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# Palladium-Catalyzed β-C−H Arylation of Aliphatic Aldehydes and Ketones Using Amino Amide as a Transient Directing Group

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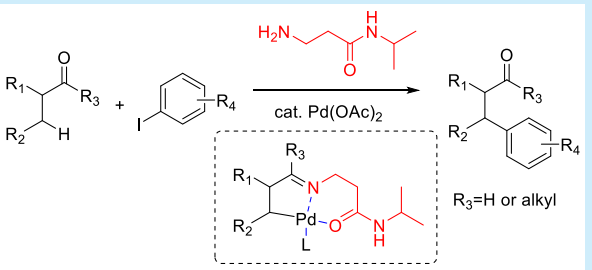
Supporting Information

**ABSTRACT:** This paper describes a new amino-amide-based transient directing group (TDG). The TDG can exhibit better performance in the Pd-catalyzed arylation of aliphatic aldehydes and ketones. This reaction showed good substrate compatibility and regioselectivity. The results indicated that 3-amino-*N*-isopropylpropionamide was more beneficial to the β-arylation of aliphatic aldehydes than other TDGs under relatively mild conditions.



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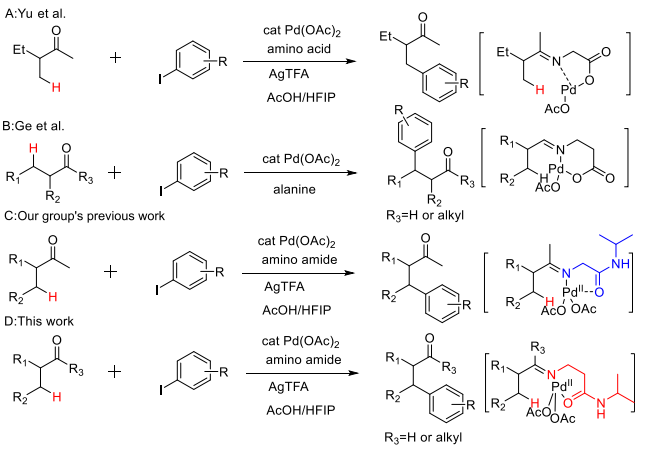
Transition-metal-catalyzed reactions are of great significance in modern organic synthesis. In the past two decades, transition-metal-catalyzed C−H bond activation has been a hot topic in the field of organic synthesis. In particular, it plays an important role in the functionalization of nonactivated C−H bonds.[1−3] In that light, the C−H functionalization process enables the synthesis of pharmaceuticals, natural products, and chemical materials to be significantly simplified.[4] Particularly, directed C−H activation has emerged as an efficient step in the formation of C−C bonds and an atom-economic strategy.[5−8] To date, the γ,δ-C−H bond arylation of the amino group,[9,10] the β,γ,δ-C−H bond arylation of aldehyde and ketone,[11−13] and the arylation of remote orientation have been achieved.[14,15]

Aliphatic aldehydes and ketones are regarded as common structural moieties and the key intermediates in pharmaceuticals, natural products, and chemical synthesis.[16,17] In addition, carbonyl compounds also show great value in organic conversion.[18−20] However, only a few documents elaborated the C−H functionalization of aldehyde/ketone orientation over transition metal catalysts.[21−24] Such methodology is severely hindered by the aldehyde's weak coordinating capacity, the sensitivity toward oxidation, and the undesired insertion of metal into the acyl C−H bond. To overcome those problems, a method using preinstalled imine or oxime directing group (DG) C−H function was reported. Nevertheless, installing or removing DG was sometimes incompatible with the existence of advanced intermediates of other functional groups.[6,25−32]

To solve this challenge, some researchers proposed the concept of a transient directing group (TDG). That is, the DG is reversibly combined with the substrate and the metal to play a directing role.[33−35] Previously, Jun's group employed 2-aminopyridine as a TDG, and the C−H bond functionalization of aldehyde was achieved by Rh catalyst.[36−39] This method was then successfully applied to the Pd catalytic C(sp$^3$)−H activation response.[28] Yu's group first reported the Pd-catalyzed arylation of *o*-alkyl benzaldehydes and ketones with natural amino acids as a TDG. In the reaction, a catalytic amount of amino acid was reversibly involved in C(sp$^3$)−H activation. Note that aliphatic aldehydes cannot be transformed by their method (Scheme 1A). Recently, Ge and co-workers used 3-aminopropionic acid as a TDG to complete the Pd-catalyzed arylation of aliphatic aldehydes and ketones (Scheme 1B).[40,41]

**Scheme 1. Pd-Catalyzed β-C−H Arylation of Aliphatic Aldehydes and Ketones**




Inspired by the successful identification of TDGs for ketones (Scheme 1C),[13,42] we explored an amino amide which could be used as a TDG for the β-C−H activation of both aliphatic aldehydes and ketones. When we investigated the effect of the DG; we observed that a six-membered ring formed by chelation with Pd(II), and the DG was more effective than the five-membered ring.[43−45] Therefore, we hypothesized that amino

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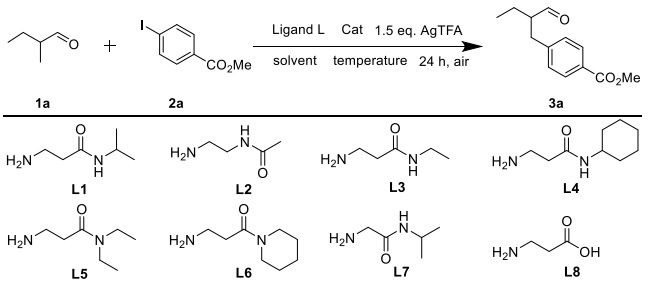
amide could further promote $\beta$-C−H activation by forming the six-membered chelation. Herein, we designed a modified $\beta$-alanine (3-aminoalaninamide) as a new TDG to arylate the unactivated $\beta$-C−H bonds of aliphatic aldehydes and ketones simultaneously (Scheme 1D).

At the beginning of the experiment, we synthesized a series of amino amide compounds to investigate their role in Pd-catalyzed arylation of aldehydes and ketones (**L1**−**L8**) (Table 1). We carried out a model reaction with 2-methylbutanal (**1a**) and methyl 4-iodobenzoate (**2a**) as substrates (Table 1). We screened many common solvents. Among them, hexafluoroisopropanol (HFIP) and acetic acid as cosolvents showed good solvation effects (Table 1, entries 1−7, and Supporting Information (SI)). When HFIP and acetic acid (9:1) were used as a mixed solvent, **3a** was obtained in a relatively high yield of 82% (entry 6). Then we screened the temperature and the amount of TDG of the reaction. As described in Table 1, when we decreased the reaction temperature from 100 to 80 °C (entries 11 and 6), the yield was significantly improved. The above-mentioned results suggested that temperature has a significant effect on the reaction. Screening of the amount of catalyst indicated that either low or high loading was not beneficial for the reaction (entries 8 and 9). Other reaction parameters, including transition metal catalysts and the types of additives, were tested. $Pd(TFA)_2$, $Pd(acac)_2$, $PdCl_2$, $Pd(PPh_3)_2Cl_2$, and $Pd(CH_3CN)_2Cl_2$ can catalyze the reaction, but the yield was greatly reduced compared to that with $Pd(OAc)_2$ (entries 12−17). As shown in Table 1 (entries 18−20), only AgF showed a certain promotion of the product yield, and AgOAc and $Ag_2CO_3$ were inactive.

Following that, we screened the TDGs (entries 21−27), and when TDG **L2** was used, no target product was found. This result suggested that the carbonyl group should be located between two nitrogen atoms. To further elucidate the role of DG, TDG **L3** containing a small size structure unit was synthesized, and the yield was found to be greatly reduced (entry 22). Meanwhile, we synthesized several TDGs containing a large size structure unit, and low yields were also obtained (entries 24−26). Therefore, it can be presumed that the moderate size of the structure moiety attached to the N atom of the amide is critical, and either overly large or small sizes were disadvantageous to the reaction. Particularly, when **L7** was used as TDG, the yield is trace, which suggested that a five-membered palladacycle intermediate was unsuitable for this process (entry 26). Compared to **L8**, **L1** exhibits good catalytic activity. Therefore, we speculate that **L1** does not act through its hydrolysate. By analyzing the data in Table 1, we obtained an optimal reaction condition with 10 mol % of $Pd(OAc)_2$, 50 mol % of **L1**, and 1.5 equiv of AgTFA in HFIP/AcOH (9:1) at 80 °C for 24 h.

Under optimal conditions, we next examined the scope of substrates of aliphatic aldehydes and aryl iodides (Scheme 2). We used 2-methylbutyraldehyde (**1a**; see SI) as a substrate, and other aryl iodides reacted with it. Both electron-deficient and electron-rich aryl iodides gave moderate to good yields (**3a**, **3b**, **3c**, **3d**, **3f**). When investigating the effect of different substitution positions on the benzene ring on the reaction yield, we found that the yield was higher when the substituent was in the *para* position (**3a**, **3g**, **3f**, **3h**), but this phenomenon was not observed for methoxy (**3c**, **3e**). We also screened heteroaryl iodides, but unfortunately, we did not observe the products (**3n**, **3o**). Importantly, when 2-methylpropionaldehyde (**1b**; see SI) having two reaction sites was used, only one

**Table 1. Optimization of Reaction Conditions**[a]




| entry | metal | ligand | additive | solvent | yield (%)[b] |
|---|---|---|---|---|---|
| 1 | $Pd(OAc)_2$ | **L1** | AgTFA | HFIP | 36.4 |
| 2 | $Pd(OAc)_2$ | **L1** | AgTFA | AcOH | trace |
| 3 | $Pd(OAc)_2$ | **L1** | AgTFA | HFIP/AcOH (1:1) | 45.5 |
| 4 | $Pd(OAc)_2$ | **L1** | AgTFA | HFIP/AcOH (3:1) | 40.9 |
| 5 | $Pd(OAc)_2$ | **L1** | AgTFA | HFIP/AcOH (5:1) | 50 |
| 6 | $Pd(OAc)_2$ | **L1** | AgTFA | HFIP/AcOH (9:1) | 82 |
| 7 | $Pd(OAc)_2$ | **L1** | AgTFA | HFIP/AcOH (14:1) | 48 |
| 8[c] | $Pd(OAc)_2$ | **L1** | AgTFA | HFIP/AcOH (9:1) | 41 |
| 9[d] | $Pd(OAc)_2$ | **L1** | AgTFA | HFIP/AcOH (9:1) | 45.5 |
| 10[e] | $Pd(OAc)_2$ | **L1** | AgTFA | HFIP/AcOH (9:1) | 45.5 |
| 11[f] | $Pd(OAc)_2$ | **L1** | AgTFA | HFIP/AcOH (9:1) | 54.5 |
| 12 | $Pd(TFA)_2$ | **L1** | AgTFA | HFIP/AcOH (9:1) | 34.2 |
| 13 | $Pd(acac)_2$ | **L1** | AgTFA | HFIP/AcOH (9:1) | 43.2 |
| 14 | $Pd(pph_3)_4$ | **L1** | AgTFA | HFIP/AcOH (9:1) | 41 |
| 15 | $PdCl_2$ | **L1** | AgTFA | HFIP/AcOH (9:1) | 18.2 |
| 16 | $Pd(pph_3)_2Cl_2$ | **L1** | AgTFA | HFIP/AcOH (9:1) | 45.5 |
| 17 | $Pd(MeCN)_2Cl_2$ | **L1** | AgTFA | HFIP/AcOH (9:1) | 34.1 |
| 18 | $Pd(OAc)_2$ | **L1** | AgOAc | HFIP/AcOH (9:1) | NR |
| 19 | $Pd(OAc)_2$ | **L1** | $Ag_2CO_3$ | HFIP/AcOH (9:1) | NR |
| 20 | $Pd(OAc)_2$ | **L1** | AgF | HFIP/AcOH (9:1) | 29.5 |
| 21 | $Pd(OAc)_2$ | **L2** | AgTFA | HFIP/AcOH (9:1) | NR |
| 22 | $Pd(OAc)_2$ | **L3** | AgTFA | HFIP/AcOH (9:1) | 38.6 |
| 23 | $Pd(OAc)_2$ | **L4** | AgTFA | HFIP/AcOH (9:1) | trace |
| 24 | $Pd(OAc)_2$ | **L5** | AgTFA | HFIP/AcOH (9:1) | 50 |
| 25 | $Pd(OAc)_2$ | **L6** | AgTFA | HFIP/AcOH (9:1) | 45.5 |
| 26 | $Pd(OAc)_2$ | **L7** | AgTFA | HFIP/AcOH (9:1) | trace |
| 27 | $Pd(OAc)_2$ | **L8** | AgTFA | HFIP/AcOH (9:1) | trace |

[a]Conditions: **1a** (0.4 mmol), **2a** (0.2 mmol), Pd source (0.02 mmol), ligand (0.1 mmol), AgTFA (0.3 mmol), solvent (1 mL), 80 °C, 24 h. [b]Yields correspond to isolated products. [c]With 30 mol % of ligand. [d]With 70 mol % of ligand. [e]60 °C, 24 h. [f]100 °C, 24 h.



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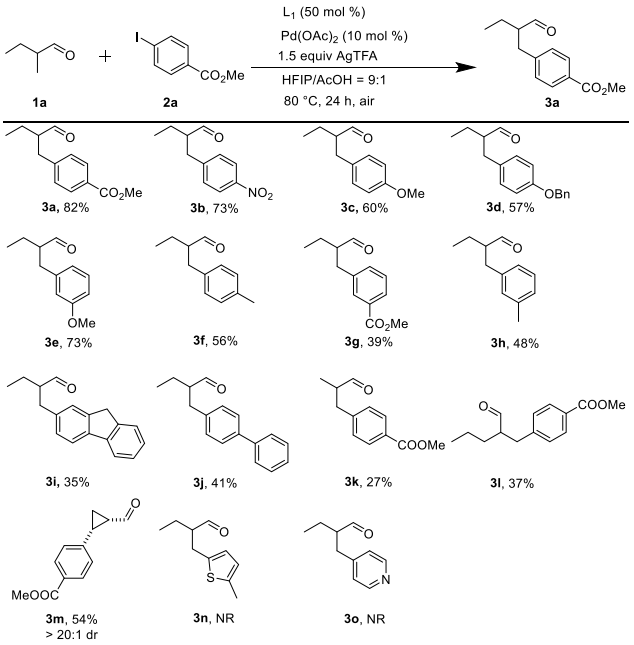
**Scheme 2. Pd-Catalyzed $\beta$-C($sp^3$)−H Arylation of Aliphatic Aldehydes**[a]



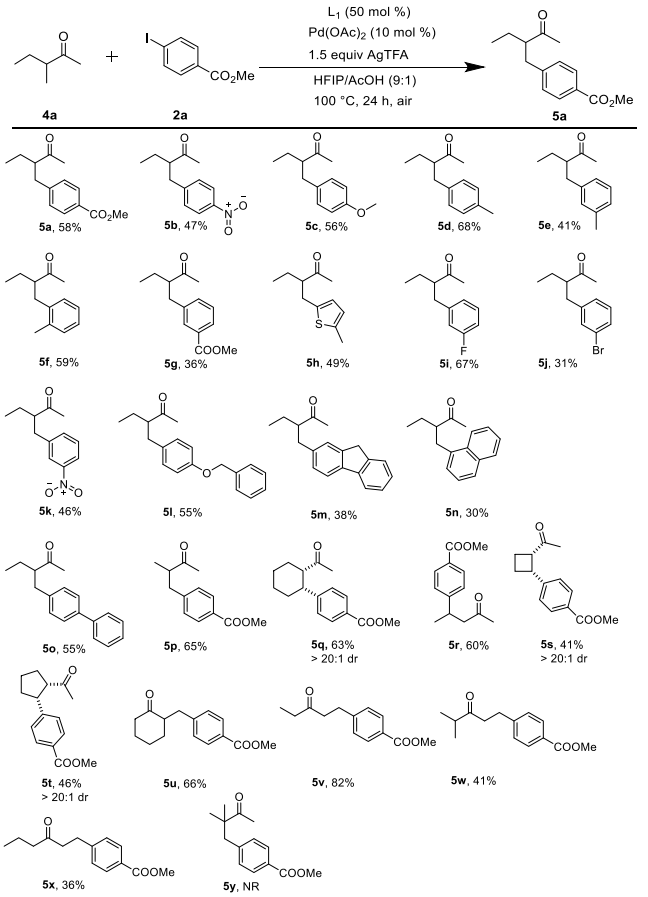

[a]Conditions: aliphatic aldehydes **1** (0.4 mmol, 2.0 equiv), ArI **2** (0.2 mmol, 1.0 equiv), $Pd(OAc)_2$ (10 mol %), AgTFA (1.5 equiv), HFIP/AcOH = 9:1 (0.2 M), under air, 80 °C, 24 h. Yields correspond to isolated products.

monosubstituted product was observed (**3k**). In addition, we also obtained high diastereomeric products when cyclic aldehyde was used as a substrate (**3m**).

Based on this strategy, we then explored the arylation of aliphatic ketones (**4a**; see SI) and investigated the range of aliphatic ketones and aryl iodides under new conditions (Scheme 3). Both electron-deficient and electron-rich aryl iodides gave moderate to good yields (**5a**, **5b**, **5c**, **5d**, **5l**), and then, when examining the effect on reaction yield of different substitution positions of the substituent on the benzene ring, we obtained a conclusion similar to that of the aldehyde (**5a**, **5b**, **5d**, **5e**, **5f**, **5g**), in which the yield was higher than that when the substituent was in the *para* position. We also examined other types of iodobenzene and obtained a moderate yield (**5m**, **5n**, **5o**). Various chain ketones were also screened and gave good to moderate yields (**5p**, **5r**, **5v**, **5w**, **5x**). Particularly, when 3-methyl-2-butanone (**4b**; see SI), 2-methyl-3-pentanone (**4e**; see SI), and symmetrical 3-pentanone (**4c**; see SI) having two or more reaction sites were used, only one monosubstituted product was observed (**5p**, **5v**, **5w**). In addition, we also obtained high diastereomeric products when cyclic aldehyde was used as a substrate (**5q**, **5s**, **5t**).

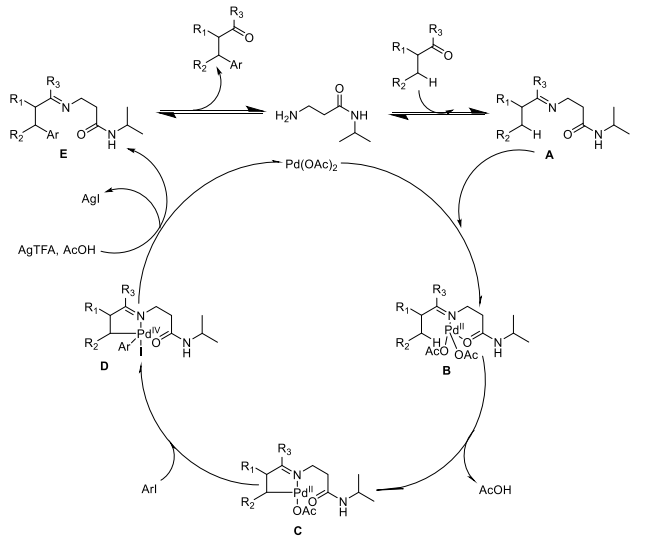
On the basis of our experiments and previous research results,[13] we proposed a plausible reaction mechanism for Pd-catalyzed arylation of aliphatic aldehydes and ketones with amino amide as a TDG (Scheme 4). First, the aldehyde and 3-amino-*N*-isopropylpropionamide as TDG are condensed to form the imine intermediate **A**. Next, the $\beta$-imino amide intermediate is coordinated with Pd to form a palladium complex **B**. Again, intermediate **B** eliminates one molecule of acetic acid to form the [5,6]-bicyclic palladium intermediate **C**, and then, intermediate **D** is formed by the oxidative addition of intermediate **C** with an aryl iodide. Finally, intermediate **D** forms

**Scheme 3. Pd-Catalyzed $\beta$-C($sp^3$)−H Arylation of Aliphatic Ketones**[a]




[a]Conditions: aliphatic ketones (0.2 mmol, 1.0 equiv), ArI (0.4 mmol, 2.0 equiv), $Pd(OAc)_2$ (10 mol %), AgTFA (1.5 equiv), HFIP/AcOH = 9:1 (0.2 M), under air, 100 °C, 24 h. Yields correspond to isolated products.

**Scheme 4. Proposed Reaction Mechanism**




intermediate **E** by reductive elimination accompanying a ligand dissociation process and iodide abstraction by AgTFA to release the desired product and TDG 3-amino-*N*-isopropylpropionamide.



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In summary, 3-amino-*N*-isopropylpropionamide as a new TDG is effectively involved in Pd-catalyzed arylation of aliphatic aldehydes and ketones. The TDG is found effective for the activation of the C−H bond of the unactivated methyl group and the cyclic methylene group. This reaction showed good substrate compatibility and regioselectivity. The results indicated that 3-amino-*N*-isopropylpropionamide was more beneficial to the *β*-arylation of aliphatic aldehydes than other TDGs under relatively mild conditions. The *β*-amino amide produced results by the [5,6]-bicyclopalladium intermediate between Pd and TDG better than those of glycinamide. This research broadens the range of applications for TDGs. The same TDG can be applied to activate the inert C−H bond of aliphatic aldehydes and ketones simultaneously. At present, our laboratory attempts to find a new amide-like DG with better universality based on previous research, which can make it suitable for C−H activation of all types of aldehydes and ketones.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b00366.

Experimental details, spectral and analytical data for all reaction products (PDF)

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### Notes

The authors declare no competing financial interest.

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