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Letter

Methylene C(sp^3)−H β,β'-Diarylation of Cyclohexanecarbaldehydes Promoted by a Transient Directing Group and Pyridone Ligand

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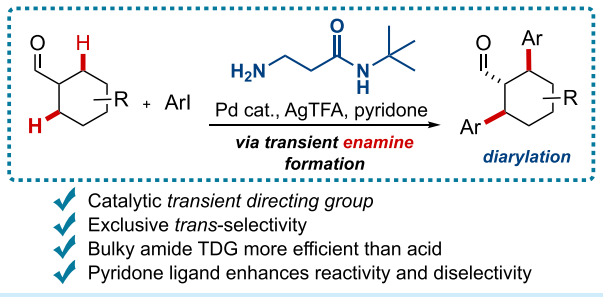
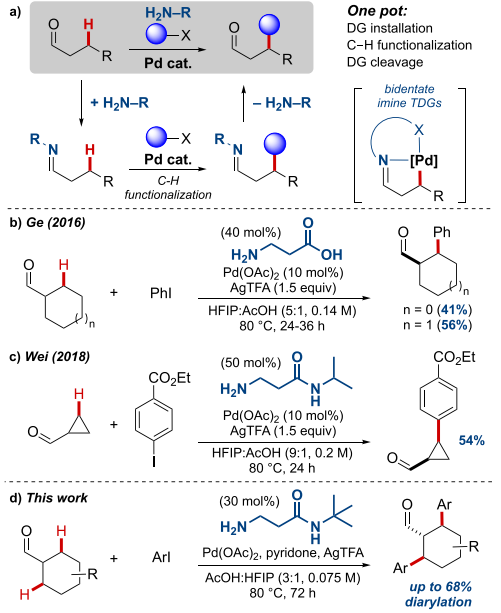
ABSTRACT: A hindered β-amino amide transient directing group effects di-*trans*-arylation of cyclohexanecarbaldehydes. The amide N-substituents are shown to affect yield and can enhance the rate of arylation compared with the α-amino acid. Addition of a pyridone ligand further enhanced reactivity. The reaction is successful for a range of aryl iodides, and various substituted cyclohexane carboxaldehydes, providing functionalized products from simple feedstocks. A mechanism is proposed evoking a transient enamine.



Transition metal catalyzed C−H functionalization has the potential to improve chemical syntheses and reveal unprecedented retrosynthetic disconnections to access novel molecular scaffolds.[1] In recent years, transient imine directing groups have emerged as the next generation of directing groups for C(sp^3)−H functionalization of aldehydes/ketones and amines.[2−8] By this approach, the directing group (DG) installation and removal steps occur in one pot with the key C−H functionalization, often through a reversible imine linkage (Scheme 1a). In contrast to powerful amide bound directing groups,[1c,d] a transient strategy removes the requirement for additional nonproductive steps and allows directing groups to be installed catalytically. Furthermore, this directly reveals valuable functionality, such as aldehydes, for further diversification.

In 2016, Yu first reported glycine as a transient directing group (TDG) for the C(sp^3)−H arylation of *o*-tolualdehydes and aliphatic ketones.[4] Subsequently, further examples of transient directing groups for carbonyl C−H functionalization have emerged for β-arylation of aliphatic ketones,[5] as well as benzylic[6] and *ortho*-functionalization[7] of benzaldehyde derivatives. Aliphatic aldehydes are less explored,[8] with examples of β-arylation from Ge,[8a] ourselves,[8b,d] and Wei.[8c] In these cases, transient imines have been evoked as the proximal directing group, with distal secondary anionic or neutral coordinating groups. However, it is notable that to date there have only been five individual examples (in two reports)[8a,c] that demonstrate the challenging β-methylene functionalization of aldehydes. Ge showed that using β-alanine as a TDG enabled β-monoarylation of both cyclohexyl- and cyclopentylcarboxaldehydes, with a *cis*-geometry proposed in both cases (Scheme 1b), and acyclic 2-ethylbutanal and pentanal underwent β-arylation in lower yields.[8a] Wei later showed that cyclopropylcarboxaldehyde was suitable for β-monoarylation using an isopropyl amide of β-alanine as the TDG, with the aldehyde in excess (Scheme 1c).[8c]

Scheme 1. Methylene C(sp^3)−H Functionalization of Aldehydes with Transient Directing Groups



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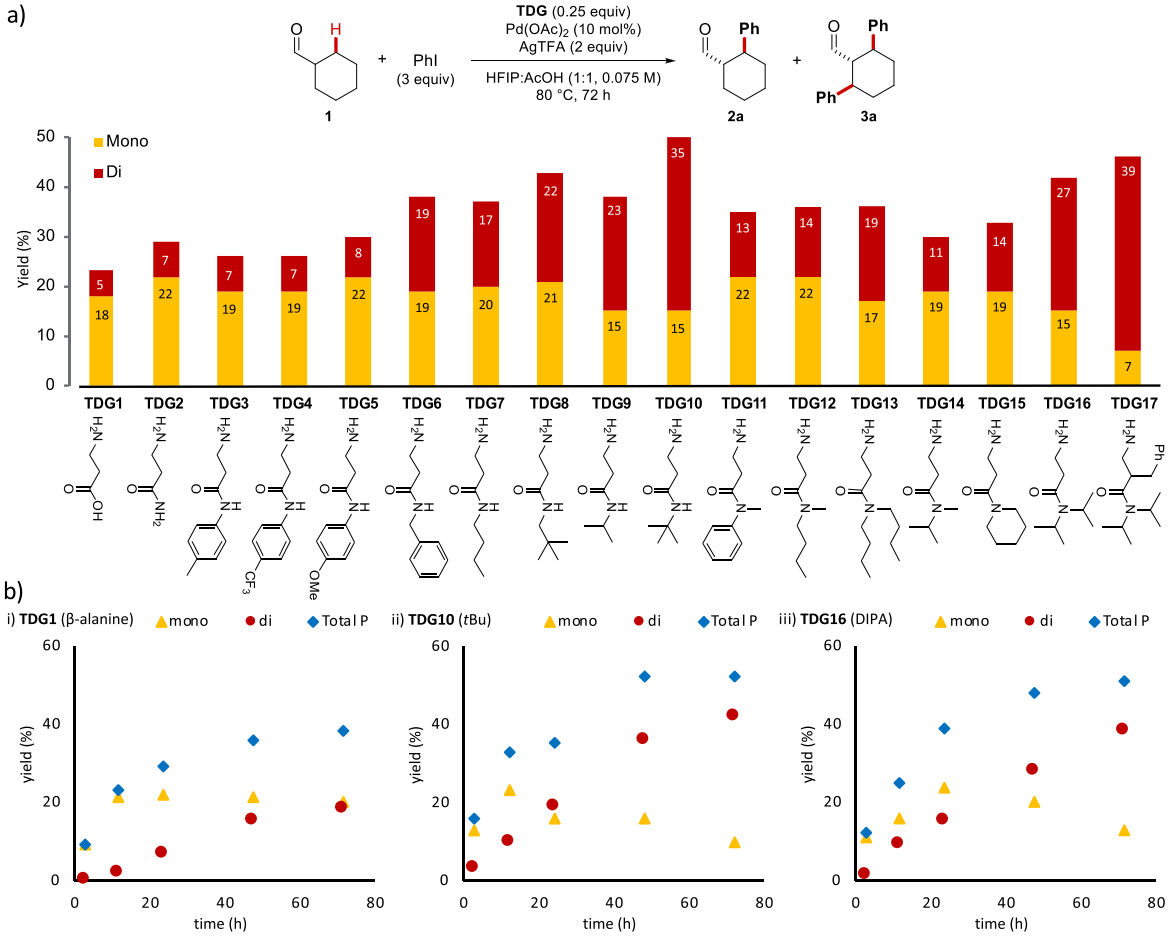

Figure 1. (a) Effect of amide transient directing groups on methylene C(sp^3)–H arylation of cyclohexanecarboxaldehyde; results are averages of two runs. (b) Reaction profiles using (i) *β*-alanine, (ii) *t*Bu-amide **TDG10**, and (iii) DIPA-amide **TDG16**. Solvent system: HFIP/AcOH (5:1). Total P = yield of mono **2a** + di **3a**. Yields determined by ^{1}H NMR using 1,3,5-trimethoxybenzene as an internal standard.

Here we report the development of a *trans,trans-β,β′*-methylene-diarylation of cyclohexanecarbaldehydes (Scheme 1d). The reaction proceeds via a dual catalytic cycle using catalytic palladium and a catalytic amine transient directing group bearing a *β*-amide functionality. The use of a pyridone additive achieves high yields of the diarylated product. Palladium coordination via an X,L-type enamine ligand is proposed.

Our previously reported conditions gave complete chemoselectivity for methyl groups, and secondary aldehydes were not tolerated.[8b] To overcome this, we initially screened a library of directing groups for the *β*-arylation of cyclohexanecarboxaldehyde with aryl iodides, under lower temperature and concentration conditions (80 °C, 0.15 M). No reaction was observed with directing groups that would form a 5-membered chelate, or with 6-membered chelation where the secondary binding group was a sulfonamide, methyl ether, or sulfonic acid.[9] Pleasingly, arylation was observed at the *β*-methylene when using *β*-alanine **TDG1**, as used by Ge, as well as with amide **TDG3**. Both mono- and diarylated products were *trans*-configured as determined by the coupling constants for the *CH*CHO and *CH*Ph signals in the ^{1}H NMR.[11]

To tune reactivity we then examined *β*-amino-amides with different amide substituents, using a TDG loading of 25 mol % and a prolonged reaction time (Figure 1a). Under these conditions, the efficiency of the amide **TDG3** was improved in comparison to acid **TDG1**. Primary amide **TDG2** could also promote the reaction. Changing the electronics of the aromatic amide by using *p*-trifluoromethyl **TDG4** and *p*-methoxy **TDG5** groups made little difference to the yield or mono-/diselectivity. Improved yields were seen with benzyl amide **TDG6** which furnished a 38% yield of a 1:1 mixture of the mono- and diarylated products. Secondary *N*-alkyl amides exhibited improved reactivity, aided by increasing the steric bulk from *n*-butyl **TDG7** to neopentyl **TDG8**. The most sterically demanding *tert*-butyl **TDG10** furnished a 50% total yield with notable diselectivity. Tertiary amides (**TDG11**–**TDG17**) were also reactive, with the highest yield for the most hindered diisopropyl amide **TDG16**.

These results, and the preference for bulky amide substituents, suggest the distal binding for these components is through the carbonyl oxygen, not the amide nitrogen, in a 6-membered chelate.[12] Installing a benzyl group on the backbone of the DIPA amide (**TDG17**) gave a slight improvement in yield compared to diisopropylamide **TDG16**.[5a]

To aid our understanding of the reaction and as a further comparison of these TDGs, reaction profiles were investigated using *β*-alanine **TDG1**, *tert*-butyl amide **TDG10**, and diisopropylamide **TDG16**, using 5:1 HFIP/AcOH as solvent, which gave improved yields. A peak in the yield of monoarylated product occurred early in the reaction, which was then gradually converted to the diarylated species over

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time. A faster reaction was observed with the amide directing groups, along with more rapid conversion of the monoarylated product **2a** to di **3a**.

Optimization continued with *t*Bu-amide **TDG10** to drive conversion to the diarylated species. We examined the inclusion of additives to assist in the proposed concerted metalation deprotonation step. As Yu had described previously in the C(sp^3)−H arylation of amines, pyridones can be effective ligands to transient C−H activation.[3d] Here, inclusion of pyridone ligands was found to enhance the yield and rate of formation of the diarylated aldehyde product **3a**, with the optimal ligand being 5-(trifluoromethyl)pyridin-2-ol (**4**).[9]

The loadings of the $Pd(OAc)_2$, AgTFA, ArI, TDG, and ligand were optimized using a DOE approach, resulting in a 68% yield of diarylated aldehyde **3a** (by ^{1}H NMR; average of two runs) using 5 equiv of iodobenzene, 30 mol % **TDG10**, 8 mol % of $Pd(OAc)_2$, 2.1 equiv of AgTFA, and 70 mol % of pyridone **4**.[9,10] Under these conditions, a final reaction profile was obtained (Figure 2), showing rapid formation of the

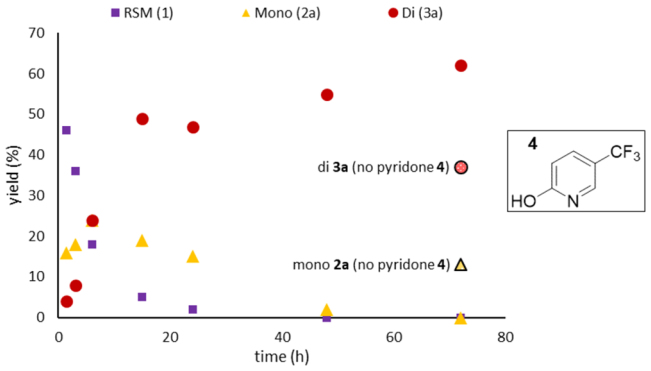
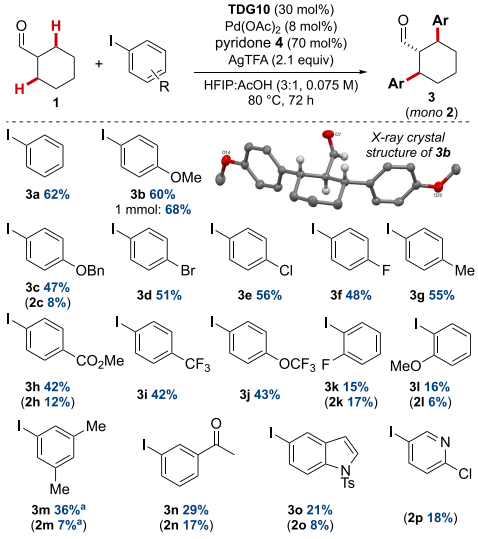


Figure 2. Reaction profile under optimized conditions, with each point from an individual reaction. Results when omitting the pyridone ligand quoted at 72 h. Yields determined by ^{1}H NMR using 1,3,5-trimethoxybenzene as an internal standard.

diarylated product in the early stages of the reaction, which slowed as the remaining starting material was consumed and the monoarylated species was slowly converted to the diarylated product (Figure 2). In the absence of the pyridone ligand, the yield and selectivity for the diarylated product were reduced. Importantly, in the absence of the amine TDG, the arylated products were not formed.[9]

The scope of the aryl iodide was then investigated, to form diarylated cyclohexanecarboxaldehydes (Scheme 2, 0.2 mmol **1**). A 62% isolated yield of diarylated **3a** was achieved with iodobenzene, and 4-iodoanisole gave diarylated aldehyde **3b** in 60% yield, which gave an improved 68% yield on a 1 mmol scale. The *trans,trans*-stereochemistry was confirmed by X-ray crystallography. The 4-benzyl ether derivative resulted in a slightly lower yield of diarylated product **3c** with small amounts of the monoarylated species **2c**. 4-Halophenyl groups were installed in good yields (**3d**−**g**). 4-Iodotoluene formed diarylated product **3g** in 55% yield. Electron-withdrawing groups in the 4-position led to slightly reduced yields (**3h**−**3j**). 4-Iodobenzoate gave 43% of **3h** with an additional 12% of the monoarylated species **2h**. *ortho*-Substituted aryl iodides caused a significant drop in yield (**3k** and **3l**). *meta*-Substituents, including a potentially reactive methyl ketone (**3n**), were more well tolerated. Ditosylindole **3o** was isolated in 21% yield, with

Scheme 2. Scope of Aryl Iodides

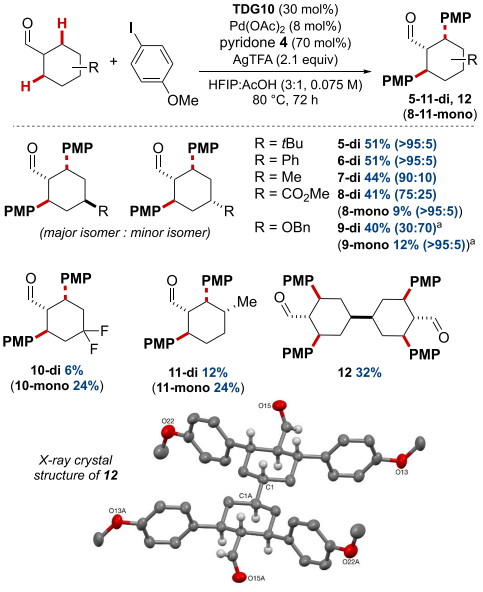


[a]Isolated as a mixture; ratios of product calculated from the relative integrals of the aldehyde signals.

a small amount of the monoarylated species **2o**. 2-Chloro-5-iodopyridine gave an 18% yield of monoarylated **2p**.

We then investigated the effect of substituents on the cyclohexyl ring (Scheme 3). The *trans,trans*-configuration was

Scheme 3. Diarylation of Cyclohexanecarbaldehydes



[a]Isolated as a mixture; product ratio calculated from the relative integrals of the aldehyde signals. PMP = paramethoxyphenyl.

observed exclusively in each case for the arylation. Groups in the 4-position of the ring generally favored the all-equatorial product (**5**−**9**). The size of the 4-substituent influenced the selectivity; for example, the *tert*- butyl derivative gave a 51% yield of a single diarylated product (**5-di**). The phenyl group also gave all-equatorial **6-di**, using a *cis*/*trans* mixture of the starting material. The smaller methyl substituent gave small amounts of a minor isomer of **7-di** with the methyl group axial. An ester was tolerated at the 4-position of the aldehyde, giving

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the diarylated product as a 3:1 mixture of **8-di** isomers, with monoarylated all-equatorial **8-mono** isolated in 9% yield. An *O*-benzyl group was tolerated, giving 40% of the diarylated product, surprisingly for this substrate the major isomer of **9-di** was that with an axial benzyloxy group (12% of the monoarylated species **9-mono** was also isolated). A difluoro substituent at the 4-position gave a higher proportion of monoarylation product **10-mono** to **10-di**.

A 3-Me group gave the monoarylated product in 24% yield, with the PMP group installed at the least hindered position, and 12% of the all-equatorial 1,2,3,4-functionalized aldehyde **11-di**. A one-pot tetrarylation was possible on a substrate with two cyclohexylcarbaldehyde groups connected at the four position, providing major isomer **12** in 32% yield (75% yield per arylation). A crystal structure of **12** confirmed the all-equatorial stereochemistry.

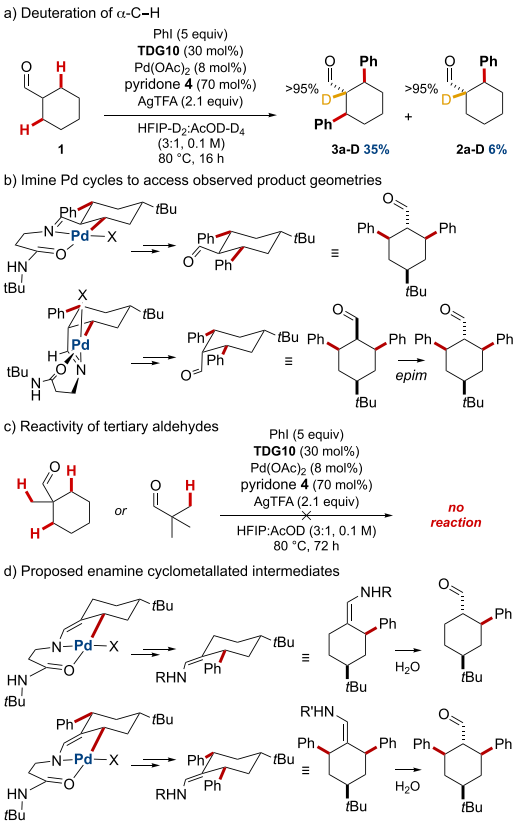
Surprisingly, cyclohexane rings had unique reactivity. Other ring sizes (3-, 4-, 5-, 7-, and 8-) and acyclic 2-ethylbutanal did not form significant amounts of the diarylated products.[9] The monoarylated product was isolated in low yield for the cyclopentane substrate (17% monoarylated using 4-iodoanisole). However, under these conditions using the 3- and 4-membered rings only starting material was returned. In the larger 7-/8-membered rings, the major products were a mixture of α–β-unsaturated aldehydes.[9]

Therefore, we considered the mechanism of the reaction, aiming to explain these interesting reactivity and stereochemical observations. Conducting the arylation in deuterated solvents revealed full deuteration of the α-C–H for the mono- and diarylated products (Scheme 4a). This is consistent with enamine formation under the reaction conditions. Deuteration at the benzylic positions was not observed in the products, suggesting an irreversible C–H activation. The stereochemical outcome of the *tert*-butyl derivative provided further insight. In an imine mechanism, the only possibilities suitable to form the all-equatorial product would be (i) a *trans*-equatorial palladacycle giving the observed product directly or (ii) a *cis* palladacycle with the imine in the axial position, with the observed product formed on aldehyde epimerization (Scheme 4b). Other potential palladacycles would result in the wrong product.[9]

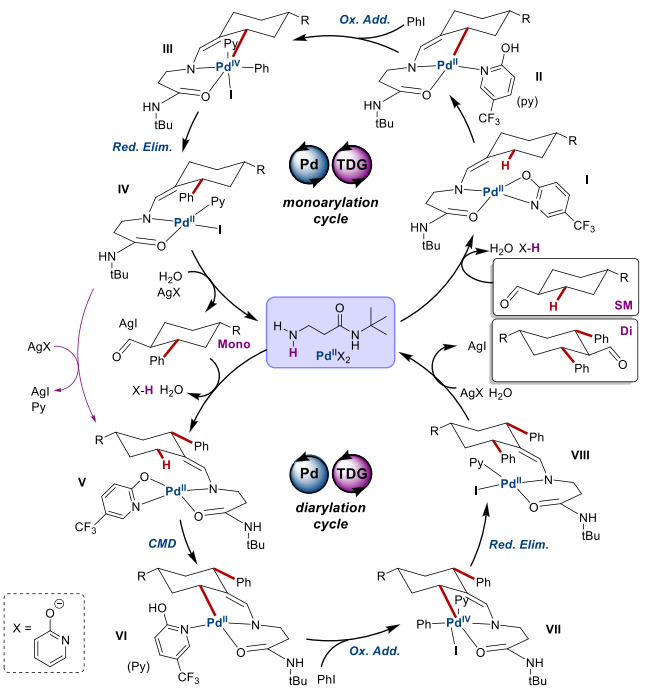
Notably, the tertiary aldehyde methylcyclohexane carboxaldehyde was unreactive, as was pivaldehyde, which present more reactive methyl C–H bonds (Scheme 4c). Given these results we propose an alternative role for the transient directing group, as a X,L enamine ligand, rather than an imine (Scheme 4d). This cannot be achieved with the tertiary aldehydes. The enamine geometry is well aligned with the C–H bonds for the *trans*-arylation on the 6-membered ring. However, such an intermediate would likely lead to increased ring strain, in comparison to an imine mechanism for both small and medium sized rings, or to poorer overlap of the β-C–H bond. The observed stereochemistry can be rationalized though enamine coordination of the Pd^{II} catalyst with the cyclohexyl ring in a chair conformation and with large 4-substituents equatorial. The second arylation would then occur in the same manner, with the installed Ar group also equatorial. Hydrolysis of the enamine would give the favored *trans*-product as observed. Unfortunately, attempts to characterize potential intermediates were unsuccessful.

Consequently, we propose a catalytic cycle involving an enamine-derived Pd cycle (Scheme 5). The aldehyde first condenses with the amine and forms an X, L enamine ligand with the Pd^{II} catalyst (**I**). C–H activation occurs at the proximal C–H promoted by the pyridone, affording cyclometalated intermediate **II**. Oxidative addition and reductive elimination steps install the first aryl group giving complex **IV**.

Scheme 4. Mechanistic Considerations



Scheme 5. Proposed Catalytic Cycle



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The palladium and directing group can be turned over by hydrolysis, or complex **IV** could ligand exchange to give **V** to enter the diarylation cycle directly, explaining the initial rapid formation of the diarylated species (cf. Figure 2).

In summary, we have developed a palladium catalyzed *trans*-selective diarylation of cyclohexane carboxaldehydes enabled by a transient directing group and promoted by a pyridone ligand. Hindered secondary or tertiary β-amino alkyl amides provide effective transient directing groups. The addition of a pyridone ligand provides enhanced reactivity and selectivity for the diaryl product. Varying functionality was tolerated on the aryl iodides and the cyclohexanecarbaldehyde scaffold, with most giving good selectivity for the all-equatorial products, giving highly functionalized 3D structures in one step from simple starting materials. We propose the role of the added amine is to form a coordinating enamine as the true transient directing group for Pd^{II}.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c00124.

Initial TDG screen, *trans*-stereochemistry determination, additional optimization reactions, raw data for reaction profiles, screen of pyridone ligands, DOE procedure and results, deuteration experiments, X-ray data for **3b** and **12**, experimental procedures and characterization data (PDF)

Accession Codes

CCDC 1970804−1970805 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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(9) See Supporting Information for details.

(10) The observation from the DOE study was that a relatively large loading of pyridine (70 mol%) enabled increased ArI loading without causing adverse side reactions.

(11) This reassigns the stereochemistry of the product reported by Ge (ref 8a) and is confirmed by X-ray analysis of the diarylated products **3b** and **12**.

(12) Yu first demonstrated the use of a β-amino amide TDG for transient C(sp^3)−H functionalization of *o*-tolualdehydes, binding through the carbonyl oxygen; see ref 6b.

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