confirmation by Kaguya and LADEE of the lunar Na trend between November and April provides the strongest evidence yet for an annual variation of the Na exosphere. This trend is likely the cumulative response of Na to meteoroid streams, whose annual activity peaks from November through January and then subsides until the summer. The substantial residence time for Na at the surface suggested by this interpretation inevitably leads to the conclusion that Na migrates toward the poles like other volatiles (e.g., water) in these cycles of adsorption and redesorption. The K measurements show a strong but, contrary to Na, short-lived response to the Geminids meteoroid shower. Outside of the meteoroid streams, K shows a regular variation across a lunation that correlates strongly with the abundance of potassium in the lunar bulk soil. Combined, these results and recent studies of the Mercurian exosphere (*23*, *24*) indicate a pronounced role for meteoroid impact vaporization and surface exchange in determining the composition of surface-bounded exospheres. However, the details of how the exosphere depends on surface composition and responds to meteoroid streams are not yet understood.

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SUPPLEMENTARY MATERIALS

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Materials and Methods
Supplementary Text
Figs. S1 to S5
References (*25*–*34*)

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ORGANIC CHEMISTRY

Functionalization of C(sp^3)–H bonds using a transient directing group

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Proximity-driven metalation has been extensively exploited to achieve reactivity and selectivity in carbon–hydrogen (C–H) bond activation. Despite the substantial improvement in developing more efficient and practical directing groups, their stoichiometric installation and removal limit efficiency and, often, applicability as well. Here we report the development of an amino acid reagent that reversibly reacts with aldehydes and ketones in situ via imine formation to serve as a transient directing group for activation of inert C–H bonds. Arylation of a wide range of aldehydes and ketones at the β or γ positions proceeds in the presence of a palladium catalyst and a catalytic amount of amino acid. The feasibility of achieving enantioselective C–H activation reactions using a chiral amino acid as the transient directing group is also demonstrated.

Precoordination of a metal with functional groups in substrates has been extensively exploited to control selectivity and promote reactivity in metal-catalyzed or -mediated reactions (*1*–*5*). The same approach has been successfully implemented in directed C–H activation reactions (*6*–*11*). However, the covalent installation and removal of directing groups is a major drawback for synthetic applications. First, an additional two steps must be added to the synthetic sequence. Second, the conditions for installation or removal of the directing groups are sometimes incompatible with other functional groups present in advanced synthetic intermediates. It is therefore highly desirable to devise a functionally tolerant reagent that can be reversibly linked to the substrate and can serve as a directing group. Upon C–H activation and subsequent functionalization, this reagent would dissociate from the product and transiently link to another substrate molecule so that only a catalytic quantity of the directing group would be needed (Fig. 1A). This approach has been successfully implemented in Rh(I)-catalyzed C(sp^2)–H activation reactions in a number of pioneering examples. Jun *et al*. reported the use of 2-amino pyridine as a transient directing group for Rh-catalyzed activation of aldehydic C–H bonds (*12*) (Fig. 1B). Recently, using a related strategy, Mo and Dong reported a Rh-catalyzed α-alkylation of ketones via a vinyl C–H activation step, featuring an enamine intermediate with a pyridine moiety as the transient directing group (*13*). Bedford *et al*. developed a Rh-catalyzed ortho-arylation through reversible in situ transesterification of catalytic amounts of phosphinite ligands with the phenol substrate (*14*). The strategy of using catalytic directing groups has also been employed by Lightburn *et al*. (*15*) and Grünanger and Breit (*16*) to achieve selectivity in Rh-catalyzed hydroformylation reactions.

In conjunction with our efforts to develop Pd-catalyzed C(sp^3)–H functionalizations (*17*, *18*), we have extensively investigated the feasibility of Pd(II)-catalyzed C(sp^3)–H activation of aldehydes and ketones using a wide range of potential transient directing groups, including those previously developed for Rh(I) catalysts. Unfortunately, the resultant Pd(II) complexes bound to the bidentate iminopyridine or iminooxazoline are unreactive toward cleavage of sp^3 C–H bonds under various conditions. The development of monoprotected amino acid ligands (*19*, *20*) and the recent use of amino acids as bidentate directing groups in C–H functionalizations of peptides (*21*) led us to speculate that an amino acid could serve as a suitable transient directing group. We reasoned that the amino acid could be reversibly tethered to an aldehyde or ketone substrate via an imine linkage under appropriate conditions. In a similar manner to that operative in our dipeptide chemistry, the imine moiety and the carboxylate could form a bidentate directing group to enable subsequent C–H functionalization (Fig. 1C).

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We chose arylation of 2-methylbenzaldehyde **1a** with 4-iodoanisole as the model reaction for optimization. Benzaldehyde derivatives are known to readily form imine linkages with amino acids (*22*). After extensive experimentation, we found that the desired C(sp^3)–H selective mono-arylation product **2a** could be observed in 18% nuclear magnetic resonance (NMR) yield when the reaction was conducted in hexafluoroisopropyl alcohol (HFIP) with 10 mol % $Pd(OAc)_2$ (OAc, acetate), 40 mol % glycine, and 1.5 equivalents of silver trifluoroacetate (see table S1, entry 5). The use of acetic acid (AcOH) as the solvent improved the yield to 52%, albeit with considerable decomposition of the starting material (table S1, entry 6). We speculated that the low mass balance stemmed from a rate mismatch between the imine formation step and the following C–H cleavage step, leading to decomposition of the accumulated imine species. Therefore, we reasoned that the addition of water would reduce the concentration of the imine intermediate and prevent decomposition during the reaction. Indeed, when a 9:1 mixture of AcOH and H_2O was used as the solvent, we were able to achieve 93% conversion and 71% NMR yield, along with formation of the diarylated product in 11% yield (table S1, entry 8). By switching the limiting reagent to the aryl iodide, we obtained the desired mono-arylated product exclusively in 81% NMR yield (table S1, entry 10). We also evaluated a variety of amino acids and found that the side chain of the amino acid does not have a marked effect on the efficiency of this transformation (table S1, entries 10 to 13). As expected, N-protected glycine led to a complete loss of reactivity, consistent with the hypothesis that imine formation is crucial for enabling C–H activation (table S1, entry 14).

Under optimal conditions, we next examined the scope of C–H arylation (Fig. 2). The arylation of 2-methylbenzaldehyde **1a** proceeded with a wide range of aryl iodides in good yields. Both electron-donating (**2a** to **2c**) and electron-withdrawing (**2f** to **2n**) substituents are well tolerated at either the para or meta position of the aryl iodide (72 to 83% yield). The use of a sterically hindered ortho-substituted aryl iodide led to a reduced yield (**2d**, 43%). The reaction can accommodate a range of functional groups, including halides (F and Br), nitro groups, aldehydes, ketones, esters, and even free carboxylic acid groups. More importantly, this reaction is compatible with heteroaryl iodides as coupling partners (**2o** to **2v**), overriding the strong coordination of heteroatoms to the metal catalyst. This feature renders the reaction particularly useful for the synthesis of biologically active compounds bearing heterocycles. Finally, benzaldehydes with various ortho, meta, and para substituents were effectively arylated with 1-iodo-3-nitrobenzene, providing the corresponding products in good yields under the standard conditions (**2w** to **2ad**). The use of the analogous ketone substrate 2′-methylacetophenone produced the arylated product in low yield, presumably because that ketimine is more difficult to form.

We next investigated whether the same strategy could be applied to aliphatic ketone substrates, which are versatile and widely used synthetic intermediates (*23*). Although β-arylation of ketones via reaction pathways other than β-metal insertion has been limited to the substrates without α-substitution (*24*, *25*), directed C(sp^3)–H activation of ketones has only been studied through the intermediacy of preformed oximes (*9*, *26*, *27*). We were aware that direct arylation of ketones using a transient directing

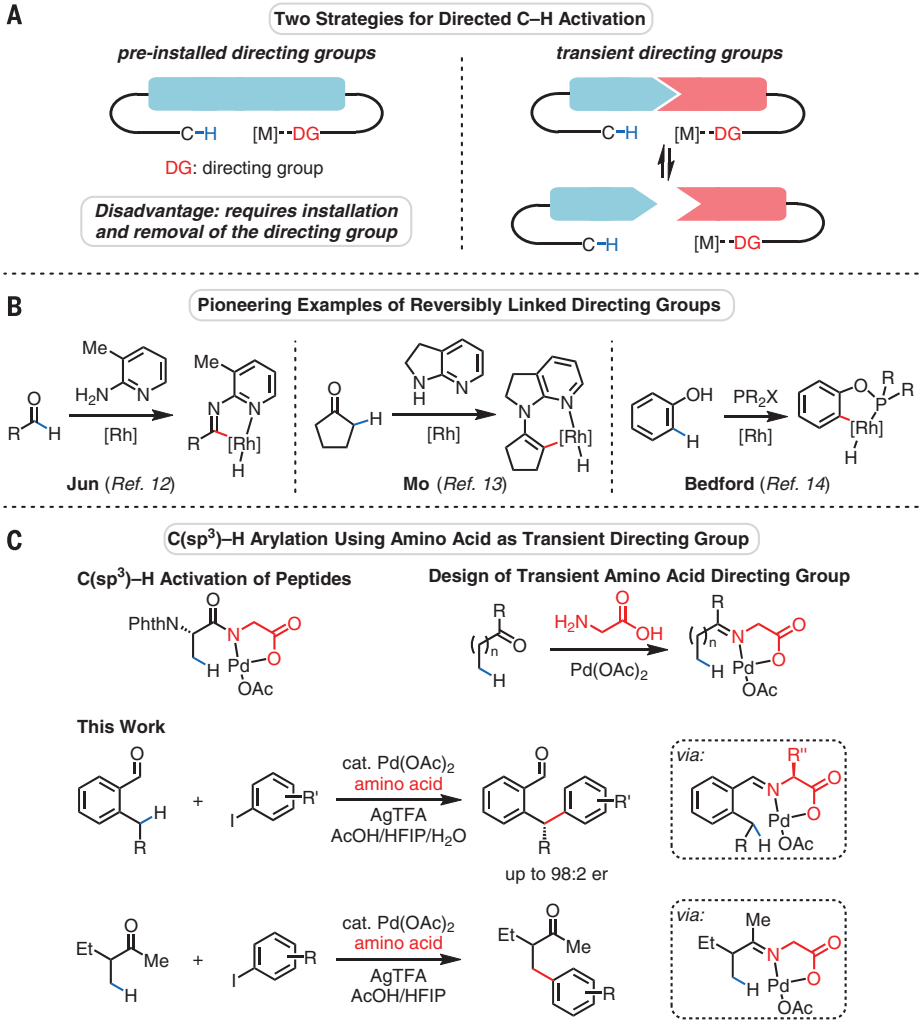


Fig. 1. C–H activation using transient directing groups. (**A**) Two strategies for directed C–H activation. M, metal. (**B**) Pioneering examples of reversibly linked directing groups. Me, methyl; X, leaving group. (**C**) C(sp^3)–H arylation using an amino acid as a transient directing group. Phth, phthalimido; Et, ethyl; TFA, trifluoroacetic acid.

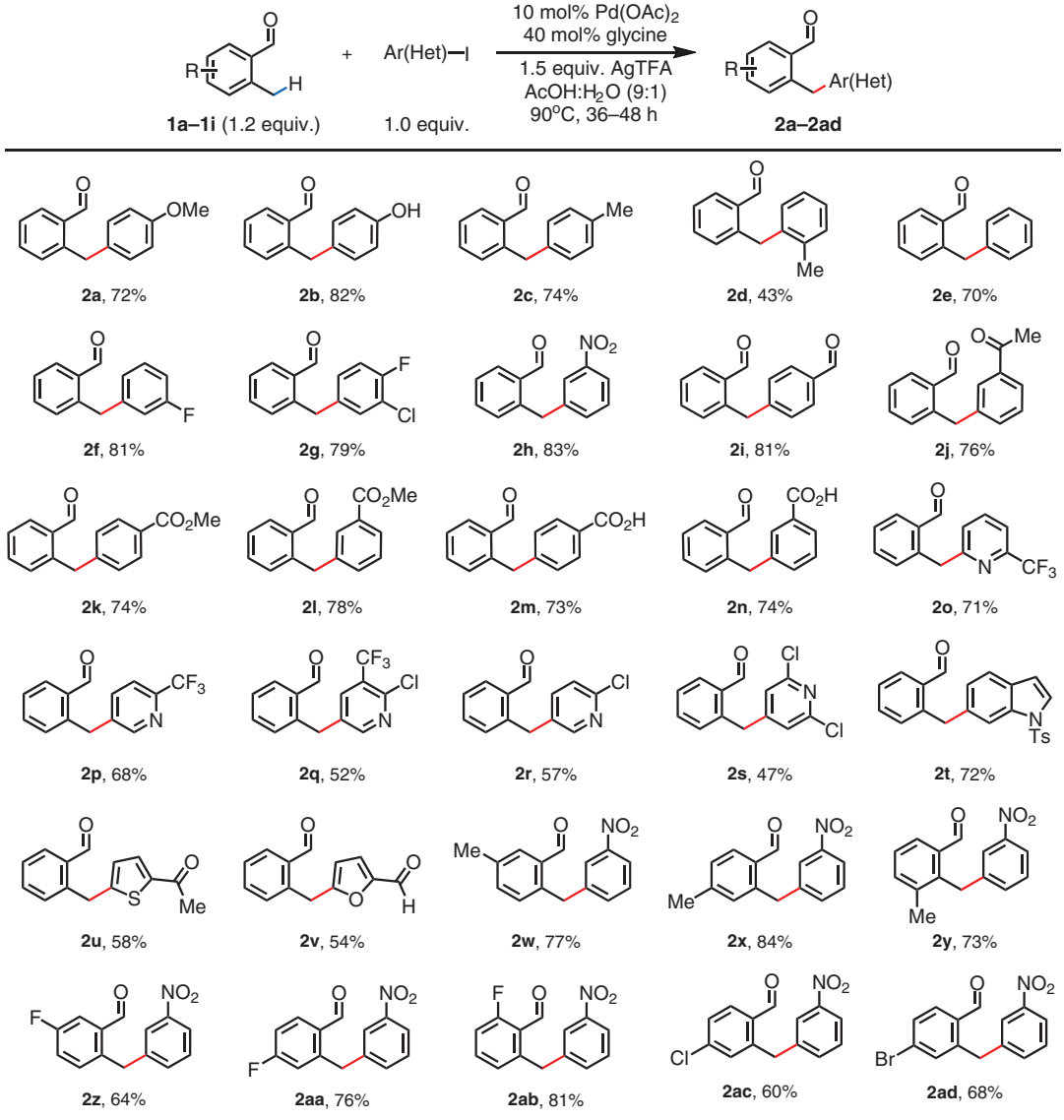


Fig. 2. Palladium-catalyzed benzylic C(sp^3)–H arylation of aldehydes. Ar(Het), (hetero)aryl.

For each entry number (in boldface), data are reported as isolated yield. See supplementary materials for experimental details.

group would pose several challenges: First, in situ formation of ketimines is generally less favored than that of aldimines. Second, one of the ketimine *E*/*Z* isomers may not be reactive if the orientation of the imino acid directing group is not suitable for directing palladium in proximity to the target C–H bond. Third, tautomerization of imines to enamines may occur as a competing pathway, which would generate an ineffective directing group. With these considerations in mind, we further optimized the reaction conditions for ketone arylation. Although the initial investigation with 3-methyl-2-pentanone (**3a**) provided <2% yield of the desired product under the optimal conditions for aldehydes (table S2, entry 1), we found that by using 50 mol % glycine and a 3:1 mixture of HFIP:AcOH as the solvent, the yield of β-arylation product **4a** could be substantially improved to 71% (table S2, entry 7). However, a variety of amino acids with side chains proved inferior and led to diminished yields (table S2, entries 9 to 11).

We then explored the scope of ketones and aryl iodides under the new conditions. As illustrated in Fig. 3, a wide range of aryl iodides with electron-donating or -withdrawing substituents were well tolerated (**4a** to **4f**). Moderate to good yields were achieved after conducting the reaction with a variety of linear, α-branched, and cyclic ketones (**4g** to **4r**). We found that this method can activate methylene C(sp^3)–H bonds in cyclic substrates, producing the corresponding syn products with excellent diastereoselectivity (**4o** to **4q**). Furthermore, one example of γ-arylation was observed when β-C(sp^3)–H bonds were absent in the substrate (**4s**). However, aliphatic aldehydes are not suitable substrates because competing reaction pathways lead to the decomposition of the starting material under the current conditions.

Because carrying out Pd-catalyzed enantioselective C–H insertion reactions remains a substantial challenge (*19*, *28*–*30*), we wondered whether the enantioselective C–H arylation could be achieved by using a chiral reversible directing agent. Thus, benzaldehydes bearing methylene C(sp^3)–H bonds were investigated in the presence of a chiral amino acid. This transformation is difficult due to the more sluggish C–H activation, as well as the requirement of discrimination between the two enantiotopic C–H bonds. On the basis of our proposed intermediate in Fig. 1C, we envisioned that the enantioselection could be realized through the steric interaction between the R group (R ≠ H) and the bulky side chain R″ of the amino acid. Indeed, when 40 mol % L-valine (R″ = isopropyl)

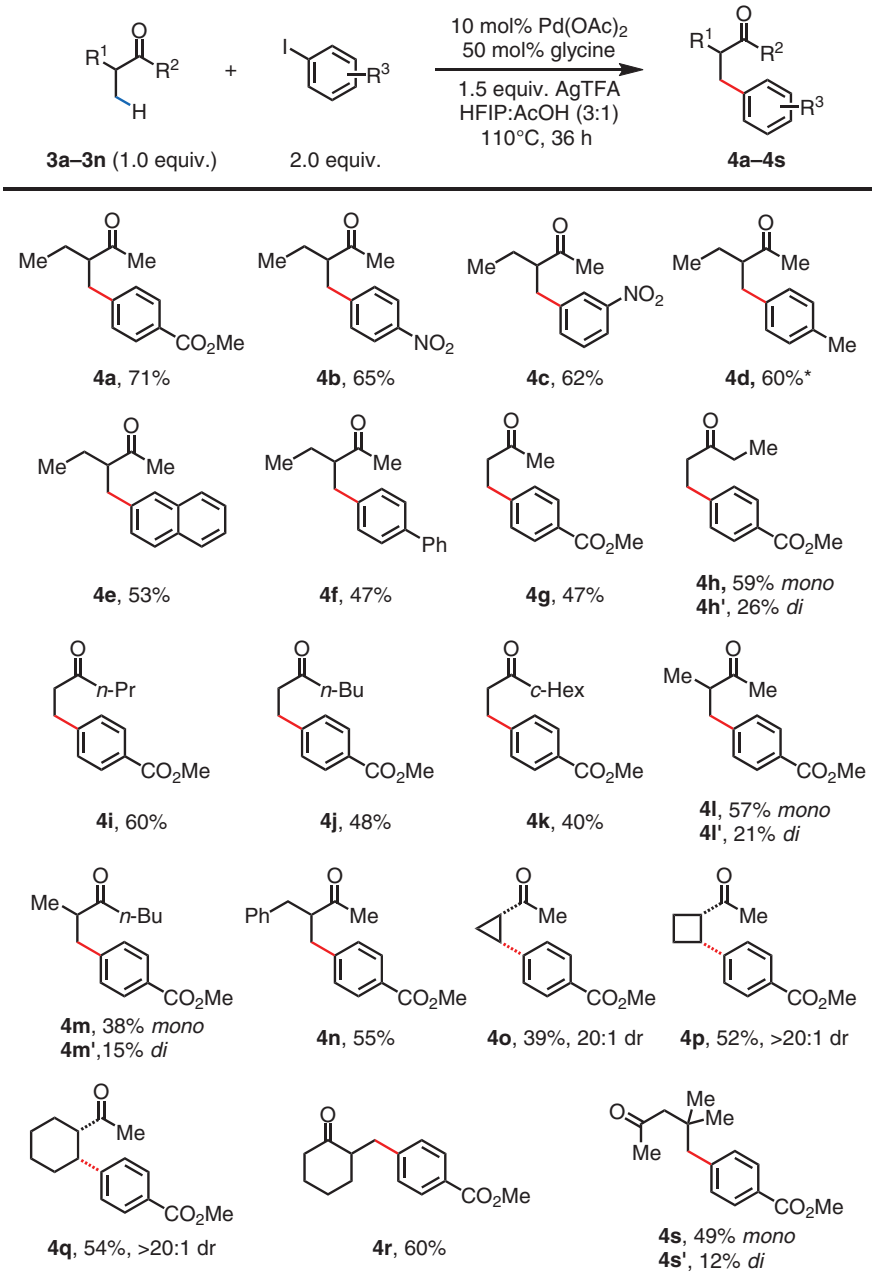
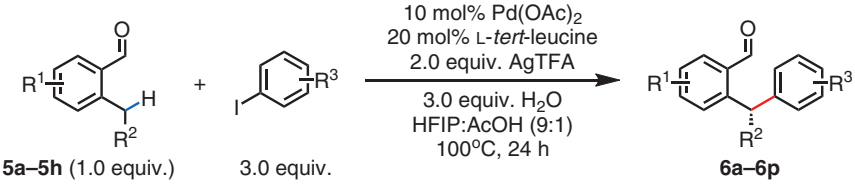


Fig. 3. Palladium-catalyzed C(sp^3)–H arylation of ketones. Pr, propyl; Bu, butyl; Hex, hexyl; dr, diastereomeric ratio.

For each entry number (in boldface), data are reported as isolated yield. See supplementary materials for experimental details. * Reaction performed at 130°C with 3.0 equiv. aryl iodide.

was used instead of glycine, the arylation of 2-ethyl-5-(trifluoromethyl)benzaldehyde (**5a**) provided the desired product **6a** with an enantiomeric ratio (er) of 85:15 (table S3, entry 4). Consequently, we speculated that a more sterically encumbered amino acid should lead to superior enantioselectivity. When we performed the reaction using L-*tert*-leucine (R″ = *tert*-butyl), we achieved excellent enantioselectivity (98:2 er), albeit in only 30% NMR yield (table S3, entry 5). Reducing the ratio of ligand-to-Pd from 4:1 to 2:1 resulted in a substantially enhanced yield (87%), without any erosion of enantioselectivity (table S3, entry 6). Apparently, sterically bulky L-*tert*-leucine is less prone to imine formation, allowing the free form of the amino acid to coordinate with Pd(II) and deactivate the catalyst. Finally, the addition of 3 equivalents of water led to nearly identical results (table S3, entry 8). However, the presence of water has proved to be beneficial to other aldehyde substrates.

Under optimized conditions, the enantioselective arylation of **5a** proceeded effectively with a wide range of aryl iodides bearing various functional groups at the para or meta position (**6a** to **6i** in Fig. 4). With respect to the scope of aldehydes, the reaction is compatible with ester (**6j**), trifluoromethyl (**6k**), and halogen substituents (**6l** to **6n**). Halogen-substituted benzaldehydes exhibited higher reactivity, and the palladium catalyst loading could be reduced to 5 mol %. Moreover, the methylene C(sp^3)–H bond on longer side chains could also be activated (**6o** and **6p**), thus greatly expanding the scope of aldehydes for this reaction.



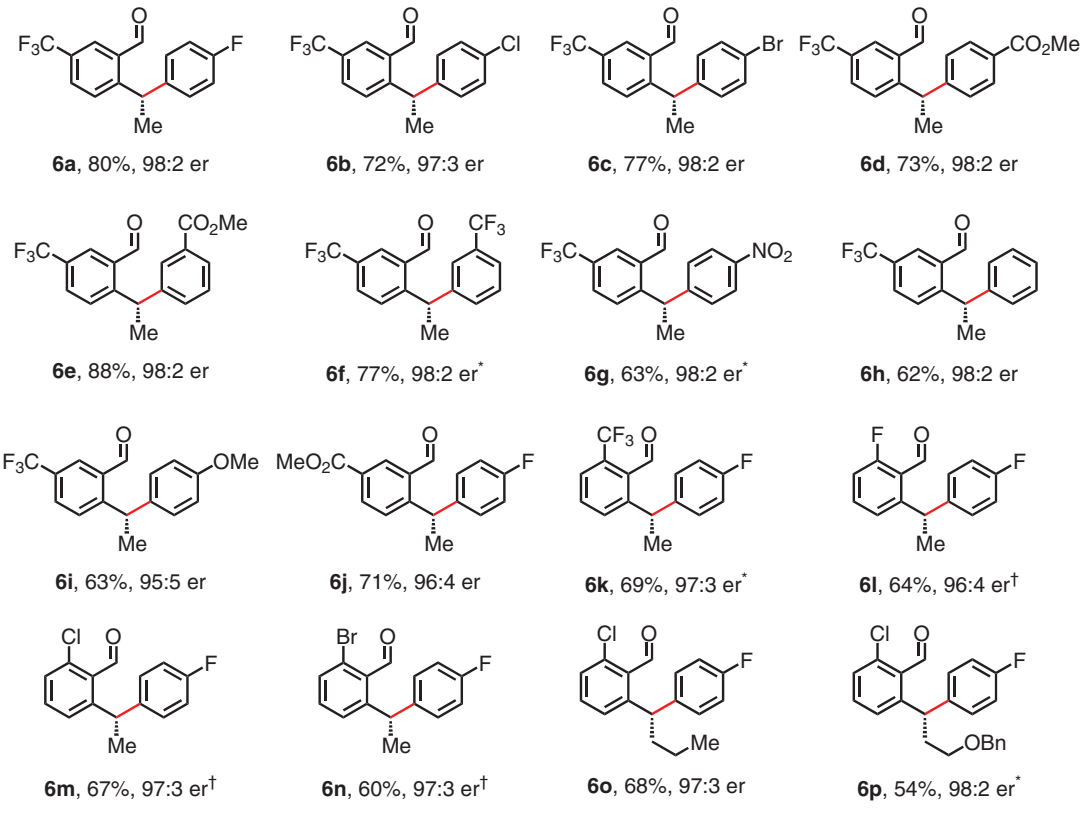


Fig. 4. Palladium-catalyzed enantioselective benzylic C(sp^3)–H arylation of aldehydes. HPLC, high-performance liquid chromatography.

For each entry number (in boldface), data are reported as isolated yield. Enantiomeric ratios (er) were determined by chiral HPLC analysis. See supplementary materials for experimental details. *Reaction performed at 110°C. †Reaction performed with 5 mol% $Pd(OAc)_2$ and 10 mol% L-*tert*-leucine.

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SUPPLEMENTARY MATERIALS

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Supplementary Text
Tables S1 to S9
NMR Spectra
HPLC Spectra
X-ray Crystallographic Data
Reference (*31*)

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