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Palladium(II)-Catalyzed Selective Arylation of Tertiary C–H Bonds of Cyclobutylmethyl Ketones Using Transient Directing Groups

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Abstract

We report the first example of selective Pd(II)-catalyzed tertiary C−H activation of cyclobutylmethyl ketones using a transient directing group. An electron-deficient 2-pyridone ligand was identified as the optimal external ligand to enable tertiary C−H activation. A variety of cyclobutylmethyl ketones bearing quaternary carbon centers was readily accessed without preinstalling internal directing groups in up to 81% yield and >95:5 regioisomeric ratios of tertiary C−H arylation to β-methylene (β-methyl) or γ-C−H arylation.

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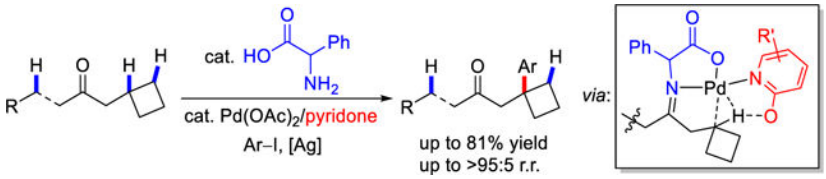

A Pd(II)-catalyzed tertiary C−H activation of cyclobutylmethyl ketones using a transient directing group is reported. An electron-deficient 2-pyridone ligand was identified an external ligand to enable tertiary C−H activation. A variety of cyclobutylmethyl ketones bearing quaternary carbon centers was readily accessed in up to 81% yield and >95:5 regioisomeric ratios of tertiary C−H arylation to β-methylene (β-methyl) or γ-C−H arylation.

Keywords

C−H activation; arylation; palladium; transient directing group; synthetic methods

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Conflict of interest

The authors declare no conflict of interest.

The activation of typically inert C–H bonds and their subsequent transformation into new functional groups via transition metal catalysis has emerged as a promising platform for enabling new disconnections in synthesis campaigns. While a wide range of Pd-catalyzed C−H activation reactions has been discovered in the past decade,[1–2] the majority of these reports have targeted primary and secondary C−H bonds, with only a handful of examples reporting tertiary C−H activation.[3–4] Shuto and Hoshiya et al. reported a Pd-catalyzed tertiary C−H arylation and alkylation of cyclopropanes using 8-aminoquinoline[5], a strongly coordinating auxiliary, as the preinstalled directing group (Scheme 1a).[3a, 3b] Rao and Sheng et al. also demonstrated a Pd-catalyzed cascade C−H activation on the tertiary C−H functionalization of cyclobutanes using the same bidentate 8-aminoquinoline directing group (Scheme 1b).[4] From the vantage point of practicality, C−H activation reactions which do not require the installation and removal of bespoke, exogenous directing groups such as 8-aminoquinoline will invariably be much more attractive in terms of both atom and step economies. The constraints of such exogenous directing groups may be overcome in one of two ways: the development of ligand-accelerated C−H activation reactions which may be directed by functional groups native to the target molecules,[6–7] or by the development of reactions which use reversibly attached transient directing groups.[8–11] Considering the widespread presence of cyclobutane motifs among biologically significant molecules,[12] we embarked on the development of a tertiary C−H bond arylations in cyclobutylmethyl ketones using a transient-directing-group (TDG-) strategy (Scheme 1c).

Herein, we report the first example of Pd-catalyzed tertiary β- C−H arylation of cyclobutylmethyl ketones using an α-amino acid as the transient directing group. The use of a pyridone ligand was found to be crucial in this reaction.

To test the feasibility of our approach, we first attempted the tertiary C−H bond arylation of 1-cyclobutylpropan-2-one (**1a**) with methyl 4-iodobenzoate (**2a**) on the basis of our previous work in β-methylene C−H arylation.[8b, 8d] The results of the pyridone ligand evaluation are summarized in Table 1. In the absence of ligand, a 5% yield of the arylated product was observed. We found that electron-deficient pyridone ligands led to improved yields compared to the ligand-free conditions, which is in agreement with prior observations in Pd-catalyzed C−H activation reactions.[7] It is also noteworthy that all the tested pyridone ligands gave the desired product with a high regioisomeric ratio (>95:5 r.r.) to γ-C−H arylation.[7a] The use of 5-nitropyridone (**L4**) as the ligand gave the desired product in significantly increased yield (58%), and the yield could be further optimized to 71% by using 50 mol% **L4** in the presence of 10 mol% $Pd(OAc)_2$, 30 mol% DL-phenylglycine (**TDG1**), 0.7 equiv Ag_3PO_4, 2.5 equiv **1a**. With 20 mol% DL-phenylglycine (**TDG1**), the yield dropped to 48%. When 30 mol% **L4** or 50 mol% Ag_3PO_4 was used in this reaction, the desired products were obtained in 43% and 55% yield, respectively. While further screening of TDG derived from amino acids did not provide significant improvement, this finding guided us to design and synthesize other related amino acid amides as TDG for evaluation. Although preliminary exploration afforded inferior yields (see the Supporting Information for details of reaction optimization), the feasibility of developing other types of TDG for tertiary C–H bonds is valuable.

With the optimal conditions in hand, the substrate scope of the tertiary C−H arylation reaction was examined with respect to the aryl iodides (Table 2). Most of the tested aryl iodides, bearing either electron-withdrawing groups (**3a**−**3h**) or electron-donating groups (**3i**−**3j**) on the phenyl ring, had little influence on the yield, providing the corresponding products in moderate to good yields and a high regioisomeric ratio (>95:5 r.r.). In this arylation reaction, fluoro- (**3e**, **3o**), chloro- (**3f**, **3p**), and bromo- (**3g**) substituted aryl iodides worked well, offering opportunities for the further derivatization of the reaction products. Functional groups such as ester (**3a**, **3m**), nitro (**3b**, **3n**), ketone (**3k**), and alcohol (**3t**) were also tolerated and showed comparable reactivity. Notably, formyl- and coordinative cyano-substituted aryl iodides still underwent the arylation to afford the desired products (**3l**, **3q**), albeit in low yield.

We next investigated the scope with respect to cyclobutylmethyl alkyl ketones, which are potentially more challenging substrates than **1a** due to the possibility of β-C−H bonds on either side of the ketone being activated (Table 3). Indeed, rerouting the selectivity from the β-methylene C−H bond to the sterically hindered β-tertiary C−H bond remains an unsolved challenge in Pd(II) catalysis. To our delight, this arylation enabled by pyridone ligand occurred highly selectively at the β-tertiary C−H bond in the majority of cases. The arylation of β-methyl or β-methylene C–H bonds is largely disfavored, presumably due to the stereochemistry of the transient imines or the enhanced s character of the tertiary C−H bond in cyclobutanes. For example, ketone substrates bearing alkyl (**4b**−**4e**), methoxy (**4f**), phenylpropyl (**4g**) or benzyl (**4h**) functional groups selectively afforded the β-tertiary C−H arylated product in 43 to 66% yield with up to > 95:5 r.r.. The ketone **4a**, containing a readily accessible β-methyl C−H bond, also afforded site selectivity for the tertiary C–H bond (75:25 r.r.). However, when we changed the alkyl group to a phenyl group (**4i**), no reaction was observed under the standard conditions. Likewise, no desired product was observed when 1-cyclohexylpropan-2-one (**4j**) was employed as the substrate.

In conclusion, we have developed the first example of a tertiary C–H arylation of cyclobutylmethyl ketones using an α-amino acid as a transient directing group (TDG) to construct quaternary carbon centers. An electron-deficient 2-pyridone ligand was identified as an external ligand to enable tertiary C−H activation. This protocol will facilitate the synthesis of novel cyclobutane motifs containing quaternary carbon centers, which are potentially highly valuable in the creation of diverse cyclobutanecentered compound libraries in early drug discovery.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

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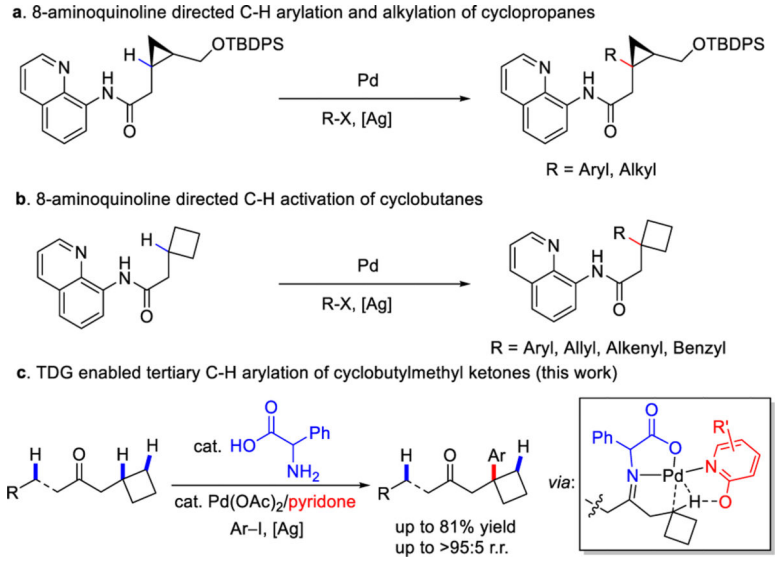
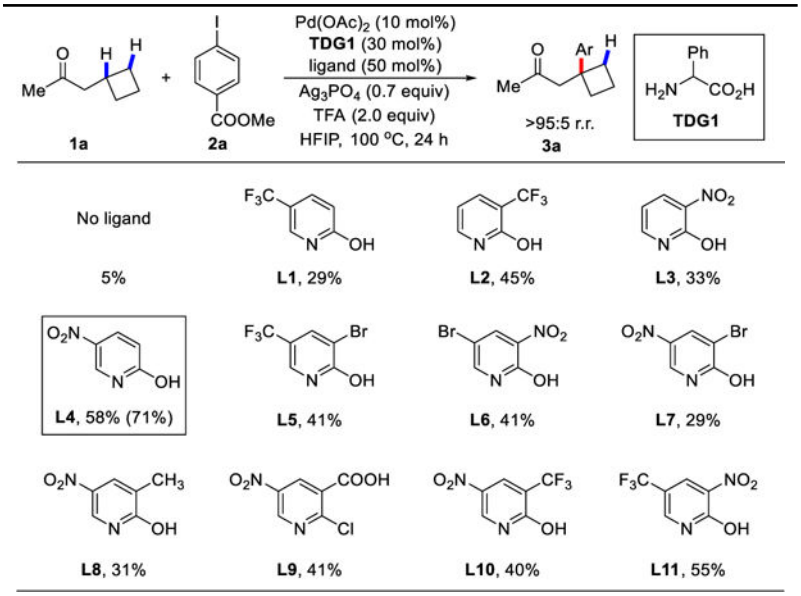


Scheme 1.

Pd-catalyzed tertiary C−H bond activation

Table 1.

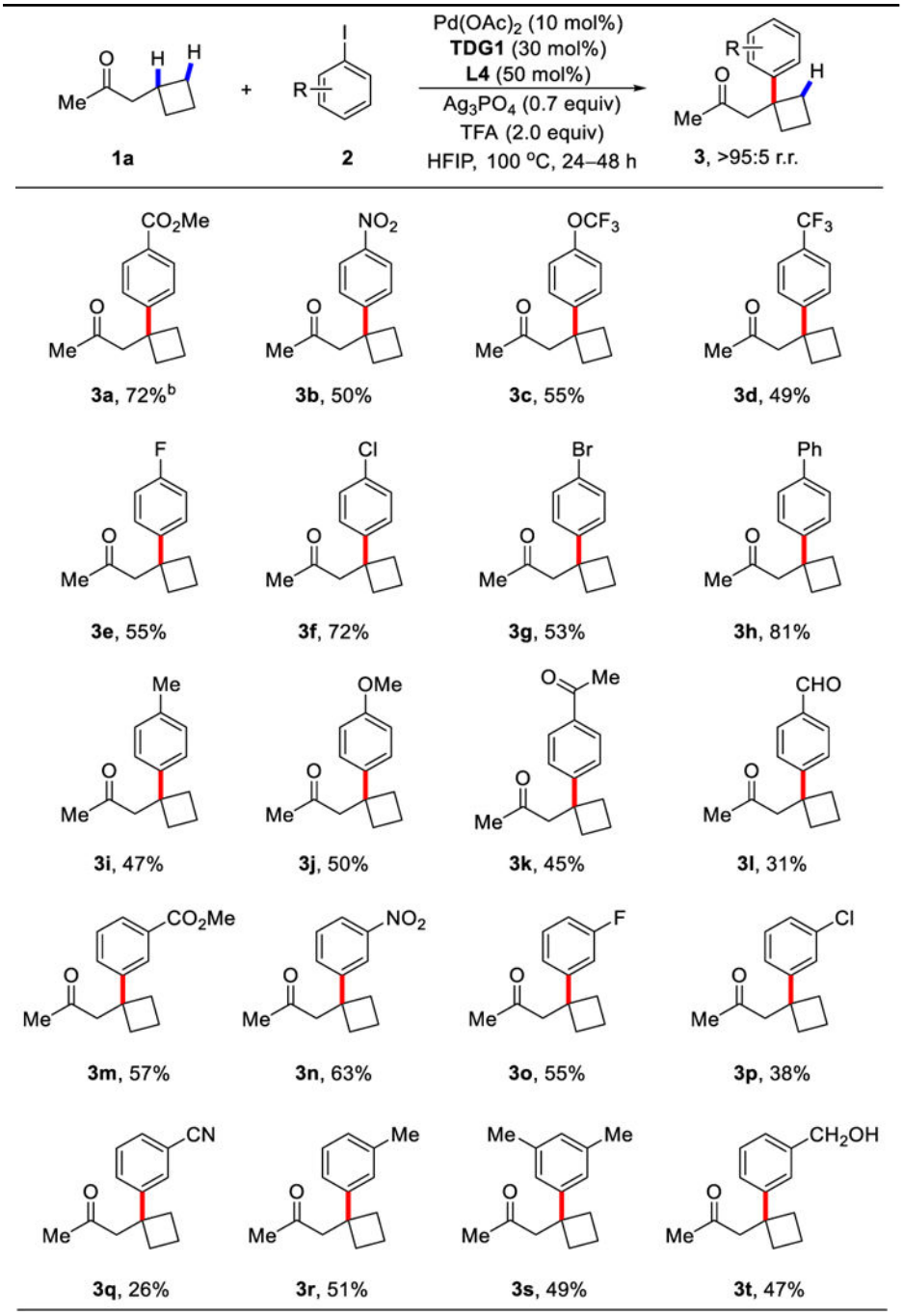
Ligand Evaluation for Tertiary C−H Arylation of **1a**[a]



[a]Conditions: **1a** (0.2 mmol, 2.0 equiv), methyl 4-iodobenzoate **2a** (1.0 equiv), $Pd(OAc)_2$ (10 mol %), **TDG1** (30 mol %), ligand (50 mol %), Ag_3PO_4 (0.7 equiv.), HFIP (0.6 mL), 100 °C, under air, 24 h.

Table 2.

Scope of Aryl Iodides[a]

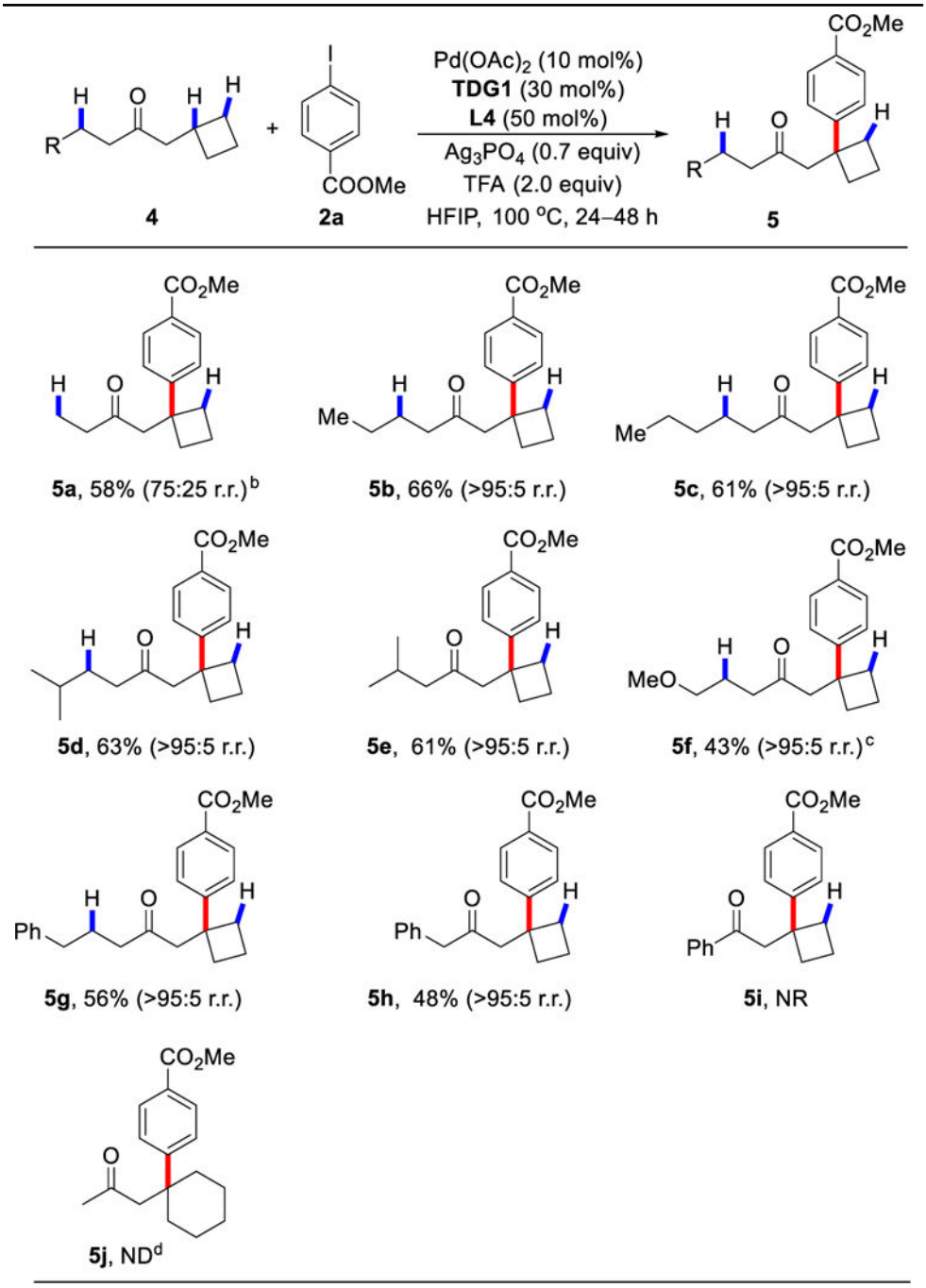


[a]Conditions: **1a** (0.25 mmol, 2.5 equiv), **2** (0.1 mmol, 1.0 equiv), $Pd(OAc)_2$ (10 mol %), **TDG1** (30 mol %), **L4** (50 mol %), Ag_3PO_4 (70 mol %), CsOAc (1.0 equiv.), HFIP (0.6 mL), 100 °C, under air, 24−48 h.

[b]3% di-arylation product on β-tertiary and γ-methylene C−H bonds was observed

Table 3.

Scope of Ketones[a]



[a]Conditions: **4** (0.25 mmol, 2.5 equiv), **2a** (0.1 mmol, 1.0 equiv), $Pd(OAc)_2$ (10 mol %), **TDG1** (30 mol %), **L4** (50 mol %), Ag_3PO_4 (70 mol %), CsOAc (1.0 equiv.), HFIP (0.6 mL), 100 °C, under air, 24−48 h.

[b]The ratio of r.r. was determined by ^1H NMR analysis of the crude reaction mixture.

[c] 2% di-arylation product on β-tertiary and γ-methylene C-H bonds was observed.

[d] A trace amount of methylene C−H activation product was observed