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Palladium Catalyzed Regioselective C4-Arylation and Olefination of Indoles and Azaindoles

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Abstract. A convergent strategy for the synthesis of biologically relevant C4-substituted indole scaffolds was demonstrated using Pd(II)-catalyzed remote C–H functionalization of indoles and azaindoles. The reaction displays high regioselectivity for the C4-position of indole-3-carbaldehydes using glycine as an inexpensive transient directing group. Notable features of this transformation include the selective formation of six-membered palladacyle and excellent functional group tolerance.

Keywords: C-H activation; Palladium; Transient directing group; Indoles; Regioselective

In the past decade, directing group assisted C–H activation has been established as an extremely powerful and efficient strategy for accessing complex heterocyclic skeletons.[1] Successful execution of these approaches is also finding applications in natural product synthesis.[2] Recently, more challenging distal C–H bond functionalization gained a lot of attention.[3] Although excellent progress was made in the transition-metal catalyzed C-H activation reactions facilitating a variety of directing groups, only limited reports were available for the aldehyde-directed C-H functionalization, probably due to the weak coordinating ability of the carbonyl group.[4] This issue is often addressed by converting the aldehyde group into more competent imine or oxime-directing groups.[5] However, such methods require additional synthetic steps for the installation and removal of the directing group, which impede the overall reaction efficiency. An alternative strategy of forming the directing group transiently, which will reversibly bind to the metal-catalyst was suggested by Jun and co-workers for the Rh-catalyzed hydroacylation of alkenes with aldehydes.[6,7] Following similar approach, Yu and co-workers described an elegant α-amino acid mediated Pd(II)-catalyzed sp^3 C-H arylation of *o*-tolualdehydes and aliphatic ketones.[8] The bidentate chelation of imine nitrogen and carboxylate moiety to Pd(II)-catalyst enables the activation of C-H bonds. Later, the groups of Hu[9] and Ge[10] also demonstrated sp^3 C-H arylation reactions of aliphatic aldehydes using acetohydrazone and 3-aminopropanoic acid as transient directing groups respectively. Pd(II)-catalyzed sp^2 C-H activation of benzaldehyde derivatives was realized by Sorensen and co-workers for the synthesis of fluorenones.[11] Very recently, direct *ortho* sp^2 C-H arylation of aryl ketones was illustrated by Jin and co-workers using glycine.[12] Despite these advances, transient directing group mediated Pd(II)-catalyzed C-H functionalization reactions were largely limited to aryl rings.[13] Implementation of this strategy for the C-H activation of heteroaryl rings was less studied.

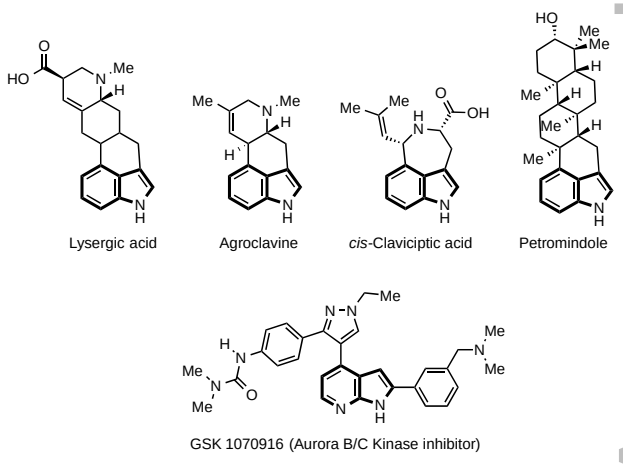

Figure 1. Biologically active C4-subsutituted indoles and azaindoles.

On the other hand, indole and azaindole skeletons are widely present in many natural and unnatural biologically active compounds and pharmaceuticals (Figure 1).[14] Transition-metal catalyzed regioselective C-H functionalization of indoles would offer a direct approach for the construction of diverse array of indole skeletons.[15] Functionalization of

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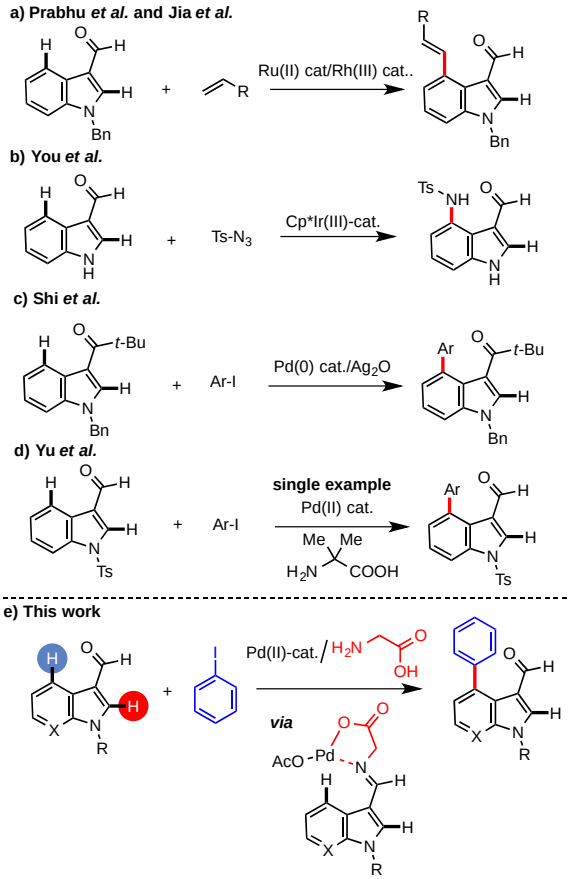
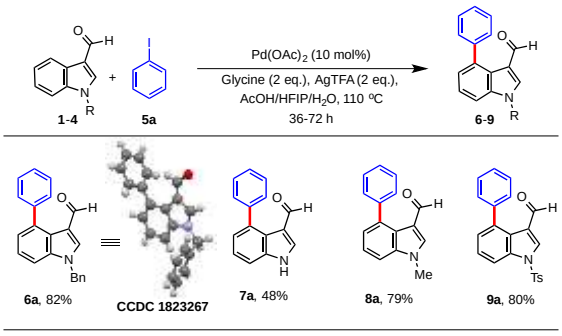
indoles at the C3 and C2-positions were well established due to the high electron density of the pyrrolic ring. In contrast, diversification of the benzenoid moiety of indoles and related heterocycles such as azaindoles at C4, C5, C6 and C7 positions has been gaining prominence only recently.[16] Inspired by the broad occurrence of C4-substituted indole skeletons, we envisioned developing a transient directing group mediated bidentate chelation strategy for the sp^2 C–H functionalization at the C4-position of indole-3-carbaldehydes. The initial challenge associated with the envisioned project was the potential competition of C4 position with C2 position.



Scheme 1. Overview of the work.

The importance of C4-decorated indoles in natural product synthesis, materials science and medicinal chemistry inspired several groups to study regioselective direct C4 functionalization of indoles. In 2013, Prabhu and co-workers reported a C4-H alkenylation of 3-formylindoles using Ru(II)-salts (Scheme 1a).[17] Jia and co-workers developed Rh(III)-catalyzed olefination of unprotected indoles and demonstrated its application in the synthesis of (-)-agroclavine and (-)-elymoclavine.[18] Around the same time, an Ir(III)-catalyzed C4-amidation was illustrated by You and co-workers using sulfonyl azides (Scheme 1b).[19] Shi and co-workers established an elegant Pd(0)-catalyzed strategy for the C4-arylation of indoles using pivaloyl directing group (Scheme 1c).[20] A single example of a transient directing group mediated C4-arylation of *N*-tosyl-3-fomylindole was reported by Yu and co-workers (Scheme 1d).[21] In spite of these elegant reports, development of a general Pd-catalyzed C4-selective arylation and olefination of indoles and azaindoles is highly desirable (Scheme 1e).

We began the investigation using cheap and commercially available glycine as the transient directing group for the C4-arylation of *N*-benzyl-1*H*-indole-3-carbaldehyde **1a** with iodobenzene **5a**.[22] Using 10 mol% of $Pd(OAc)_2$ and 2.0 equiv. of AgTFA at 110 °C, initial solvent screening was carried out and we were delighted to see the formation of desired product **6a** as a single regioisomer in 69% of NMR yield in a 1:1 solvent mixture of AcOH and HFIP (hexafluoroisopropanol). Compound **6a** was unambiguously characterized through X-ray crystallography.[23] The arylation proceeded exclusively at the C4-position by selective formation of a six-membered palladacycle intermediate (*vide infra*). No C2-arylation product was observed in the ^{1}H NMR of the crude reaction mixture. Based on the observation by Yu and co-workers,[8] we tested the effect of H_2O additive in the transient directing group mediated C4-arylation and indeed using an esoteric mixture of AcOH/HFIP/H_2O (1:1:0.1, v/v), we observed the formation of **6a** in an improved NMR yield of 86% (isolated yield of 82%). The effect of glycine as a transient directing group is evident as in the absence of glycine no reaction was observed. Other amino carboxylic or sulfonic acids were also tested instead of glycine, however only lower yields were observed in these cases. Using glycine methyl ester instead of glycine led to no reaction indicating the importance of the carboxylic acid moiety for the formation of 5-membered palladacycle intermediate.



Scheme 2. Indole arylation with different *N*-protecting groups.

To evaluate the generality of this new transformation, we tested the role of nitrogen protecting groups (Scheme 2). Unprotected or *N*-methyl or *N*-tosyl protected 3-formylindoles **2-4** provided the corresponding C4-arylated products **7a-9a** in 48%, 79% and 80% respectively (Scheme 2).

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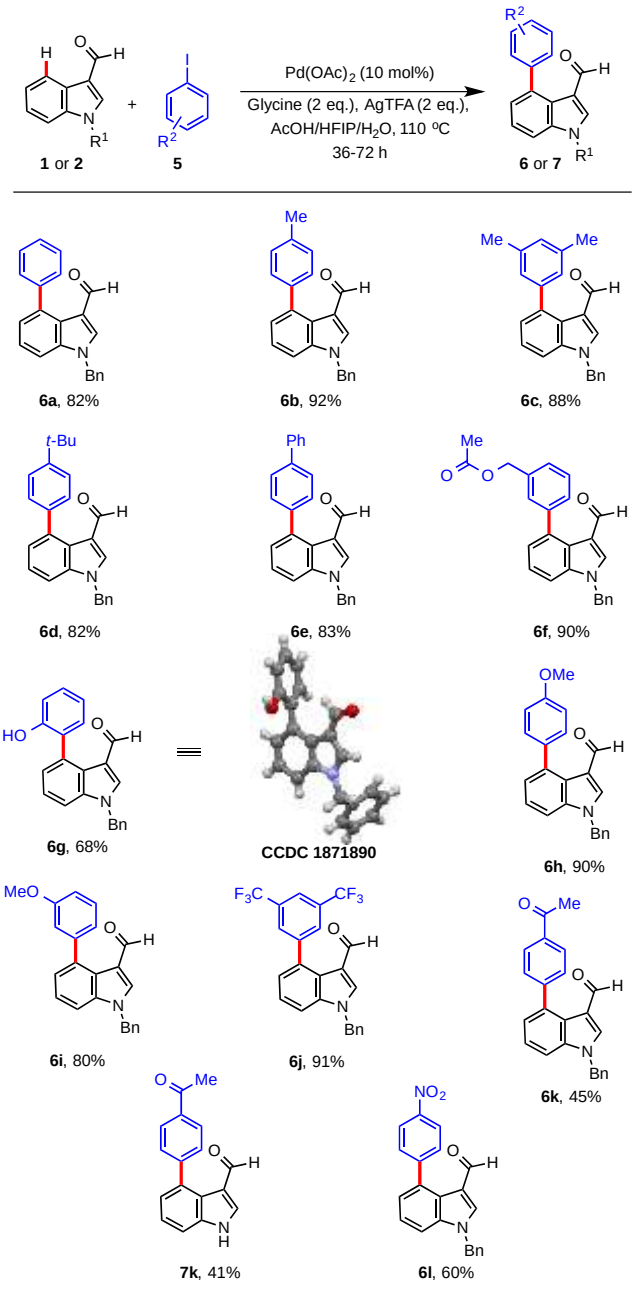
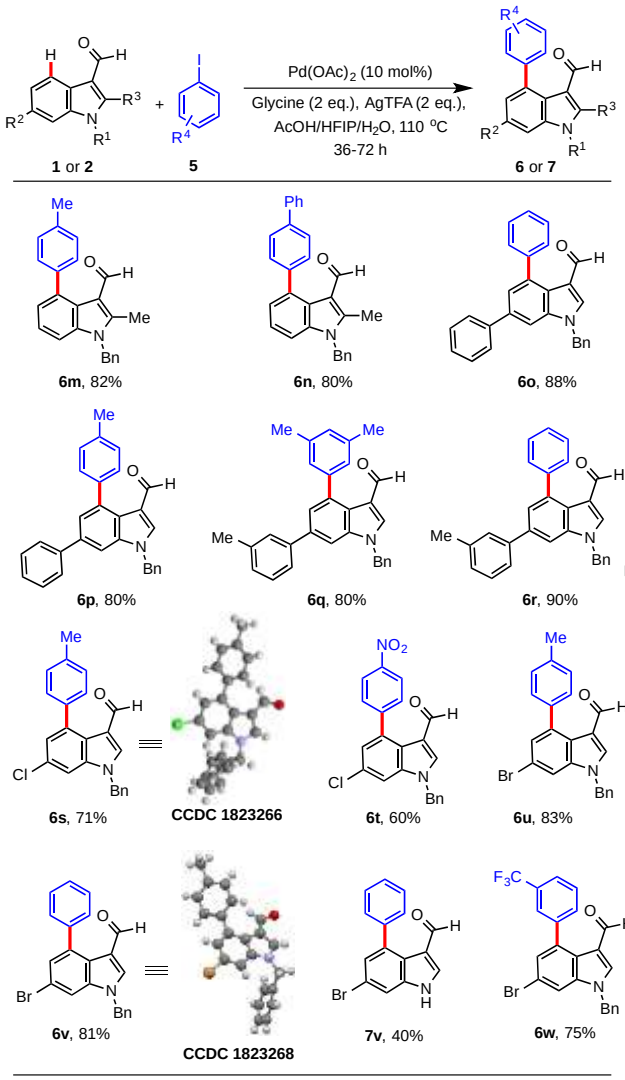


Scheme 3. Substrate scope with diverse aryl iodides.

In order to thoroughly outline the utility of this method, we systematically tested a number of aryl iodides. A wide variety of electron rich and electron poor aryl iodides were investigated. As shown in Scheme 3, the reaction is compatible with a range of substituents and 4-*tert*-butylphenyl iodide (**6d**) and 4-biphenyl iodide (**6e**) did not affect the yield and selectivity. Several valuable functional groups such as acetyl (**6f**), hydroxyl (**6g**), methoxy (**6h**, **6i**), trifluoromethyl (**6j**), keto (**6k**, **7k**) and nitro (**6l**) groups were well tolerated at different positions of the aromatic ring. Hydroxy substituent in the *ortho*-position of aryliodide resulted in only a moderate yield of 68% (**6g**) probably because of both unfavourable electronic and steric effects.



Scheme 4. Substrate scope with diverse 3-formylindoles.

We further elaborated the scope of this reaction with differently substituted 3-formylindoles (Scheme 4). Notably, 2-methyl substituted indole derivative led to selective sp^2 C□H activation to afford the corresponding products **6m**, **6n** in 82% and 80% respectively. This clearly indicates the preferential formation of cyclic six membered palladacycle intermediate by C4-H sp^2 C-H activation. The reaction was also applicable to 6-aryl substituted indolyl aldehydes (**6o**-**6r**). Intriguingly, 6-chloro and 6-bromo indoles provided the corresponding functionalized products (**6s**-**6v**) in synthetically useful yields. The structures of **6s** and **6v** were confirmed unambiguously by X-ray crystallography.[23] In the case of C5-substituted indole, the reaction was sluggish and even after prolonged heating, no product was observed probably because of increased steric hindrance.

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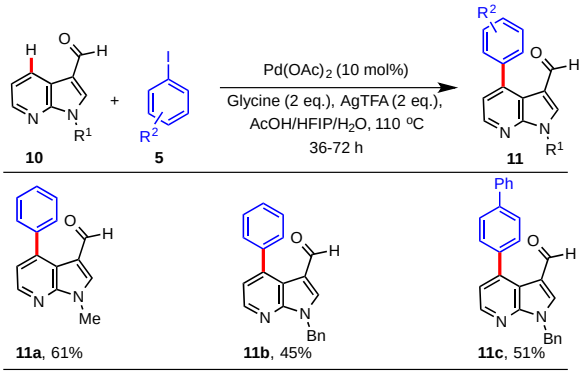
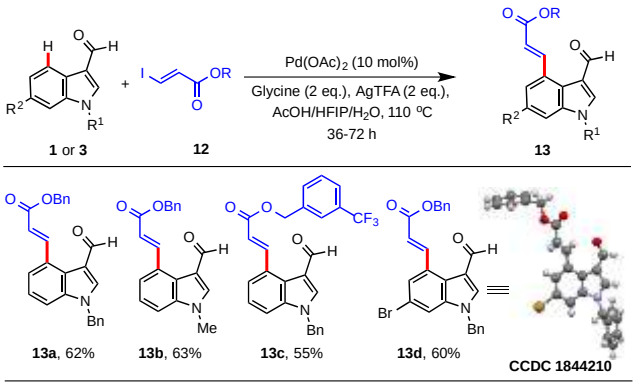


Scheme 5. Scope of the reaction with 7-azaindoles.

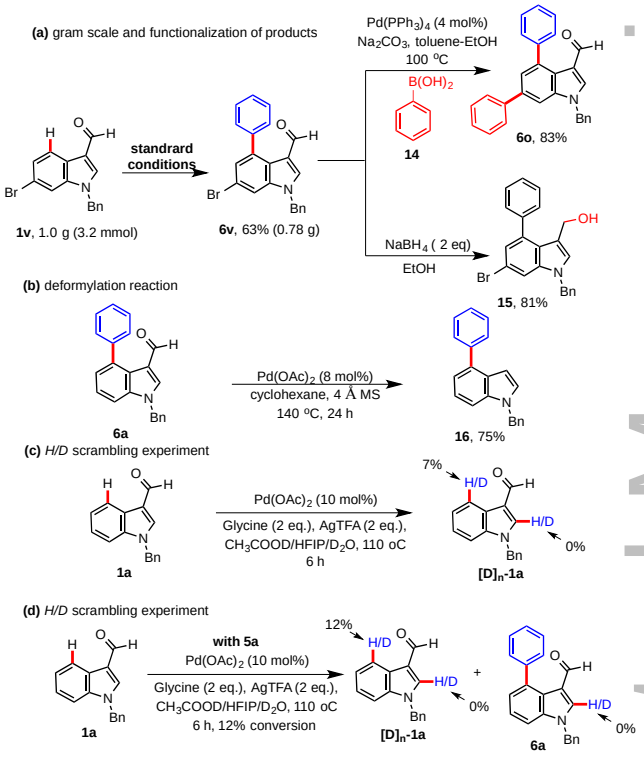
The versatility of this Pd(II)-catalyzed C–H activation was further expanded to biologically active and therapeutically important azaindole core (Scheme 5).[24] As expected, *N*-methyl azaindole derivative **10a** underwent the C□H activation to provide C-4 arylated azaindole **11a** in 61% using 10 mol% of $Pd(OAc)_2$. The scope of the reaction with *N*-benzyl protected azaindole aldehyde **10b** was investigated with iodobenzene (**11b**, 45%) and 4-phenyl-iodobenzene (**11c**, 51%).

Gratifyingly, the reaction was not limited to aryl iodides and alkenyl iodides also under the optimized reaction conditions found to be useful partners furnishing the corresponding 4-alkenylated indoles **13**. As demonstrated in Scheme 6, use of 10 mol% of $Pd(OAc)_2$ and glycine as the transient directing group allowed the C–H olefination at C-4 position of *N*-benzyl or *N*-methyl-indole-3-carbaldehydes with benzyl-*trans*-3-iodoacrylate **12** to afford **13a-d** in 55-63%.



Scheme 6. Scope of the reaction with vinyl iodides.

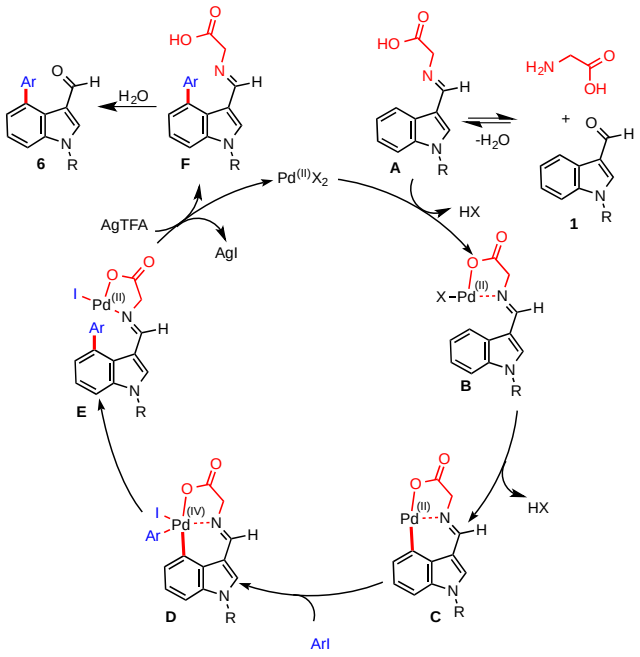
To study the scalability of the present method, the reaction of **1v** (1.0 g) with **5a** was performed on a gram scale and **6v** was obtained in 63% yield (0.78 g). The synthetic utility of the C4-arylated indole derivatives was demonstrated by carrying out Suzuki-Miyaura coupling of **6v** with phenylboronic acid **14** and **6o** was isolated in 83% yield. Reduction of **6v** using 2.0 equiv. of $NaBH_4$ gave the corresponding alcohol derivative **15** in 81% yield (Scheme 7a). The formyl directing group can be removed easily from the C4-arylated 3-formylindole **6a** under Pd(II)-catalysis to give **16** in 75% yield (Scheme 7b).[25] Our initial attempts to isolate any reaction intermediate met with no success. To gain some insights into the reaction mechanism, H/D scrambling experiments were carried out. Under the optimized reaction conditions, **1a** was treated with a mixture of $CH_3COOD/HFIP/D_2O$ (1:1:0.1 v/v) and after 6 h around 7% of H/D scrambling was observed at C4-position. Interestingly, no significant H/D exchange was observed at C2-position (Scheme 7c). Analogous experiment carried in the presence of **5a** also showed no scrambling at the C2-position of **6a** and 12% H/D exchange was observed in the recovered starting material **1a** (Scheme 7d).



Scheme 7. Gram scale synthesis, further functionalizations and mechanistic studies.

The probable reaction mechanism for the reaction is outlined in Scheme 8. Condensation of the 3-formylindole **1** with glycine provides the intermediate **A**. Coordination of imine nitrogen and carboxylate moiety to Pd(II)-species leads to five membered palladacycle intermediate **B**. Preferential formation of [5,6]-bicyclic palladium intermediate **C** proceeds *via* a regioselective C4-H activation of indoles (instead of C2-H activation of indoles). Oxidative addition of aryl iodide onto intermediate **C** generates Pd(IV)-species **D**.[26] Finally reductive elimination of **D** and iodide abstraction by silver trifluoroacetate provides the intermediate **F** and regenerates the Pd(II)-catalyst. Hydrolysis of **F** leads to the formation of C4-

substituted indolyl aldehydes and transient directing group glycine.



Scheme 8. Proposed reaction mechanism.

In summary, we have developed a transient directing group mediated Pd(II)-catalyzed C□H arylation and olefination reactions of indoles, proceeding selectively at the C4-position using commercially available and cheap glycine as the transient directing group. The reaction proceeds in the presence of water under operationally simple conditions for 3-formylindoles and 3-formylazaindoles.

Experimental Section

Typical experimental procedure for the synthesis of **6a**: In an oven dried 10 mL reaction tube, charged with magnetic stir-bar, $Pd(OAc)_2$ (4.5 mg, 10 mol%), AgTFA (88 mg, 0.4 mmol), glycine (30 mg, 0.4 mmol), and *N*-benzyl-1H-indole-3-carbaldehyde **1a** (47 mg, 0.2 mmol) were added. Commercially available iodobenzene (122 mg, 0.6 mmol), was added was added to the reaction mixture followed by acetic acid (1 mL), HFIP (1 mL) and water (0.1 mL) at room temperature. The reaction tube was capped and stirred at 110 °C temperature for 24 hours. Upon completion, the reaction mixture was cooled to room temperature. The reaction mixture was poured into the $NaHCO_3$ solution and extracted with ethyl acetate. The separated organic layer was dried under Na_2SO_4, evaporated under reduced pressure and passed through the column chromatography for purification on silica gel with petroleum ether and ethyl acetate (19:1) mixture as the eluent, giving the product **6a** (50 mg, 82% yield)

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[22] See Supporting Information for the full optimization details.

[23] CCDC 1823267 (**6a**), 1871890 (**6g**), 1823266 (**6s**), 1823268 (**6v**) and 1844210 (**13d**) contain the supplementary crystallographic data for this paper. These data are provided free of charge by The Cambridge Crystallographic Data Centre.

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UPDATE

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