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Catalytic C(sp^3)–H bond activation in tertiary alkylamines

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The development of robust catalytic methods to assemble tertiary alkylamines provides a continual challenge to chemical synthesis. In this regard, transformation of a traditionally unreactive C–H bond, proximal to the nitrogen atom, into a versatile chemical entity would be a powerful strategy for introducing functional complexity to tertiary alkylamines. A practical and selective metal-catalysed C(sp^3)–H activation facilitated by the tertiary alkylamine functionality, however, remains an unsolved problem. Here, we report a Pd(II)-catalysed protocol that appends arene feedstocks to tertiary alkylamines via C(sp^3)–H functionalization. A simple ligand for Pd(II) orchestrates the C–H activation step in favour of deleterious pathways. The reaction can use both simple and complex starting materials to produce a range of multifaceted γ-aryl tertiary alkylamines and can be rendered enantioselective. The enabling features of this transformation should be attractive to practitioners of synthetic and medicinal chemistry as well as in other areas that use biologically active alkylamines.

The development of methods catalysed by transition metals for converting C(sp^3)–H bonds into a new chemical functionality is an emerging technology that has the potential to streamline chemical synthesis[1–3]. An important feature of many C(sp^3)–H functionalization strategies is the use of coordinating groups, which locate a metal catalyst in proximity to a particular C–H bond, thereby enabling reactivity and ensuring selectivity. In an ideal situation, a native functionality present in the molecule would be capable of steering the C(sp^3)–H activation via cyclometallation. Among a limited number of examples, carboxylic acids[4,5] as well as primary and secondary amines[6] have been most successfully deployed in combination with Pd(II) catalysts to affect C(sp^3)–H functionalization reactions. However, it is more common that the native functional group needs to be modified with an additional directing auxiliary to modulate its coordinating ability, which has led to a diverse range of Pd(II)-catalysed C(sp^3)–H activation processes[7,8]. Despite the efficacy of auxiliary-augmented C(sp^3)–H activation strategies, a number of practical drawbacks of this approach exist. First, the auxiliary must be incorporated into the substrate prior to, and removed after, the C–H transformation. Second, their removal sometimes requires harsh conditions that can be incompatible with delicate molecular architectures. A third, and arguably the most compelling, limitation is that auxiliary-augmented C(sp^3)–H activation is not possible if there is no functionality in the substrate to which a directing motif can be appended. This problem is especially pertinent when considering C(sp^3)–H activation in tertiary alkylamines; there is no simple way to attach and remove a directing auxiliary within a tertiary alkylamine motif[9–16].

With an estimated 26% of all drugs and agrochemicals featuring a tertiary alkylamine[17,18], the development of robust catalytic methods to assemble and modify the structure of these important molecular features provides a continual challenge to chemical synthesis[19–28]. A selective single-step transformation of a traditionally unreactive C–H bond, proximal to the nitrogen atom, into a versatile chemical entity would be a particularly powerful strategy for introducing functional complexity to tertiary alkylamines. Despite the apparent efficacy of this ideal, practical and selective metal-catalysed C(sp^3)–H activation facilitated by tertiary alkylamine scaffolds remains an elusive transformation (Fig. 1a). A possible reason for this methodological deficiency is the ease with which the electron-rich nitrogen atom in tertiary alkylamines can undergo decomposition reactions in the presence of many transition metal salts and commonly used oxidants, thus precluding the desired C–H activation pathway (Fig. 1b)[29]. Using alternative strategies, Hartwig has reported steric-controlled Rh- (ref. [30]), Ru- (ref. [31]) and Ir-catalysed[32] C(sp^3)–H borylation at methyl groups within simple tertiary alkylamines, in some cases with selectivity at the β-position. Remote C(sp^3)–H oxidations using Pt (ref. [33]), Ru (ref. [34]), Fe[35] and W (ref. [36]) catalysts under strongly acidic conditions, wherein the transformation is guided by the C–H bond reactivity rather than the directing effect of the amine, have also been described. However, no examples of catalytic C(sp^3)–H functionalization directed by tertiary alkylamines have been reported (Fig. 1a,b). Given the ubiquity of tertiary alkylamines in biologically important molecules and the potential efficacy of a method that introduces aryl entities proximal to the nitrogen motif[37], the development of strategies involving catalytic C(sp^3)–H activation directed by tertiary alkylamines to guide building block functionalization, fragment coupling and late-stage functionalization of biologically relevant molecules is an unmet synthetic need (Fig. 1c).

Results and discussion

We reasoned that a successful Pd(II)-catalysed tertiary-alkylamine-directed C(sp^3)–H arylation strategy would depend on the effective coordination of the substrate to the metal. The nitrogen atom is nucleophilic but often sterically hindered; however, based on Ryabov's cyclopalladation studies with benzylamines[38], we proposed that the opposing steric and electronic characteristics inherent to tertiary alkylamines might synergistically combine to promote formation of the mono-amine Pd(II) complex required for C–H activation (Fig. 1b). However, the Pd(II)-ligated nitrogen motif in tertiary alkylamines will often be surrounded by a number of C–H bonds that can undergo deleterious β-hydride elimination reactions. Initial investigations revealed that a reaction between amine **1a**

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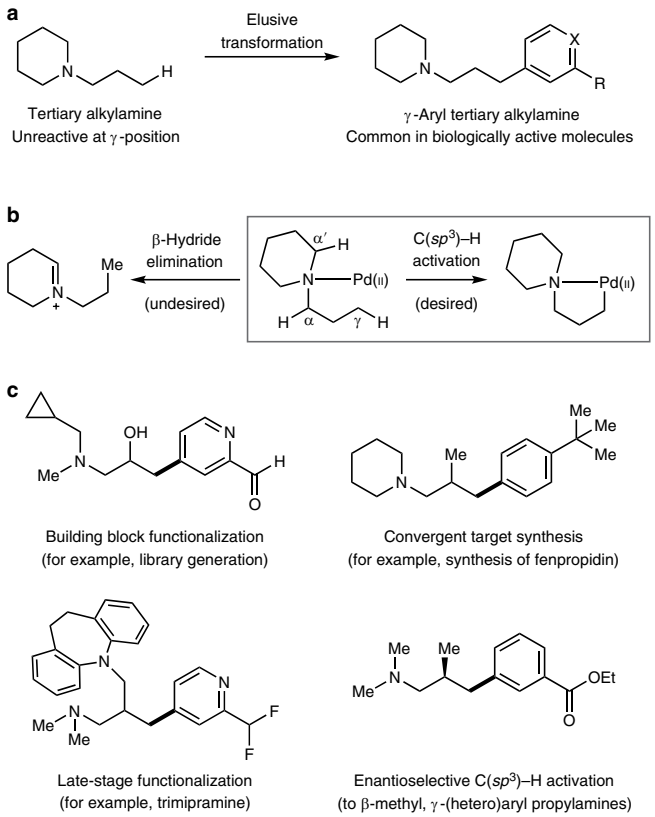


Fig. 1 | Design plan towards γ-C(sp^3)–H arylation of tertiary alkylamines. **a**, Direct methods to selectively arylate tertiary alkylamines at the γ-position do not exist. **b**, Directed C(sp^3)–H activation is a potential solution to the functionalization of tertiary alkylamines; however, the presence of C–H bonds adjacent to the nitrogen atom could lead to undesired β-hydride elimination. **c**, Applications for a Pd(II)-catalysed γ-C(sp^3)–H arylation of tertiary alkylamines, which include the functionalization of available tertiary-alkylamine building blocks, a convergent strategy for target synthesis, late-stage functionalization and enantioselective synthesis of tertiary alkylamines.

and phenylboronic acid **2a** under commonly used Pd(II)-catalysis conditions led to significant amine decomposition and no arylation (see Supplementary Fig. 1)[6]. Computational analysis revealed a lower energy pathway for an acetate-assisted β-hydride elimination (**Ts2**) (Fig. 2a) than the desired C(sp^3)–H activation (**Ts1**), supporting the experimental observations. Interestingly, inner-sphere acetate-assisted β-hydride elimination (**Ts2**) is rarely considered for this common decomposition reaction[39], yet all of our calculations converged on this pathway. We considered whether the introduction of a ligand would modulate the energetic preference for these competing pathways. While a number of directing functional groups are capable of intrinsically switching between neutral and anionic coordination to the Pd(II) catalyst, thereby supporting the use of ligands with diverse binding modes[40], the neutral coordinating nitrogen atom in tertiary alkylamines restricts the type of ligand that can be deployed for C(sp^3)–H activation. We speculated that C(sp^3)–H activation in tertiary alkylamines would be matched to the coordination properties of *N*-acetyl α-amino acid ligands[11,41,42], permitting the Pd(II) centre to accommodate the bisanionic ligand (which contains the basic acetamide needed for C–H bond cleavage), the neutral amine and the vacant coordination site required for C–H activation. Yu and co-workers have previously developed a Pd(II)-catalysed method for arylation of C(sp^3)–H bonds in *N*-alkyl sulfonamides with derivatives of aryl-boronic esters[11]. In their studies, they reported that an *N*-acetyl amino acid ligand was crucial for reactivity, with no reaction in its absence.

Interestingly, we found that including *N*-acetyl *tert*-leucine **4a** as a ligand lowered the energy of the C(sp^3)–H activation step (**Ts3**) relative to the corresponding ligand-assisted β-hydride elimination. We believe that the ligand distorts the co-planar geometry empirically required for β-hydride elimination (**Ts4**), making base-assisted C–H activation the more favoured pathway (see Supplementary Table 5), and represents an extension to the reactivity-inducing capacity of this class of ligand. Our calculations were validated by a reaction employing 25 mol.% of ligand **4a**, which produced a moderate yield of the γ-aryl alkylamine **3a**. An extensive assessment of reaction parameters revealed optimal conditions, which involved the treatment of 2.5 equiv. amine **1a** and phenylboronic acid **2a** with 10 mol.% $Pd(OAc)_2$, 25 mol.% *N*-acetyl *tert*-leucine **4a**, 2.5 equiv. Ag_2CO_3 and 2 equiv. 1,4-benzoquinone in a solution of *N*-methyl-2-pyrrolidone (NMP) at 50 °C for 15 h to afford **3a** in an 81% yield (Fig. 2b).

An initial proposal for the reaction mechanism of the C(sp^3)–H arylation directed by tertiary alkylamine begins with coordination of amine **1a** to the Pd(II)·ligand catalyst to form **Int-I**. Cyclopalladation via ligand-assisted concerted metallation deprotonation affords palladacycle **Int-II**, which undergoes transmetallation with **2a** to **Int-III**; reductive elimination of of the C(sp^3)–C(sp^2) groups, possibly facilitated by benzoquinone[43], generates amine **3a** and Pd(0), which reforms the catalytically active Pd(II)·ligand species upon oxidation with Ag(I).

Having established optimal conditions for γ-C(sp^3)–H arylation, we next explored the scope of the amine component (Table 1). The *N*-propyl piperidine scaffolds bearing different functionalities on the heterocycle underwent efficient C(sp^3)–H arylation to the desired products **3a**–**m** in generally good yields. The yields of product were slightly reduced in the presence of electron-withdrawing substituents on the heterocycle (**3e**,**f**), which may reflect the attenuated binding of the amine to the Pd(II) catalyst brought about by the inductive effect of the remote functionality. Substrates displaying Lewis-basic aromatic heterocycles were compatible with the reaction conditions, delivering γ-arylated products adorned with the functionality commonly found in pharmaceutical and agrochemical intermediates (**3h**–**j**). The reacting C(sp^3)–H bond can also be located in a 2-ethyl substituent on the piperidine ring, producing amine **3n** in useful yield. Interestingly, a substrate with the targeted C–H bond in a 3-methyl substituent on the heterocycle undergoes arylation to the 3-benzyl-piperidine derivative **3o**. This means that cyclopalladation must have involved the Pd(II) catalyst binding to the axial lone pair of the piperidine nitrogen, with the reacting methyl group also projected in the axial position. Other saturated heterocycles, including protected piperazines, morpholines and diazepanes, were compatible with the γ-C(sp^3)–H arylation (**3p**–**s**); the lower yield of pyrrolidine **3t** is due to competing β-hydride elimination. Acyclic scaffolds were also compatible with the arylation process. The *N*,*N*-dimethyl-derived tertiary alkylamines, for example, are one of the most common classes of amines featured in pharmaceutical and agrochemical agents, and a method to elaborate their structures would represent an attractive transformation. However, these substrates can contain up to eight C–H bonds adjacent to nitrogen, which means they are especially prone to β-hydride elimination on complexation with Pd(II) salts. Therefore, we were pleased to find that a range of *N*,*N*-dialkylamine derivatives smoothly reacted to form amines **3u**–**ac** in good yield, reinforcing the ligand effect in facilitating C(sp^3)–H activation over β-hydride elimination. Acyclic tertiary alkylamines displaying a variety of α- and β-substituents along the reacting alkyl chain also undergo γ-C(sp^3)–H arylation (**3v**–**y**), and useful functionality could also be incorporated into the non-reacting alkyl substituents without affecting the success of the reaction (**3ac**). In a case where

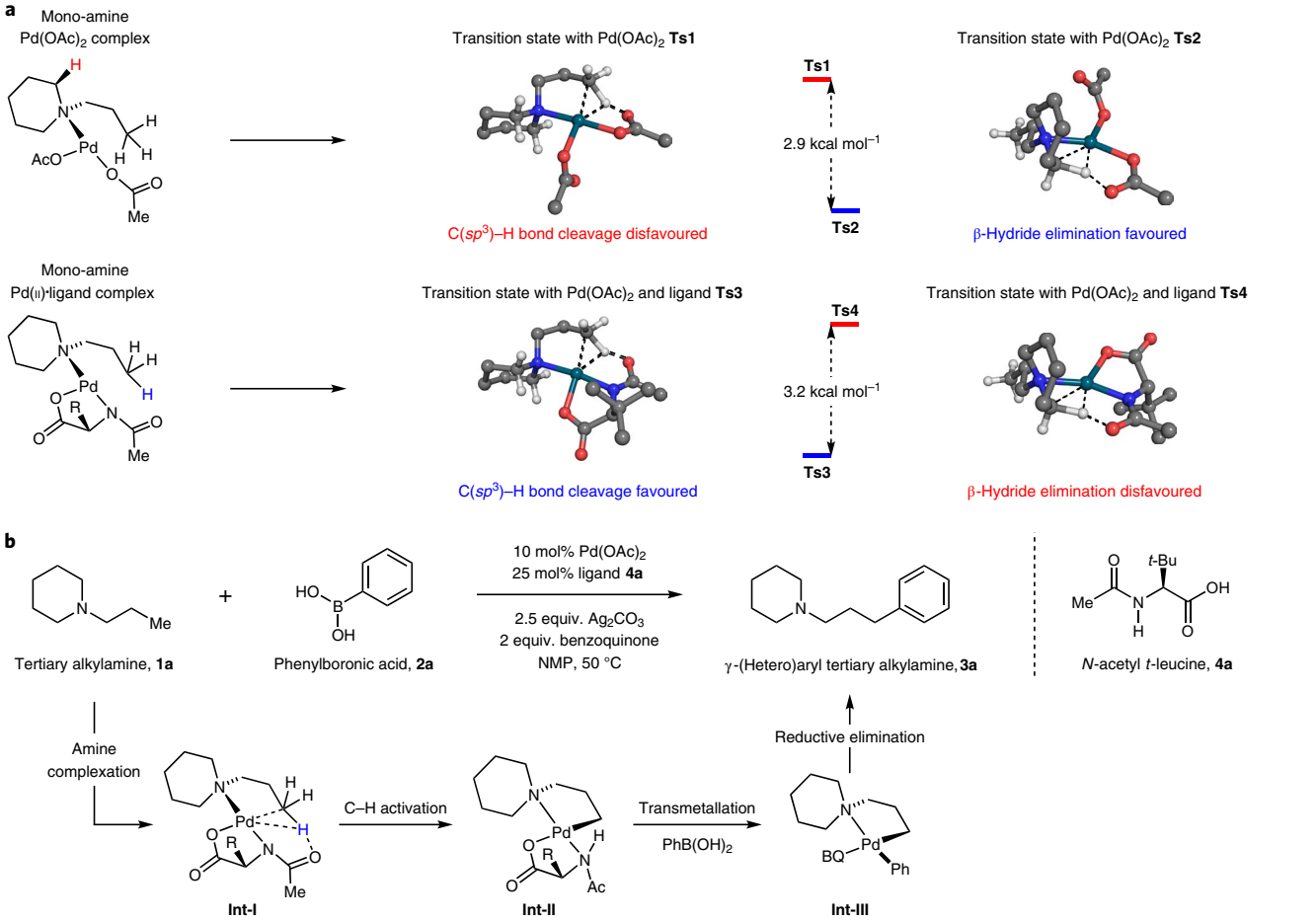


Fig. 2 | The γ-C(sp^3)–H arylation of tertiary alkylamines. a, Computational study of ligand-enabled γ-C(sp^3)–H activation. The γ-C–H activation in the amino-alkyl Pd(II) complex was found to require a higher-energy transition state (**Ts1**) than did the corresponding β-hydride elimination (**Ts2**). By contrast, with the amino acid ligand bound to the Pd(II) complex, the corresponding intermediate presented a lower-energy transition state (**Ts3**) for ligand-assisted γ-C–H activation in comparison to **Ts4** (for ligand-assisted β-hydride elimination). Calculations were conducted using B3LYP-D3(BJ)/[6-311+G(2d,p)/SDD(Pd)] IEFPCM with DMF as solvent, $T = 323.15$ K. **b**, Optimized reaction and proposed mechanism of γ-C(sp^3)–H arylation. The $Pd(OAc)_2$, the ligand **4a** and benzoquinone (BQ) are all essential for the observed reactivity. The reaction goes through one turnover in the absence of the Ag_2CO_3. While other amino acid ligands also work, **4a** gave superior yields. Ligands containing the N–Ac motif were superior to other amide and carbamate derivatives.

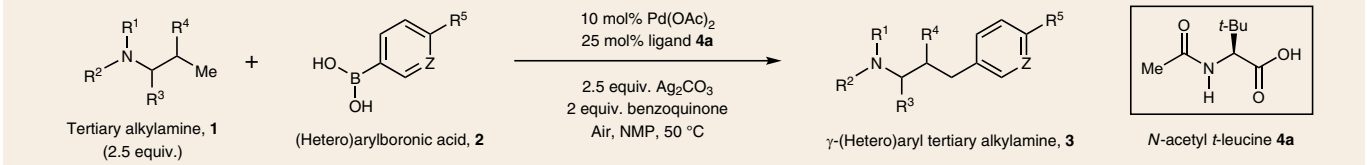
two equivalent propyl groups are present, 81% of the mono-arylated **3aa** product is isolated with only trace amounts (8%) of the competitive diarylation product observed.

Next, we evaluated the scope of the aryl-boronic acid coupling partner. Aryl groups with electron-donating and -withdrawing substituents at the *para*- and *meta*-positions were incorporated with good yields to form the γ-aryl alkylamine products (**3ad**–**am**); unfortunately, *ortho*-substituted aryl-boronic acids resulted in a lower yield (**3an**). Palladium-sensitive functionalities such as aryl bromides (**3ag**,**ah**) were tolerated under the mild reaction conditions. Heteroaryl-boronic acids, such as those containing functionalized pyridines and indoles, were successfully introduced into the tertiary amine framework (**3ao**–**ar**), offering opportunities for downstream structure modification.

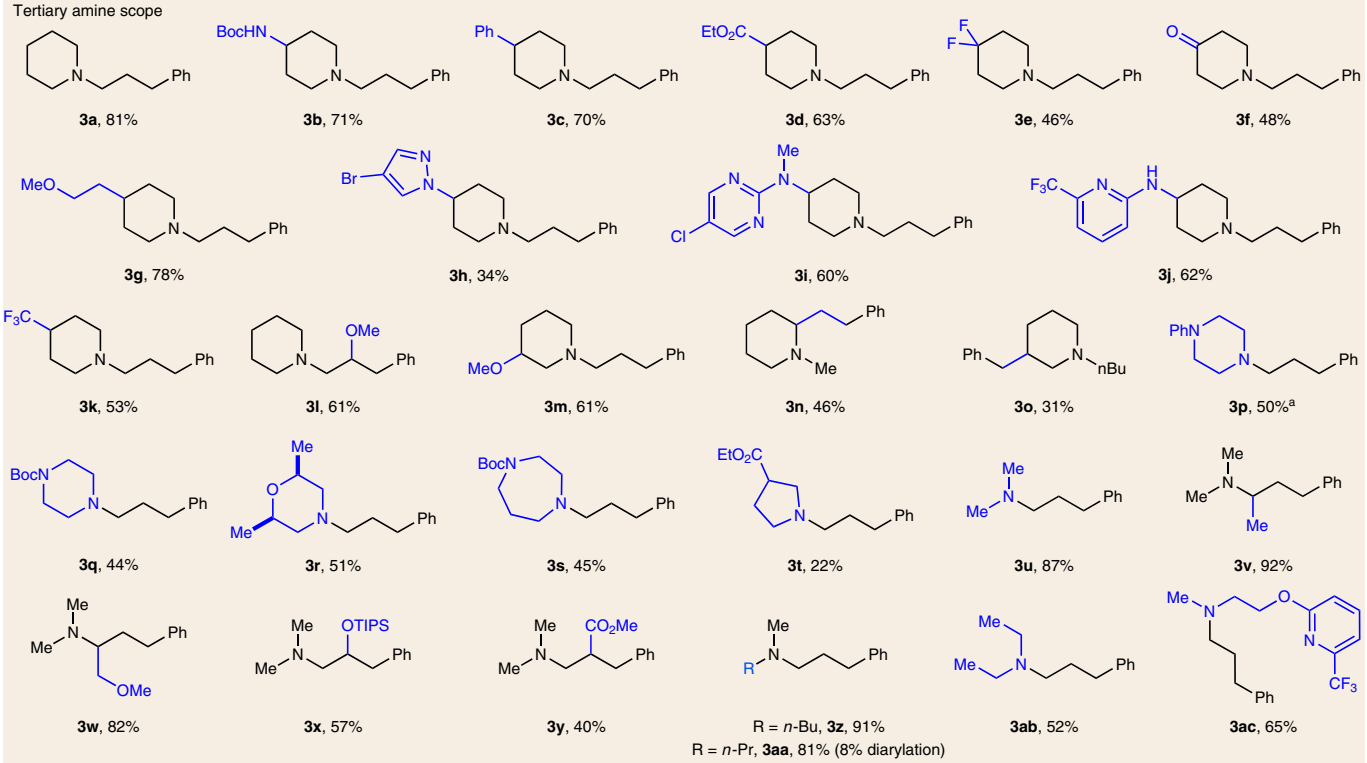
Fenpropimorph **5**, a marketed fungicide, can be synthesized in a single step from readily available materials (**1ad** and **2p**), demonstrating a convergent coupling application to target synthesis (Fig. 3a). Such a strategy would be particularly appealing for the synthesis of fenpropimorph analogues, wherein assembly via classical reductive amination or alkylation strategies may be limited by the availability of the corresponding substituted α-methyl hydrocinnamaldehyde or C3-3-aryl-1-halo-2-methylpropanes, respectively; readily available *N*-propyl amines could be directly combined with the vast array of commercial aryl-boronic acids, providing immediate access to a library of analogues. We found that *N*-propyl analogues of donezepil, ciprofloxacin and fluoxetine underwent γ-C(sp^3)–H arylation without affecting the functionality in these molecules. (**6**–**8**, Fig. 3b). The tricyclic antidepressant trimipramine, which is used to treat major depressive disorders, was also an excellent substrate for the arylation process, affording γ-(hetero) aryl tertiary alkylamine derivatives **9a**–**c** in excellent yield (Fig. 3c); 90% of the unreacted excess amine starting material can be recovered, further demonstrating the role of ligand **4a** in controlling the selectivity between potentially competing pathways. The success of this transformation demonstrates the potential of its application as a tool for late-stage functionalization of pharmaceutical agents; many different aryl groups could be transferred to already biologically active molecules, producing previously unexplored candidates that would require multistep syntheses to prepare by traditional means.

Given that the γ-C(sp^3)–H arylation process requires the presence of ligand **4a**, we questioned whether an enantioselective transformation might be possible when using prochiral *N*-isobutyl tertiary alkylamines (**1ae**–**ag**), thereby generating non-racemic β-methyl γ-aryl propylamines that would be difficult to synthesize directly by other methods. Enantioselective desymmetrization of isobutyl groups is challenging because the catalyst must

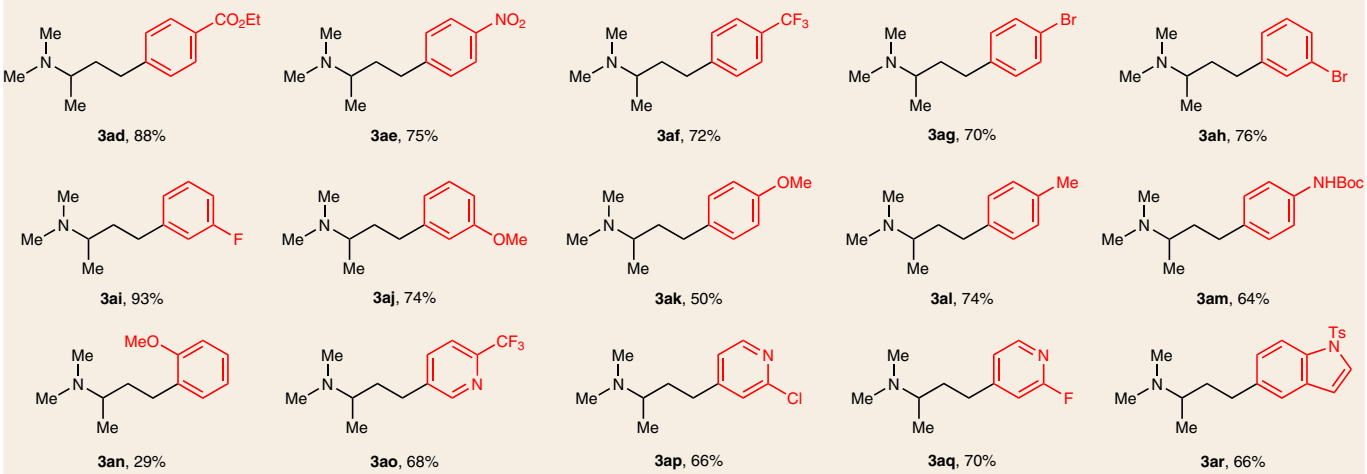
Table 1 | Scope of the γ-C(sp^3)–H arylation in tertiary alkylamines



Tertiary amine scope



(Hetero)arylboronic acid scope



[a]The reaction to produce **3p** was conducted at 60 °C under conditions otherwise identical to the optimized protocol.

sterically discriminate between an β-hydrogen atom and a relatively small β-methyl group. Furthermore, the prochiral centre is distant from the chirality in the Pd(II) catalyst, making enantioselective control more challenging[44,45]. On the basis of computational studies, we noted a distinction between two chair-like transition states that orient the non-reacting methyl group in either an equatorial (**Ts5**) or axial (**Ts6**) position; the latter transition state appears to be destabilized by pseudo-1,3-diaxial interactions between the axial *N*-Me and the non-reacting methyl group and carries an energetic cost of 2.1 kcal mol^{-1} (Fig. 3d). Under the previously optimal conditions, **1ae** (R = Me) was converted to **3as** with an e.e. of 81%; conducting the reaction in dimethylformamide (DMF) at 40 °C increased the e.e. to 90%. Interestingly, comparable enantioselectivity was observed with the *N*-acetyl alanine as ligand (86% e.e.), suggesting that steric parameters alone are not responsible for the asymmetric induction. Computational analysis suggested that the

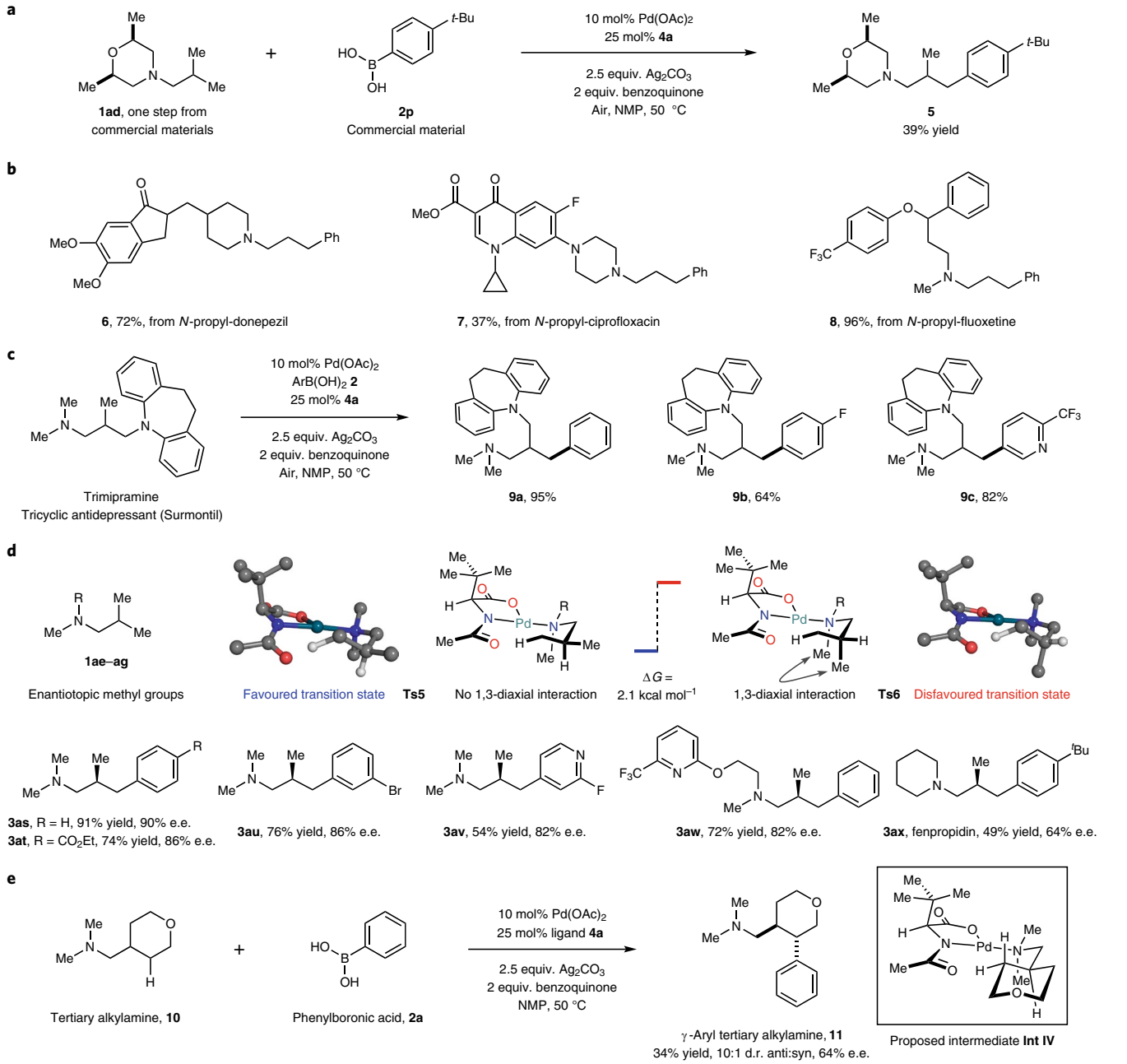


Fig. 3 | Applications and further advances of the γ-C–H arylation of tertiary alkylamines. a, Direct synthesis of the fungicide fenpropimorph from readily available materials. **b**, The γ-C(sp^3)–H arylation reaction in substrates containing pharmaceutically relevant amine fragments. **c**, Late-stage arylation of trimipramine. A range of aryl groups can be added directly to trimipramine, generating a range of previously unknown analogues in a single synthetic step. **d**, Enantioselective γ-C(sp^3)–H arylation of tertiary alkylamines. Using substrates containing reacting enantiotopic β-methyl groups, an enantioselective desymmetrizing arylation generates non-racemic β-methyl-γ-aryl tertiary alkylamine products. **e**, Preliminary investigations into methylene C–H activation of tertiary alkylamines show selectivity for the *trans* isomer on cyclic systems.

α-substituent on the ligand projects the amide moiety below the square-plane of the palladium(II) complex, which relays the chiral information to the ligated substrate and controls its conformation. The calculated e.e. (88% for **4a**, 83% for *N*-acetyl alanine) agreed with experimental values. A range of aryl-boronic acids and acyclic tertiary alkylamines exhibited good yields and e.e. values (**3as–aw**), showing only minimal erosion of the enantioselectivity compared to the parent reaction. Despite the lower levels of asymmetric induction, this enantioselective γ-C(sp^3)–H arylation methodology can be used to synthesize the fungicide fenpropidin (**3ax**) directly from readily available materials in 49% yield and with an e.e. of 64%.

To the best of our knowledge, the only enantioselective synthesis of this compound has been described as requiring six chemical steps; the synthesis of non-racemic substituted-aryl analogues of these fungicides would also be directly accessible through this method (*vide supra*)[46]. Finally, we also demonstrated that the process of γ-arylation directed by tertiary alkylamines can be applied to methylene C–H bonds (Fig. 3e). On treatment with the standard conditions, the cyclic dimethylamine derivative **10** underwent methylene C–H arylation to form **11** in a modest, but encouraging, 34% yield. Notably, **11** was produced mainly as the *trans* isomer, reflecting a proposed intermediate (**Int-IV**) prior to C–H activation that must

proceed through to a 5,6-*trans*-fused palladacycle; the e.e. of the arylation was also found to be a promising 64% (ref. [47]).

In summary, we have developed a ligand-enabled Pd(II)-catalysed γ-C(sp^3)–H arylation process capable of selectively functionalizing a range of tertiary alkylamines with aryl-boronic acids. As well as having abilities to functionalize building-block-type amines, synthesize biologically active molecules and be applied as a late-stage functionalization tool, this reaction can also be performed enantioselectively.

Online content

Any Nature Research reporting summaries, source data, extended data, supplementary information, acknowledgements, peer review information; details of author contributions and competing interests; and statements of data and code availability are available at https://doi.org/10.1038/s41557-019-0393-8.

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Data availability

The data that support the findings of this study are available within the paper and its supplementary information files. Raw data are available from the corresponding author on reasonable request.

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Author contributions

J.R., M.N. and M.J.G. conceived the project. J.R., M.N., H.A. and M.E.B. designed and performed the synthetic experiments. J.R. and N.J.F. designed and performed the computational studies. J.R., M.N., H.A., N.J.F. and M.J.G. prepared the manuscript.

Competing interests

The authors declare no competing interests.

Additional information

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