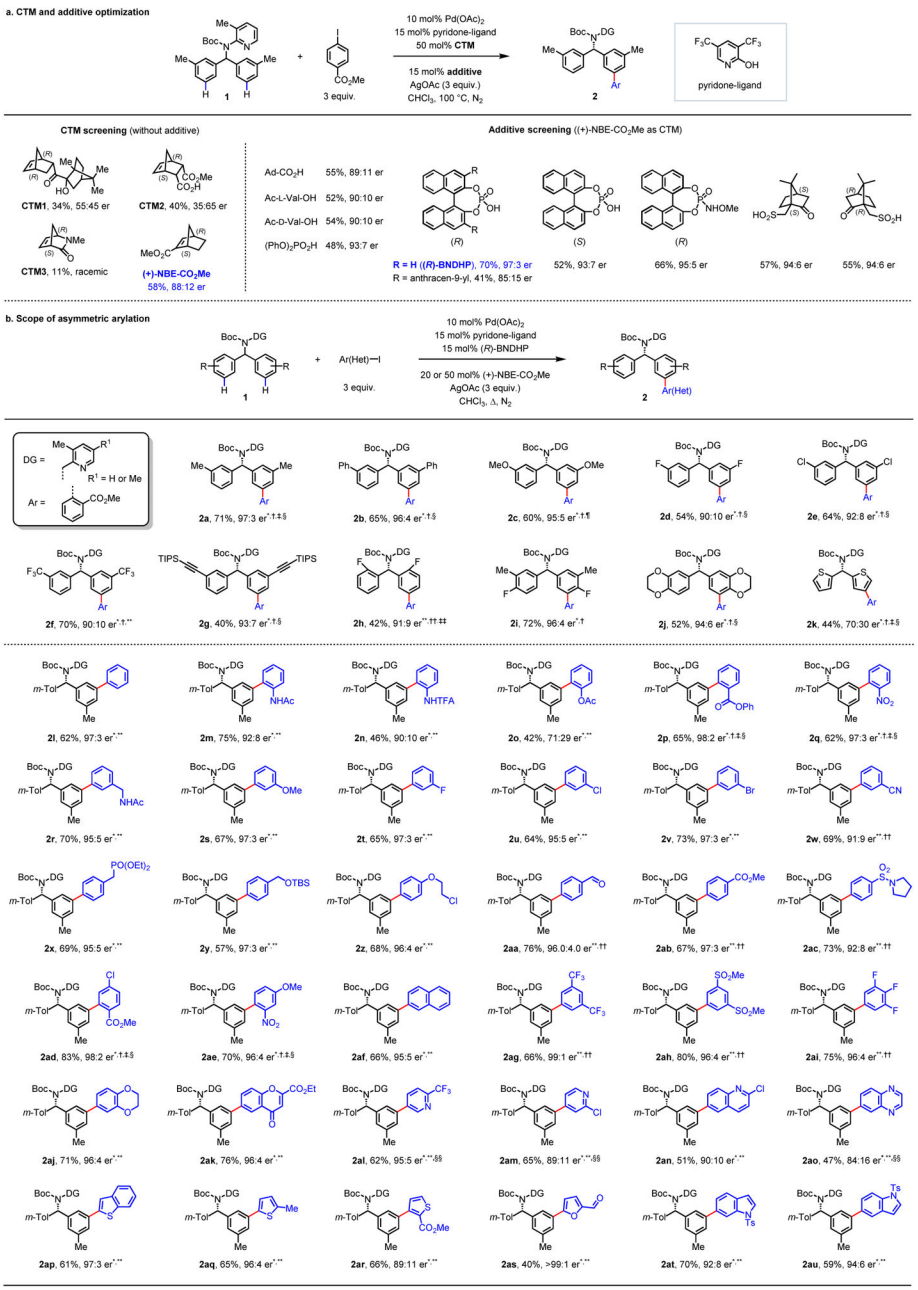

Figure 2. Enantioselective *meta*-C–H arylation of diarylmethylamines

a, CTM and additive optimization. Reaction conditions: 10 mol% $Pd(OAc)_2$, 15 mol% pyridone-ligand, 50 mol% (+)-NBE-CO_2Me, 15 mol% additive, 3 equiv. methyl 4-iodobenzoate, 3 equiv. AgOAc, $CHCl_3$, 100 °C. For each entry number (in bold), data are reported as NMR yield. **b**, Scope of asymmetric arylation. Reaction conditions: 10 mol% $Pd(OAc)_2$, 15 mol% pyridone-ligand, 20 mol% (+)-NBE-CO_2Me, 15 mol% (*R*)-BNDHP, 3 equiv. Ar–I, 3 equiv. AgOAc, $CHCl_3$, 100 °C. *R^1 = Me. †15 mol% $(PhO)_2PO_2H$. ‡1.5 equiv. Ar–I, 2 equiv. AgOAc. §80 °C. ¶60 °C. **50 mol% (+)-NBE-CO_2Me. ††R^1 = H. ‡‡20 mol% $Pd(OAc)_2$, 30 mol% pyridone-ligand, 30 mol% (*R*)-BNDHP. §§15 mol% $Pd(OAc)_2$,

23 mol% pyridone-ligand. For each entry number (in bold), data are reported as isolated yield. The absolute configuration of **2ah** was determined by X-ray crystallography. DG, directing group; Ar, aryl group; *m*-Tol, *meta*-tolyl group. Reducing the catalyst loading to 5 mol% produced comparable results for substrate **1a′** (see Table S6 in Supplementary Information).

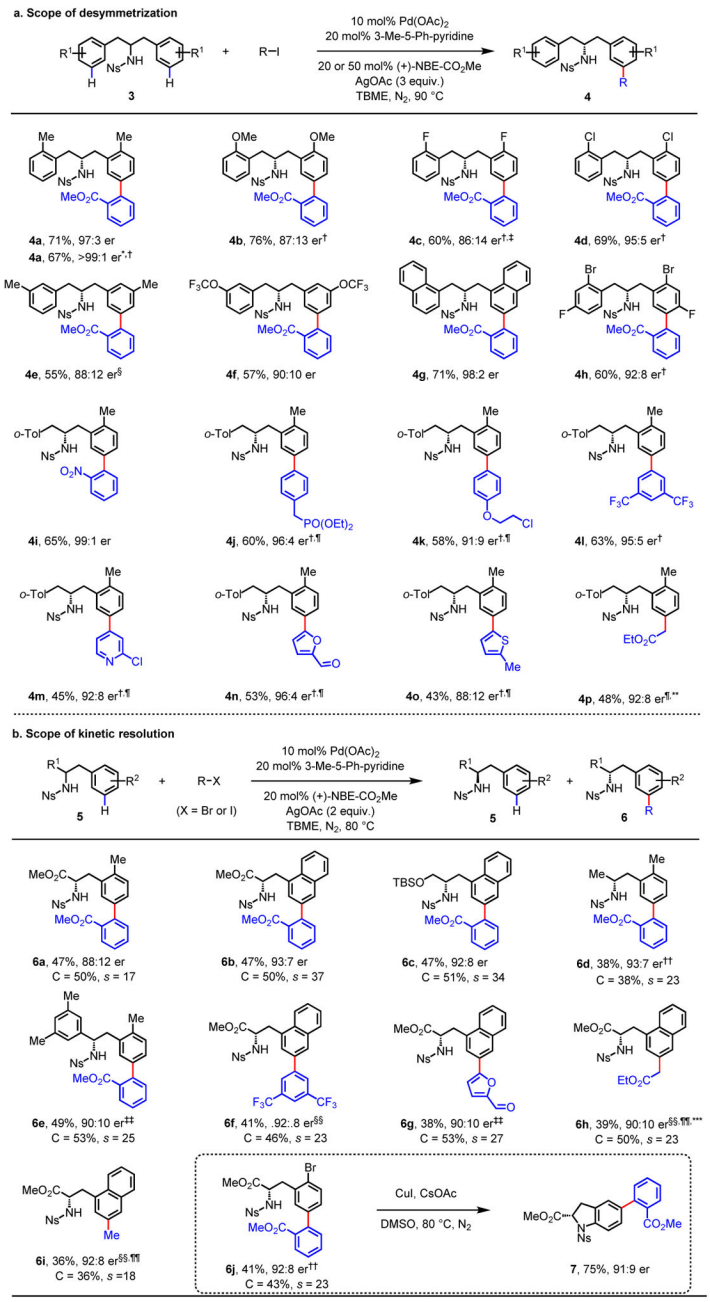

Fig. 3. Enantioselective *meta*-C–H activation of homobenzylamines

a, Scope of desymmetrization. Reaction conditions: 10 mol% $Pd(OAc)_2$, 20 mol% 3-methyl-5-phenylpyridine, 20 mol% (+)-NBE-CO_2Me, 3 equiv. R–I, 3 equiv. AgOAc, TBME, 90 °C. *Methyl 2-bromobenzoate (as arylation reagent). †50 mol% (+)-NBE-CO_2Me. ‡15 mol% $Pd(OAc)_2$, 30 mol% 3-methyl-5-phenylpyridine. §1.4 equiv. Ar–I. ¶15 mol% $Pd(OAc)_2$, 30 mol% 4-acetylpyridine (as ligand). **1.5 equiv. (+)-NBE-CO_2Me, DCM (as solvent). **b**, Scope of kinetic resolution. Reaction conditions: 10 mol% $Pd(OAc)_2$, 20 mol% 3-methyl-5-phenylpyridine, 20 mol% (+)-NBE-CO_2Me, 0.5 equiv. R–X, 2 equiv. AgOAc, TBME, 80 °C. ††1.5 equiv. R–X. ‡‡1 equiv. R–X. §§3 equiv. R–X, 3 equiv. AgOAc.

[¶¶]20 mol% 4-acetylpyridine, DCM. [***]50 mol% (+)-NBE-CO_2Me. For each entry number (in bold), data are reported as isolated yield. The absolute configurations of **4m** and **4n** were determined by X-ray crystallography. TBME, *tert*-butylmethylether; *o*-Tol, *ortho*-tolyl group; DCM, dichloromethane. Reducing the catalyst loading to 5 mol% produced comparable results for substrate **3a** (see Table S10 in Supplementary Information).

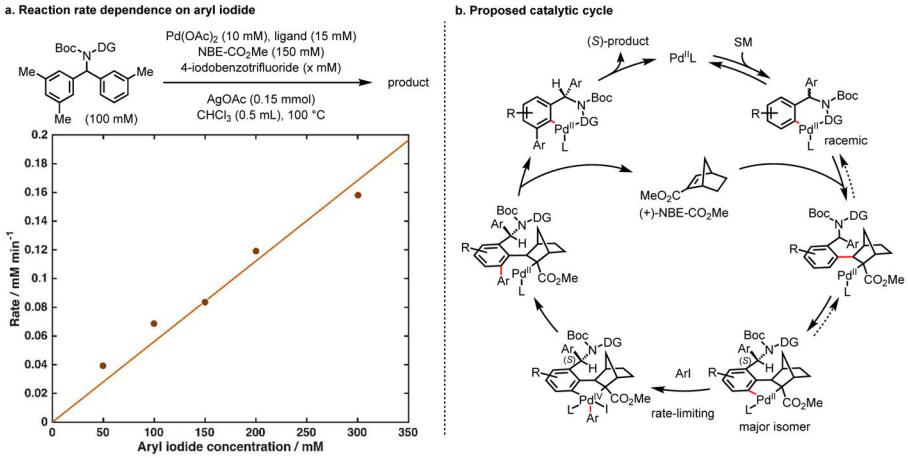

Figure 4. Mechanistic studies

a, Reaction rate dependence on aryl iodide. **b**, Proposed catalytic cycle.