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Pd^{II}-Catalyzed γ-C(sp^3)−H (Hetero)Arylation of Ketones Enabled by Transient Directing Groups

Yi-Hao Li,

Yuxin Ouyang,

Nikita Chekshin,

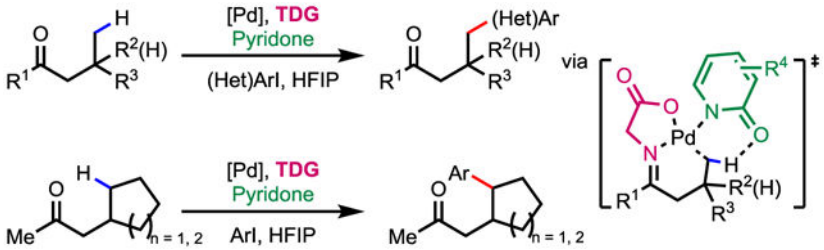
Jin-Quan Yu

Department of Chemistry, The Scripps Research Institute, 10550 N. Torrey Pines Road, La Jolla, California 92037, United States.

Abstract

Pd(II)-catalyzed γ-C(sp^3)−H (hetero)arylation of aliphatic ketones is developed using α-amino acid as transient directing groups (TDG). A variety of aliphatic ketones were (hetero)arylated at the γ-position via a 5,6-membered fused cyclopalladation intermediate to afford the remotely arylated products in up to 88% yield. The crucial ligand effect of 2-pyridone is further enhanced by reducing the loading of acid additives. Consequentially, the improved reactivity of this catalytic system has also made possible the cyclic γ-methylene C(sp^3)−H arylation of ketones. Mechanistic investigtigation and comparison to the γ-C–H arylation of aldehydes revealed a structural insight for designing site selective TDG.

Graphical Abstract



Keywords

C−H activation; Palladium; Ketones; transient directing group; arylation; pyridone ligands; palladacycle

Corresponding Author: Jin-Quan Yu − Department of Chemistry, The Scripps Research Institute, La Jolla, California 92037, United States; yu200@scripps.edu.
Yi-Hao Li − Department of Chemistry, The Scripps Research Institute, La Jolla, California 92037, United States;
Yuxin Ouyang − Department of Chemistry, The Scripps Research Institute, La Jolla, California 92037, United States;
Nikita Chekshin − Department of Chemistry, The Scripps Research Institute, La Jolla, California 92037, United States;

Supporting Information
The Supporting Information is available free of charge at
Full experimental details, mechanistic studies, computational studies and characterization of new compounds (PDF)

The authors declare no competing financial interest.

Ketones are ubiquitous functional groups in natural products and synthetic intermediates. Wide range of transformations of aliphatic ketones that rely on the reactivity of ipso- and α-carbon centers have been developed.[1] From the viewpoint of developing new synthetic disconnections, development of C–H functionalization of inert C(sp^3)–H bonds at β- or even γ-positions is of great importance. Covalent installation of imine based directing groups have been explored to achieve β-C(sp^3)–H functionalizations.[2,3] In 2016, our group realized Pd(II)-catalyzed β-C(sp^3)–H functionalization of free aliphatic ketones and o-tolualdehydes using L,X-type transient directing groups.[4] This strategy, based upon reversible imine linkage in similar fashion to that of organocatalysis, provided strong impetus for further development of directed C–H activation of ketones,[5] aldehydes[6] and amines[7] by omitting the extra steps for installation and removal of covalent directing groups. Using this protocol, β-methylene[4a,4b] or even methine[4j] C(sp^3)–H arylation of aliphatic ketones has been recently achieved (Scheme 1a).

Despite significant advances in Pd-catalyzed β-C(sp^3)–H functionalizations of ketones using TDG, this approach has met limited success towards C–H activation at the relatively remote γ-position. For example, a single example of γ-C–H arylation requires the presence of tri-methyl groups at the β-position.[4] To address this limitation, α-imino-oxy acids were developed as a covalent directing group in our laboratory. γ-C(sp^3)–H arylation using this directing group were enabled by 2-pydrione ligands (Scheme 1b).[8] Interestingly, iminyl-radical generated from α-imino-oxy acids or oxime esters effectively performed an intramolecular 1,5-HAT and forged new bonds at the γ-position (Scheme 1c).[9] However, these methods have a common limitation: extra synthetic steps are needed for the covalent installation and removal of the directing groups. Therefore, we embarked on the development of γ-C(sp^3)–H functionalization of free aliphatic ketones based upon TDG strategy.

Herein, we report the first TDG-enabled γ-selective Pd^{II}-catalyzed C(sp^3)–H (hetero)arylation of aliphatic ketones with electron-deficient 2-pyridone ligands (Scheme 1d). With the cheap and commonly available glycine (**TDG1**) as transient directing group, γ-C(sp^3)–H (hetero)arylation and cyclic γ-methylene C(sp^3)–H arylation could be achieved with up to 88% yield without the need of directing group installation and removal.

To address the challenge of the γ-C−H functionalization of aliphatic ketones, we began to search ligands and additives that can accelerate the C−H cleavage step. Guided by our previous findings on C(sp^3)−H functionalization reactions that reducing the amount of chloroacetic acid can enhance the ligand effect of 2-pyridone by minimizing the competing carboxylates.[10,11] We started testing different organic acids with lower pK_a for γ-C−H arylation of 4-methyl-2-pentanone (**1a**) with 3-nitro-5-(trifluoromethyl)-2-pyridinone (**L12**) as ligand. To our delight, the NMR yield reached to its highest at 85% (mono:di = 58:27) when 1.5 equiv of chloroacetic acid was used (Table 1, entry 5). Other pyridone ligands were also tested. Unfunctionalized 2-pyridone (**L1**) and 5-substituted 2-pyridones (**L2**-**L6**) were examined first, which resulted in the highest yield of 65%. Substitution of electron withdrawing groups at the 3-position further improved the yield to 85% (**L7**-**L10**, **L12**), except for 3,5-dinitropyridione(**L11**). Not surprisingly, less than 10% arylation product was

obtained in the absence of the ligand. Varied β-amino acids were also tested as TDG to substitute glycine (**TDG1**) which inhibited the reactivity (see the Supporting Information for detailed screening information), probably due to the preference of the 5,6-membered coordination.

With the optimized conditions in hand, a variety of aliphatic ketones with methyl/cyclic methylene γ-C(sp^3)−H bonds were tested using methyl 4-iodobenzoate as the coupling partner (Table 2). Substitution with methyl, pentyl, isohexyl and neopentyl groups at the β-position showed good reactivity (**2a**–**2d**). Larger substituents such as cyclohexyl or cyclopentyl groups were also compatible, providing **2e** and **2f** with good yields. Substrates containing phenyl, phthalimide and ether functionality were also tolerated with 48–64% yields (**2g**–**2i**). Ketones possessing β-quaternary centers could be well arylated at the γ-position with a lower loading of chloroacetic acid of 0.8 equiv, providing **2j**–**2l** with good to moderated yields. Besides, the formation of tetra-functionated product of di-*iso*-butyl ketone further illustrates the powerful reactivity of this catalytic system (**2m**). Notably, two examples of cyclic γ-methylene-C(sp^3)−H bonds could also be successfully arylated with good to moderate yields (**2n**–**2o**), providing a promising strategy for methylene C−H functionalization via 6-membered cyclopalladation. Furthermore, the reaction could be readily carried out on 3.0 mmol scale with **2b** as standard substrate, affording the desired product in 61% yield.

To broaden the synthetic application of this reaction, the scope of aryl and heteroaryl iodides was examined (Table 3). The model substrate **1b** could be functionalized with excess of aryl iodides, exhibiting a good functional group compatibility (**3a**–**3j**). Aryl iodides derived from borneol and estrone were also tested, resulting in the desired products in 51% and 62% yields, respectively (**3k**–**3l**). More importantly, heterocycles could be installed through γ-C(sp^3)−H functionalization with a modified condition. Various 4-iodopyridines derivates were tested as coupling partners. Good to moderate yields were acquired with 2-substituted 4-iodopyridines containing halogen, trifluoromethyl and methyl groups (**3m**–**3q**). For the less strongly coordinating 2,6-dichloro substituted pyridine, a total of 78% heteroarylated product was obtained (**3r**). Ketones could also be functionalized with 2 and 3-iodopyridines derivates at the γ-position, providing **3s**–**3v** in good to moderate yields. Good yields could also be achieved with other heteroaryl iodides, such as 6-iodoqunoline and 3-iodoqunoline, which broadened the application of this protocol (**3w**–**3x**). However, non-substituted iodopyridines exhibited poor reactivity, with trace product observed, probably due to the strong coordinating ability which deactivated the catalyst.

A plausible catalytic cycle is outlined in Scheme 2. Glycine reacts with aliphatic ketones reversibly to form the transient imine **A**. Palladium species then coordinates to imine **A** to generate a chelating complex **B**, which, upon binding to a pyridone ligand, undergoes C−H bond activation process to form intermediate **C**. Complex **D** is generated via oxidative addition with aryl iodides. Finally, reductive elimination of the palladium complex **D** leads to arylated **E**.

Finally, the distinct site-selectivity observed with the non-substituted acyclic ketones when compared to our recent report on corresponding aldehyde substrates[11] are investigated. With

aldehydes, the selectivity was switched to γ- with 5-membered chelating TDG. However, pentan-2-one (**1p**) containing both β-methylene and γ-methyl C(sp^3)−H bonds afforded β-C−H arylation with either 5 or 6-membered TDG (Table 4). To obtain some mechanistic insight into the lack of γ-selectivity with 5-membered chelating TDG, we conducted deuterium incorporation experiments under the standard conditions in the presence of 2-chloroacetic acid-*d* and HFIP-OD (see the Supporting Information for details). The absence of deuterium incorporation at the β- and γ-position of the arylated products suggests that the C−H cleavage proceeds irreversibly, and is expected to serve as the rate-limiting step based on our previous studies.[5e] With this experimental evidence in hand, we pursued further DFT modeling and revealed that 5,5-membered coordination is favored over the 5,6-coordination due to increased 1,2 steric strain between the methyl group of the substrate and the TDG ring, evident from the difference in distance between them. Calculated regioselectivity is in excellent agreement with experimental observations. (Scheme 3). This mechanistic study provides a valuable structural insight into how to design site selective TDG for ketones and aldehydes.[12]

In summary, we have developed a protocol for Pd^{II}-catalyzed primary γ-C–H (hetero)arylation of aliphatic ketones enabled by a simple α-amino acid TDG and 2-pyridone ligands. This reaction features broad substrate scope without extra steps of installation and removal of directing groups. Functionalization of cyclic γ-methylene C(sp^3)−H via a 5,6-membered coordination has also been demonstrated. Mechanistic study on the site selectivity of acyclic ketones and its comparison with corresponding aldehydes points to a valuable structural insight for designing site selective TDG.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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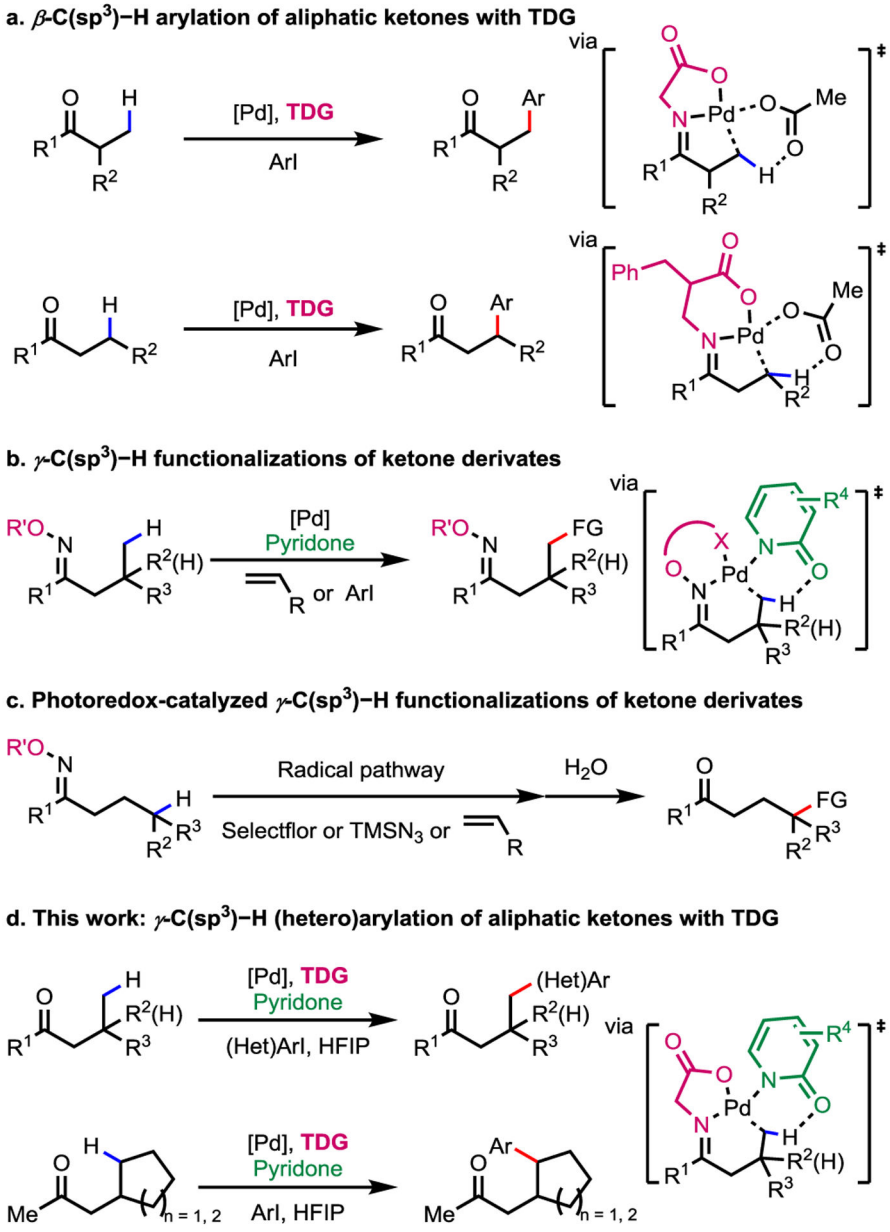
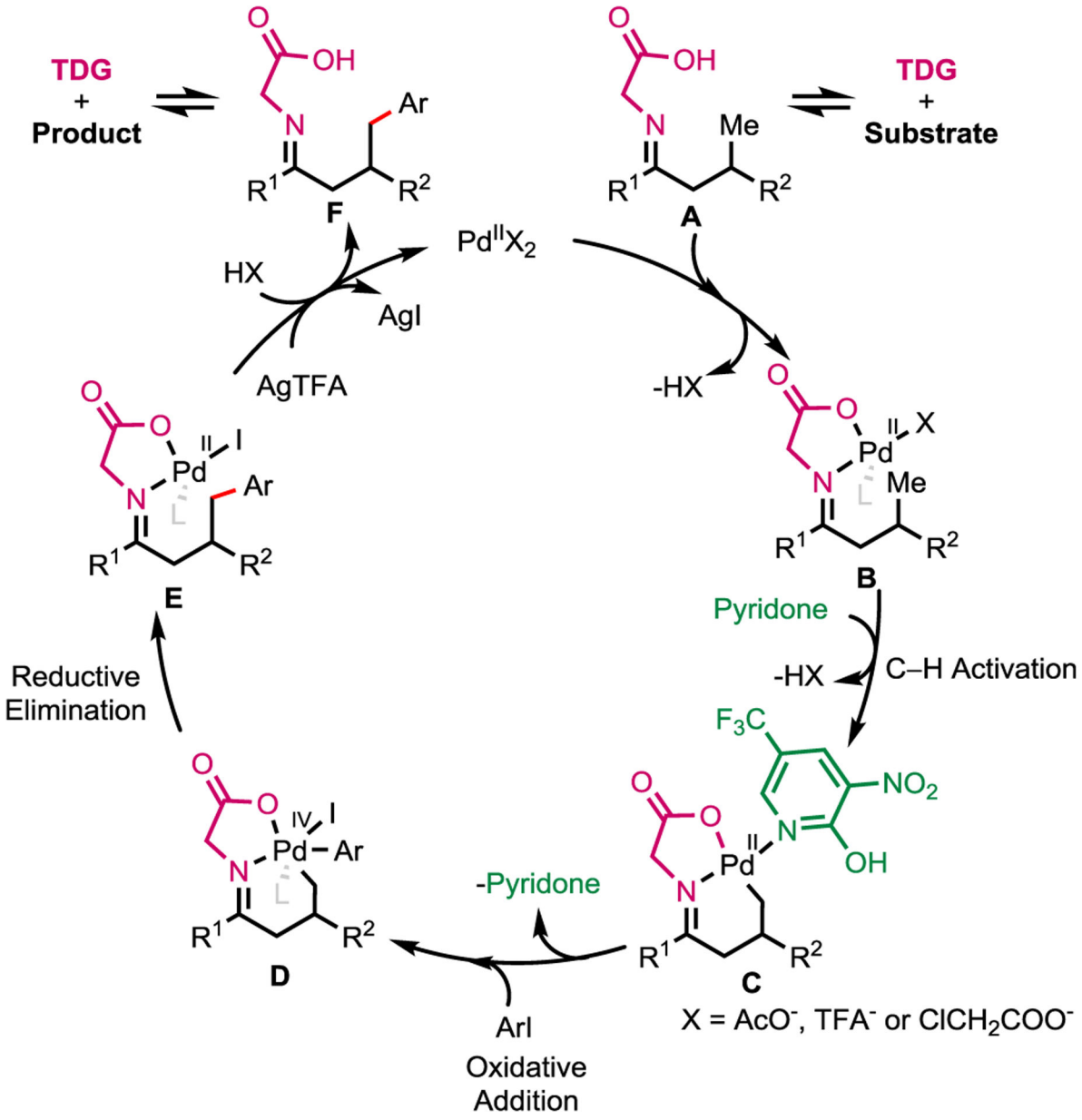
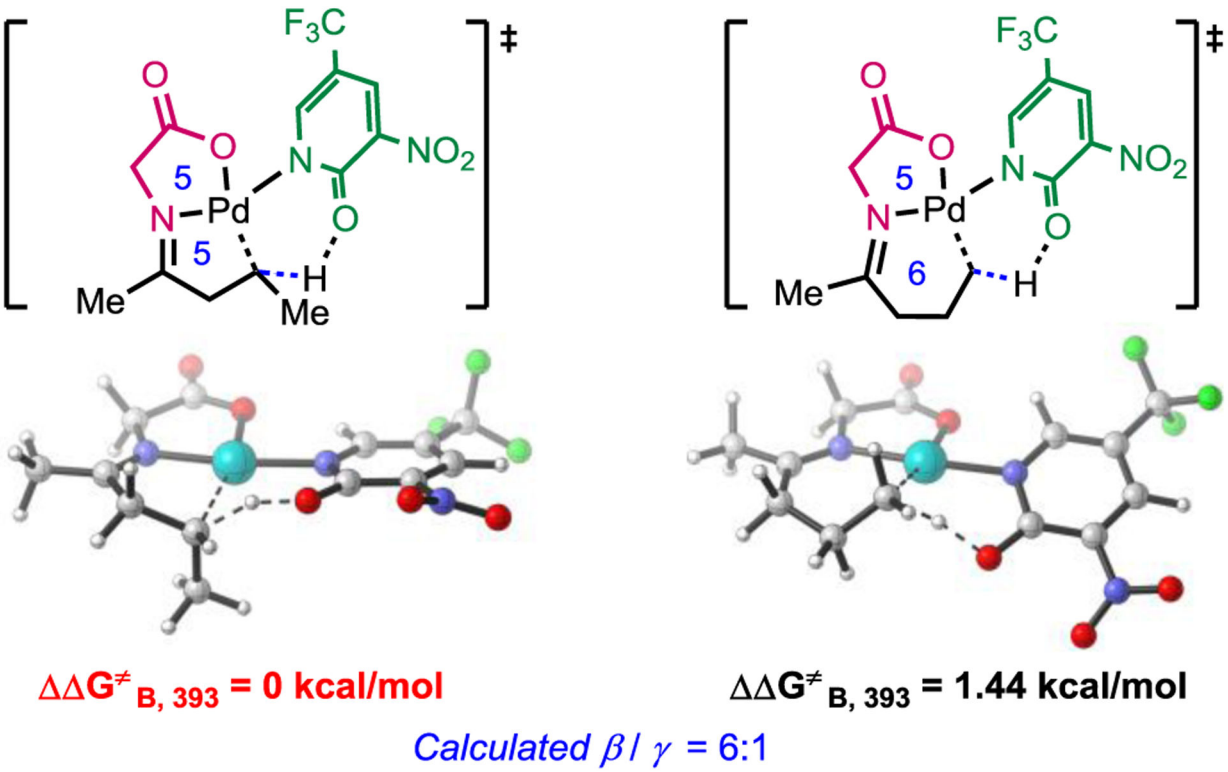


Scheme 1.

Pd^{II}-Catalyzed $C(sp^3)$−H Functionalization of Ketones directed by TDG and Covalent Auxiliaries



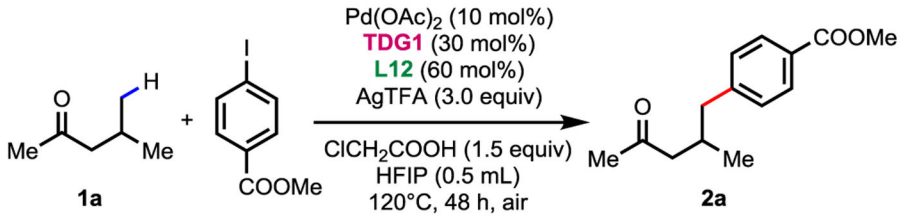
Scheme 2.
Proposed Catalytic Cycle



Scheme 3.
DFT Modeling of The TDG Influence on Site-selectivity of C(sp^3)−H Cleavage

Table 1.

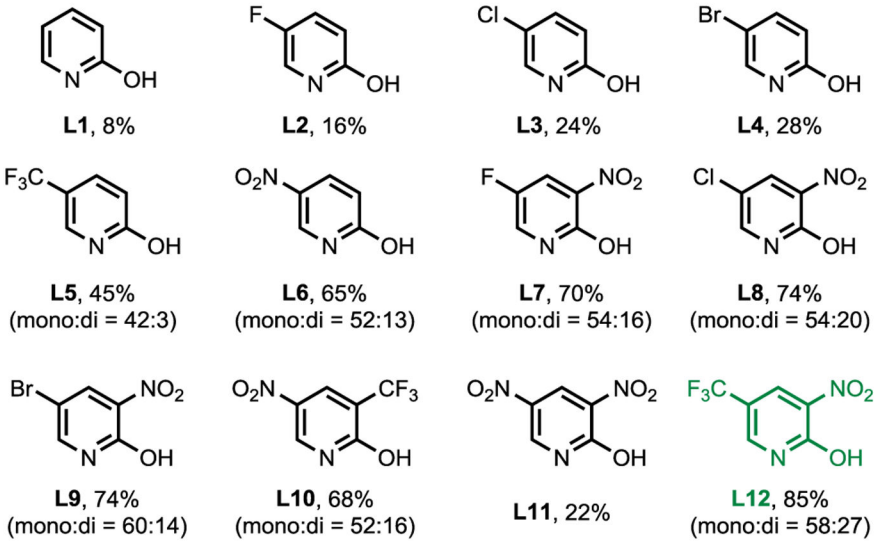
Ligand Evaluation for γ-C(sp^3)−H Arylation of Aliphatic Ketones[a, b]



Acid Evaluation:

Entry	Deviation from initial conditions	NMR Yield (%)
1	HOAc (1/3, v/v) as acid[c]	29
2	TFA (0.5 equiv) as acid[c]	37
3	Cl_3CCOOH (0.5 equiv) as acid[c]	32 (24+8)[d]
4	$ClCH_2COOH$ (1.0 equiv) as acid	83 (67+16)[d]
5	$ClCH_2COOH$ (1.5 equiv) as acid	85 (58+27)[d]
6	$ClCH_2COOH$ (2.0 equiv) as acid	72 (50+22)[d]

Ligand Evaluation:



L12 (30mol%), 68% (mono:di = 52:16) **L12** (80mol%), 80% (mono:di = 56:24) **no ligand**, 8%

[a]Conditions: **1a** (0.1 mmol, 1.0 equiv), methyl 4-iodobenzoate (2.0 equiv), $Pd(OAc)_2$ (10 mol%), **TDG1** (glycine, 30 mol%), **L12** (60 mol%), AgTFA (3.0 equiv) and $ClCH_2COOH$ (1.5 equiv) in HFIP (0. 5 mL), 120°C, under air, 48 h.

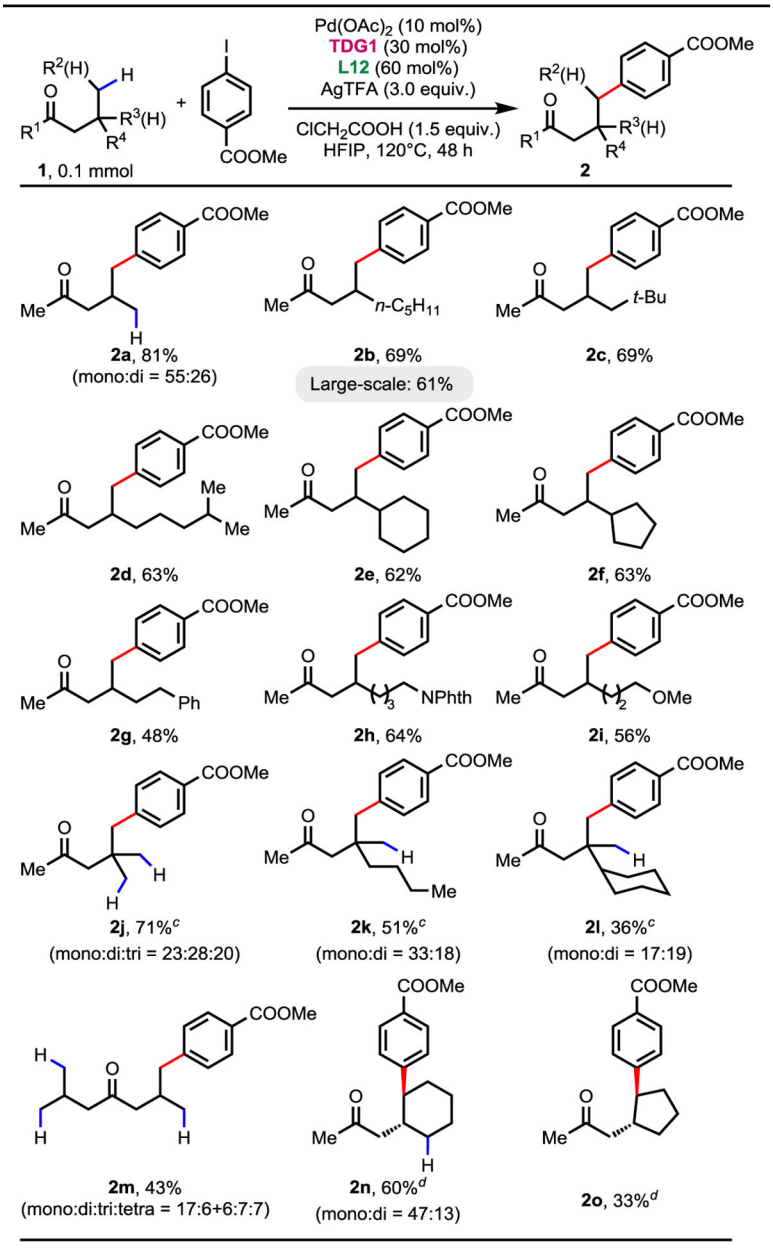
[b]Yield determined by ^1H NMR; CH_2Br_2 as internal standard.

[c]Loading that gave the highest yield within a serial of concentrations.

[d]Ratio of mono:di.

Table 2.

Scope of Ketones[a, b]



[a]Conditions: **1** (0.1 mmol, 1.0 equiv), methyl 4-iodobenzoate (2.0 equiv), $Pd(OAc)_2$ (10 mol%), **TDG1** (30 mol%), **L12** (60 mol%), AgTFA (3.0 equiv) and $ClCH_2COOH$ (1.5 equiv) in HFIP (0. 5 mL), 120°C, under air, 48 h.

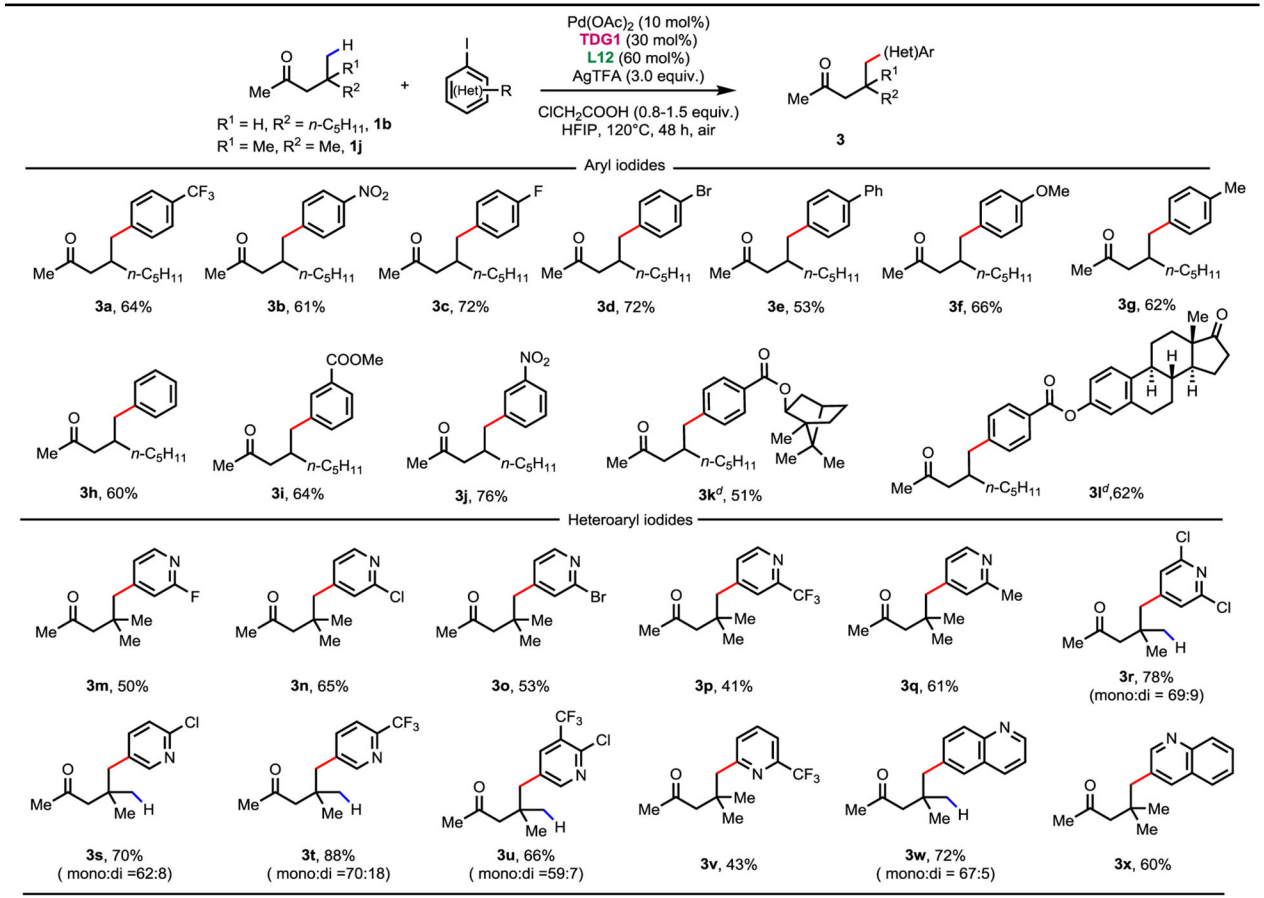
[b]Isolated yields.

[c]with $ClCH_2COOH$ (0.8 equiv) as additive

[d]The reaction condition was modified with **TDG1** (35 mol%), **L10** (80 mol%) and $ClCH_2COOH$ (1.2 equiv) in HFIP (0.45 mL).

Table 3.

Scope of Aryl and Heteroaryl Iodides[a, b, c]



[a]Conditions: **1b** (0.1 mmol, 1.0 equiv), Aryl Iodide (2.0 equiv), $Pd(OAc)_2$ (10 mol%), **TDG1** (30 mol%), **L12** (60 mol%), AgTFA (3.0 equiv) and $ClCH_2COOH$ (1.5 equiv) in HFIP (0.5 mL), 120°C, under air, 48 h.

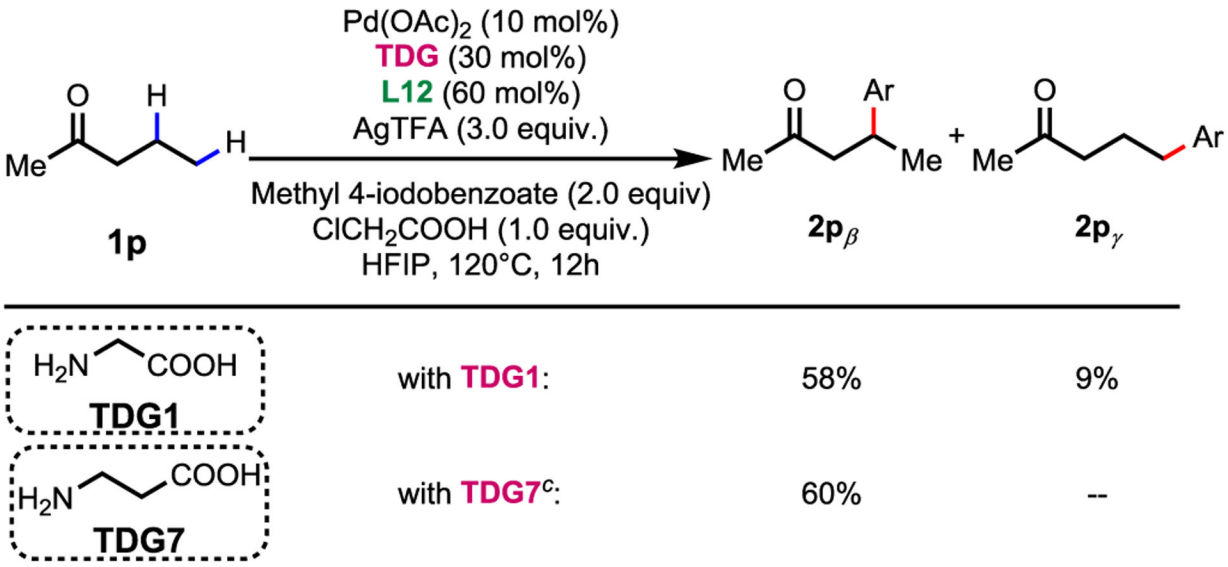
[b]Conditions: **1j** (0.1 mmol, 1.0 equiv), Heteroaryl Iodide (1.5 equiv), $Pd(OAc)_2$ (10 mol%), **TDG1** (30 mol%), **L12** (60 mol%), AgTFA (3.0 equiv) and $ClCH_2COOH$ (0.8 equiv) in HFIP (0.4 mL), 120°C, under air, 48 h.

[c] Isolated yields

[d] dr = 1:1.

Table 4.

Site-selective Arylation of Pentan-2-one with Different TDG[a, b]



[a]Conditions: **1** (0.1 mmol, 1.0 equiv), methyl 4-iodobenzoate (2.0 equiv), $Pd(OAc)_2$ (10 mol%), **TDG** (30 mol%), **L12** (60 mol%), AgTFA (3.0 equiv) and $ClCH_2COOH$ (1.0 equiv) in HFIP (0. 5 mL), 120°C, under air, 12 h.

[b]Yield and ratio determined by ^1H NMR of the crude mixture.

[c]Reaction time: 48h.