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JOURNAL OF THE AMERICAN CHEMICAL SOCIETY
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Diverse *ortho*-C(sp^2)–H Functionalization of Benzaldehydes Using Transient Directing Groups

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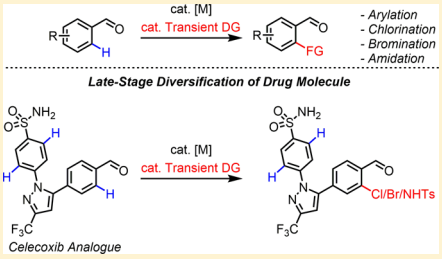
Supporting Information

ABSTRACT: Pd-catalyzed C–H functionalizations promoted by transient directing groups remain largely limited to C–H arylation only. Herein, we report a diverse set of *ortho*-C(sp^2)–H functionalizations of benzaldehyde substrates using the transient directing group strategy. Without installing any auxiliary directing group, Pd(II)-catalyzed C–H arylation, chlorination, bromination, and Ir(III)-catalyzed amidation, could be achieved on benzaldehyde substrates. The transient directing groups formed *in situ* via imine linkage can override other coordinating functional groups capable of directing C–H activation or catalyst poisoning, significantly expanding the scope for metal-catalyzed C–H functionalization of benzaldehydes. The utility of this approach is demonstrated through multiple applications, including late-stage diversification of a drug analogue.

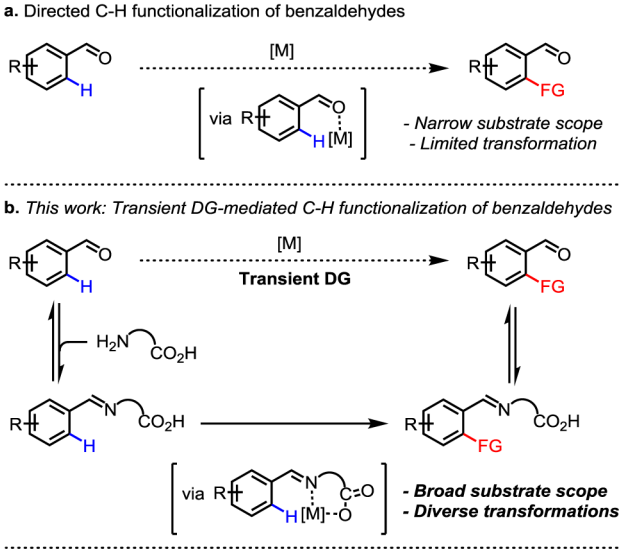


1. INTRODUCTION

Benzaldehydes are highly desirable substrates for directed C(sp^2)–H functionalization due to their abundance and synthetic versatility. Currently, however, only a handful of reports describe aldehyde-directed C–H functionalization with transition-metal catalysts.[1] The development of such methodology is impeded by the aldehyde's weak coordinating ability, susceptibility toward oxidation, and undesired metal insertion into acyl C–H bond (Scheme 1a). The weak coordinating ability of an aldehyde group is easily outcompeted by that of a wide range of functional groups, including amide, ester, and even ketone,[1e] which significantly restricts the substrate scope. Also, the scope of transformation is limited due to the difficulty of preferentially activating an inert aryl C–H bond over an aldehydic C–H bond, which can undergo either metal-free oxidation or metal insertion.[2,3] In order to address this issue, several groups have reported C–H functionalization methods using pre-installed imine or oxime directing groups.[4] However, the practicality of this strategy is compromised by additional steps required for installation/removal of the directing group.

As an alternative approach to overcome the present limitations, we focused on using the reversible imine formation between aldehyde and amines to direct metal catalysts. A pioneering study of Jun and co-workers demonstrated that 2-iminopyridyl moiety formed from reversible condensation of aldehyde and 2-aminopyridine can direct Rh insertion into acyl C(sp^2)–H bonds.[5] Also, Seayad and co-workers reported the Rh-catalyzed oxidative coupling of benzaldehydes using 4-trifluoromethylaniline to reversibly form an imine directing group.[6] More recently, our group disclosed the first Pd-catalyzed C(sp^3)–H functionalization of aldehydes and ketones using transient directing group (DG) strategy.[7] In this case,

Scheme 1. C(sp^2)–H Functionalization of Benzaldehydes



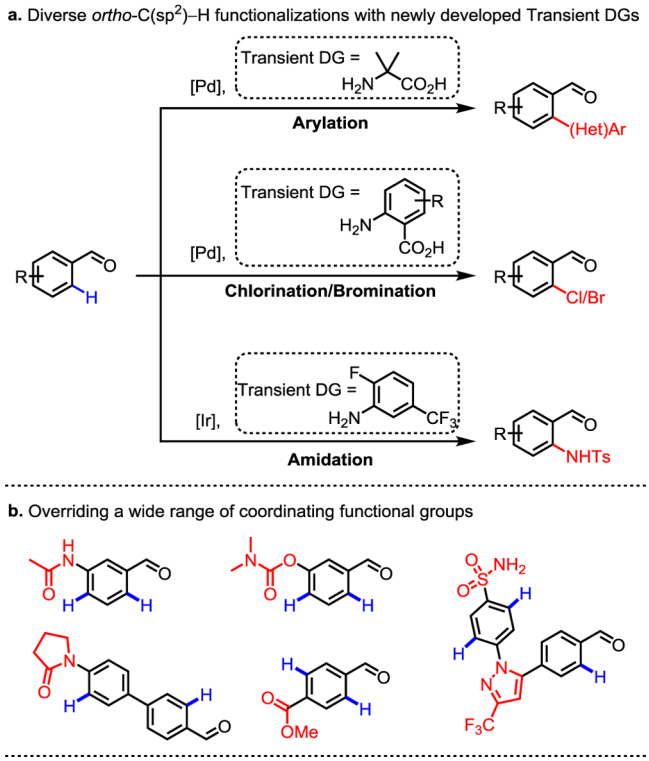
Received: October 26, 2016
Published: December 22, 2016

DOI: 10.1021/jacs.6b11188
J. Am. Chem. Soc. 2017, 139, 888–896

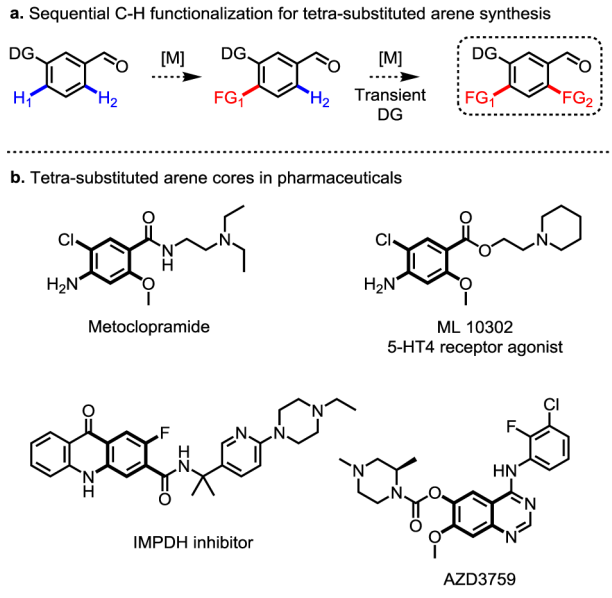
only a catalytic amount of amino acid is necessary to reversibly form an imino acid directing group for C(sp^3)−H activation. Subsequently, Hu[8] and Ge[9] also reported the C(sp^3)−H arylation of aldehyde substrates using acetohydrazide and β-Ala-OH as transient DGs, respectively. Based on these results, we further envisioned that this bidentate, transient DG strategy can be applied as a practical, and broadly useful approach for C(sp^2)−H functionalization of simple benzaldehyde substrates (Scheme 1b). First, the use of stoichiometric amount of reagents and additional steps for installation/removal of the directing group are avoided. Second, the bidentate binding mode can override other coordinating functional groups that can either direct C−H activation at other positions or poison the catalyst, which can significantly improve site-selectivity and broaden the substrate scope.

Herein, we report the development of a series of weakly coordinating transient DGs for diverse *ortho*-C(sp^2)−H functionalization reactions of benzaldehydes. Pd(II)-catalyzed arylation, chlorination, and bromination using bidentate amino acid-type transient DG, and Ir(III)-catalyzed amidation using monodentate aniline as a transient DG have been developed (Scheme 2a). To the best of our knowledge, C(sp^2)−H heteroarylation, chlorination, and bromination have not been achieved on benzaldehyde substrates to date. The aldehyde oxidation issue was circumvented by the careful choice of reaction conditions and oxidants that preferentially participate in the Pd(II)→Pd(IV) process. Also, unlike the previously reported aldehyde-directed C(sp^2)−H functionalization method,[1e] this new approach can override and tolerate the directing effects of a wide range of functional groups present within the aldehyde substrates, such as amides, carbamates, and heterocycles with complete site-selectivity (Scheme 2b). Thus, sequential C−H functionalizations in the absence and in the presence of transient DG allows multiple diversifications via C−H activation, which can lead to diverse tetra-substituted arene cores that are widespread in pharmaceuticals (Scheme 3).

Scheme 2. Diverse *ortho*-C(sp^2)−H Functionalizations Using Transient Directing Group Strategy



Scheme 3. Application toward Multi-substituted Arene Synthesis

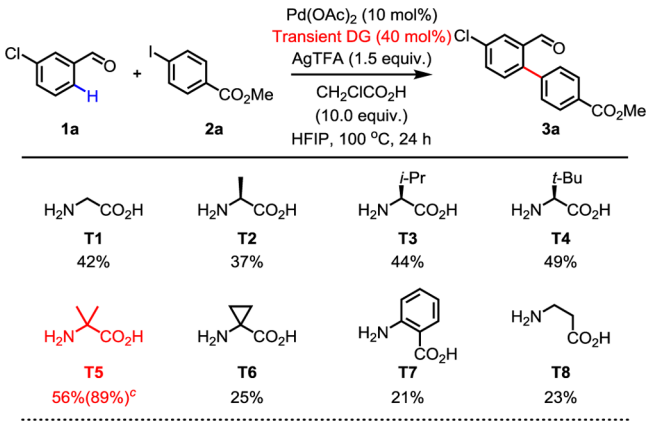


2. RESULTS AND DISCUSSION

2.1. Arylation. Our efforts to develop transient DGs to promote Pd-catalyzed C−H activation reactions have met with tremendous difficulties in the past decade. Our failure can be largely attributed to the use of strongly coordinating transient DGs which can result in formation of various unreactive Pd(II) complexes when they are covalently associated or dissociated with the substrates. In addition, the C−H insertion Pd(II) intermediates arisen from bischelation with these strongly coordinating directing group, even if generated, are often too stable for functionalization or dissociation of the transient DG. Progress was recently made by attaching a weakly coordinating carboxyl group to aldehydes and ketones via an imine linkage.[7] Based on this previous work on C(sp^3)−H arylation of aldehyde and ketone using α-amino acid as the transient DG, we began to develop diverse *ortho*-C(sp^2)−H activation reactions of simple benzaldehydes. *Ortho*-C(sp^2)−H arylation was selected as the first target as this can lead to wide range of biaryl compounds with synthetically useful formyl group. We first tested the effect of transient DG structure on the *ortho*-arylation of *m*-chlorobenzaldehyde (**1a**) with methyl 4-iodobenzoate (**2a**) (Table 1). While α-amino acids gave similar results (**T1**−**T4**), quaternary amino acid **T5** proved to be the best transient DG yielding 56% of the arylated product **3**. It is interesting to note that **T1** gave the best result for benzylic C(sp^3)−H activation in our previous study, which forms a 6-membered palladacycle unlike *ortho*-C(sp^2)−H activation (5-membered palladacycle). This implies that the 5-membered palladacycle formation is promoted by the smaller bite angle generated from the quaternary carbon center of **T5**. Indeed, cyclopropyl quaternary amino acid **T6**, which generates a larger bite angle due to the ring system, was far less effective.

DOI: 10.1021/jacs.6b11188
J. Am. Chem. Soc. 2017, 139, 888−896

Table 1. Optimization of *ortho*-C(sp^2)−H Arylation of Benzaldehyde[a,b]

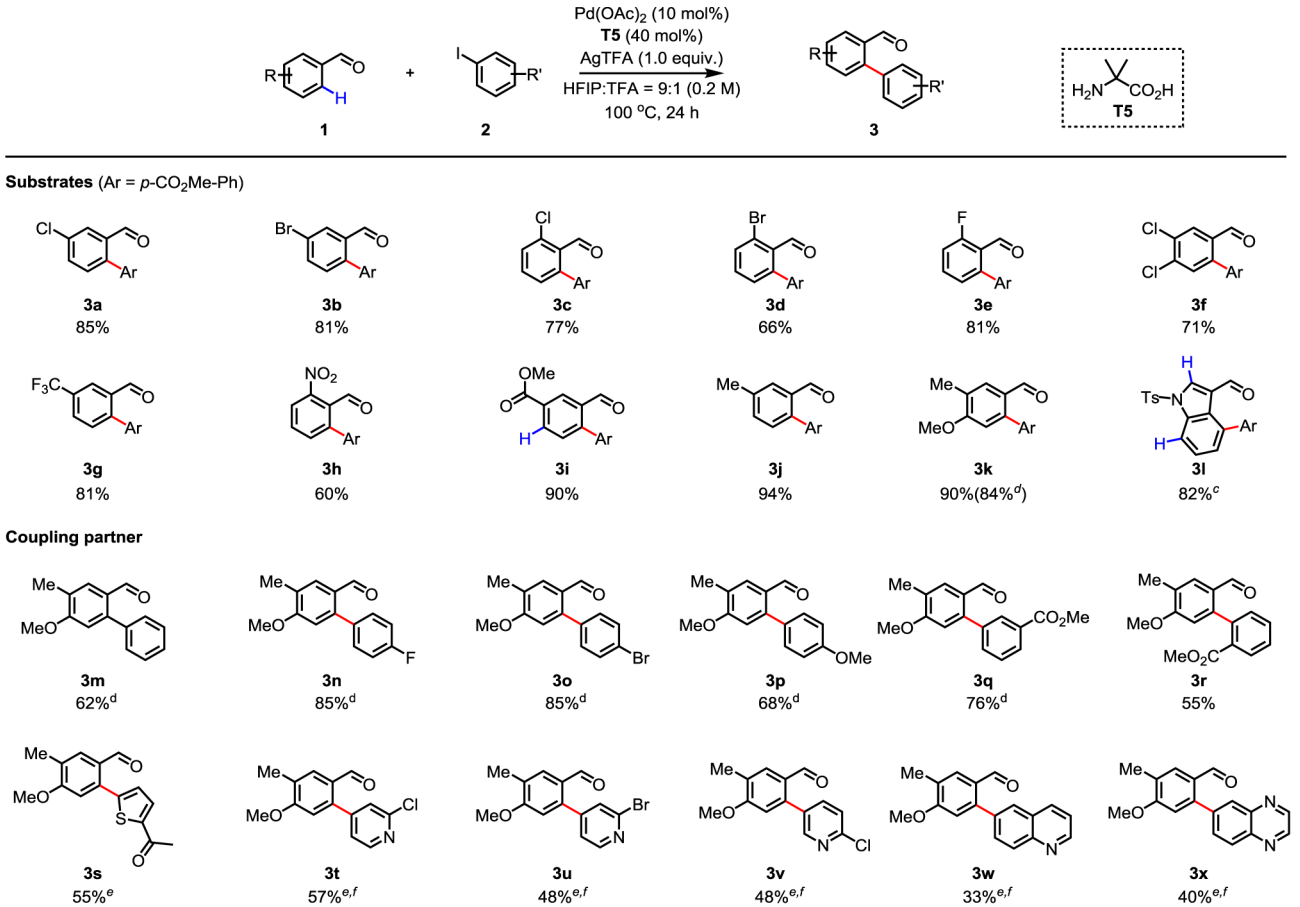


[a]Reaction conditions: substrate **1a** (0.1 mmol, 1.0 equiv), **2a** (2.0 equiv), $Pd(OAc)_2$ (10 mol%), transient DG (40 mol%), Ag(TFA) (1.5 equiv), CH_2ClCO_2H (10 equiv), HFIP (0.5 mL), 100 °C, 24 h. [b]The yield was determined by ^1H NMR analysis of the crude product using CH_2Br_2 as the internal standard. [c]HFIP:TFA = 9:1 was used instead of HFIP/CH_2ClCO_2H, and 1 equiv of Ag(TFA) was used.

Transient DGs that form 6-membered chelation (**T7**, **T8**) also afforded low yields. The result was further optimized to 89% NMR yield when the acid additive was replaced with TFA and the silver loading was lowered to 1 equiv (Table 1). A control experiment without using the transient DG gave no product formation.

With the optimized reaction conditions in hand, the *ortho*-C−H arylation was applied to different benzaldehyde substrates and aryl iodide coupling partners (Table 2). First, the scope of substrates was tested with **2a** as the coupling partner. Substrates with different halogen substitutions underwent arylation to provide the products in good to moderate yields (**3a**−**3f**). Both electron-withdrawing (**3g**−**3i**) and electron-donating substituents (**3j**, **3k**) were well tolerated to give the arylated products in excellent to moderate yields. To our delight, heterocyclic substrate 3-formylindole also underwent arylation at the 4-position to yield **3l** in 82% yield. Next, the scope of aryl iodides was tested. To prevent the decomposition of some aryl iodides, the acid was changed from TFA to AcOH or CH_2ClCO_2H. Under this modified condition, arylation was carried out smoothly regardless of the electronic property of the aryl iodide (**3k**, **3m**−**3p**). Also, both *meta*- and *ortho*-substituted aryl

Table 2. Scope of *ortho*-C(sp^2)−H Arylation of Benzaldehydes[a,b]



[a]Reaction conditions: substrate **1** (0.1 or 0.2 mmol, 1.0 equiv), **2** (2.0 equiv), $Pd(OAc)_2$ (10 mol%), **T5** (40 mol%), Ag(TFA) (1.0 equiv), HFIP:TFA = 9:1 (0.2 M), 100 °C, 24 h. [b]Isolated yields. [c]Substrate **1** (0.1 or 0.2 mmol, 1.0 equiv), **2** (3.0 equiv), $Pd(OAc)_2$ (10 mol%), **T5** (40 mol%), Ag(TFA) (2.0 equiv), HFIP (0.2 M), CH_2ClCO_2H or AcOH (10 equiv), 100 °C, 24 h. [d]110 °C. [e]Substrate **1** (0.1 mmol, 1.0 equiv), **2** (2.0 equiv), $Pd(OAc)_2$ (10 mol%), **T5** (20 mol%), Ag(TFA) (3.0 equiv), HFIP:AcOH = 1:1 (0.2 M), 110 °C, 24 h. [f]$Pd(OAc)_2$ (15 mol%) and **T5** (30 mol%) were used.

DOI: 10.1021/jacs.6b11188
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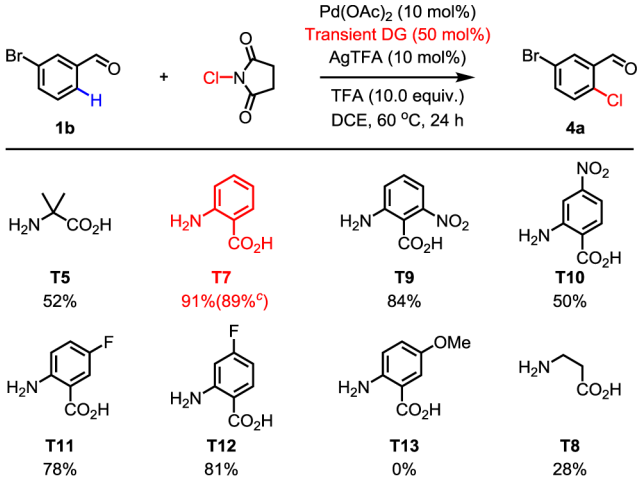
iodides were tolerated (**3q**, **3r**). Lastly, arylation with heteroaryl iodides was tested. We envisioned that the transiently formed bidentate directing group can sufficiently outcompete the coordinating ability of heterocyclic moieties and allow C−H heteroarylation. While simple iodopyridines and iodothiophenes did not yield any product, we were able to achieve heteroarylation when the 2-position of the heterocycles were substituted. The model substrate reacted with 2-acetyl-6-iodothiophene to give the product **3s** in 55% yield. With higher catalyst loading, iodopyridines also yielded heteroarylation products **3t**−**3v** in synthetically useful yields. Albeit low yield, heteroarylation also proceeded with both iodoquinoline and iodoquinoxaline to afford **3w** and **3x**, respectively.

2.2. Chlorination/Bromination. Aryl halides are extremely useful compounds due to their distinct role as precursors for organometallic reagents[10] and versatile application via transition-metal-catalyzed cross-coupling reactions.[11] Based on a number of reports on transition-metal-catalyzed C−H halogenation,[12] we sought to apply our transient DG strategy toward *ortho*-halogenation of benzaldehydes using *N*-halosuccinimide (NXS) as the oxidant. We first investigated the *ortho*-chlorination of **1b** with NCS as the chlorinating reagent. To our delight, we found that using **T5** as the transient DG with catalytic amount of AgTFA can yield the chlorinated product **4a** in 52% NMR yield (Table 3). Next, the transient DG

Table 3. Optimization of *ortho*-C(sp^2)−H Chlorination of Benzaldehyde[a,b]

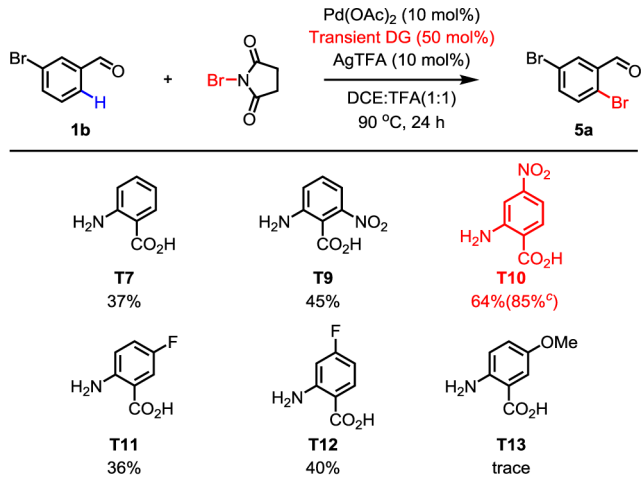


[a]Reaction conditions: substrate **1b** (0.3 mmol, 1.0 equiv), NCS (1.5 equiv), $Pd(OAc)_2$ (10 mol%), transient DG (50 mol%), Ag(TFA) (10 mol%), TFA (10 equiv), DCE (3 mL), 60 °C, 24 h. [b]The yield was determined by ^{1}H NMR analysis of the crude product using CH_2Br_2 as the internal standard. [c]30 mol% of transient DG was used.

scaffold was screened to further improve the result. It was interesting to find that unlike arylation, anthranilic acid **T7** proved to be the optimal transient DG for *ortho*-chlorination. While having electron-withdrawing groups on the anthranilic acid gave similar or lower yields (**T9**−**T12**), having electron-donating group completely inhibited the reaction (**T13**). Also, **T8** showed lower reactivity as transient DG for chlorination. Under optimized conditions, the NMR yield drops to 52% when catalytic Ag(TFA) is not added. The substantial enhancing effect of the catalytic Ag(TFA) is intriguing, and we believe that Ag(I) activates the NCS oxidant toward Pd(II)→Pd(IV) process by interacting with the halogen atom but without forming stoichiometric AgCl.

Next, we screened the reaction conditions for *ortho*-bromination using NBS as the brominating reagent. Gratifyingly, the *ortho*-brominated product **5a** was obtained in 37% NMR yield using similar reaction conditions with chlorination at higher temperature (Table 4, **T7**). Further screening of

Table 4. Optimization of *ortho*-C(sp^2)−H Bromination of Benzaldehyde[a,b]



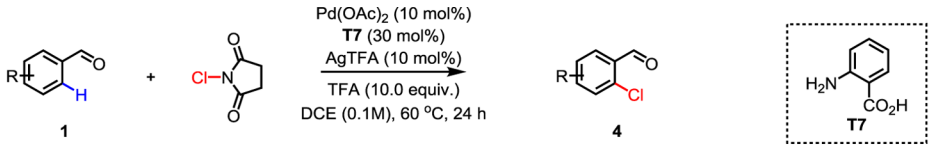
[a]Reaction conditions: substrate **1b** (0.3 mmol, 1.0 equiv), NBS (1.2 equiv), $Pd(OAc)_2$ (10 mol%), transient DG (50 mol%), Ag(TFA) (10 mol%), DCE:TFA = 1:1 (3.0 mL), 90 °C, 24 h. [b]The yield was determined by ^{1}H NMR analysis of the crude product using CH_2Br_2 as the internal standard. [c]1.0 equiv of *p*-TsOH was used as additive.

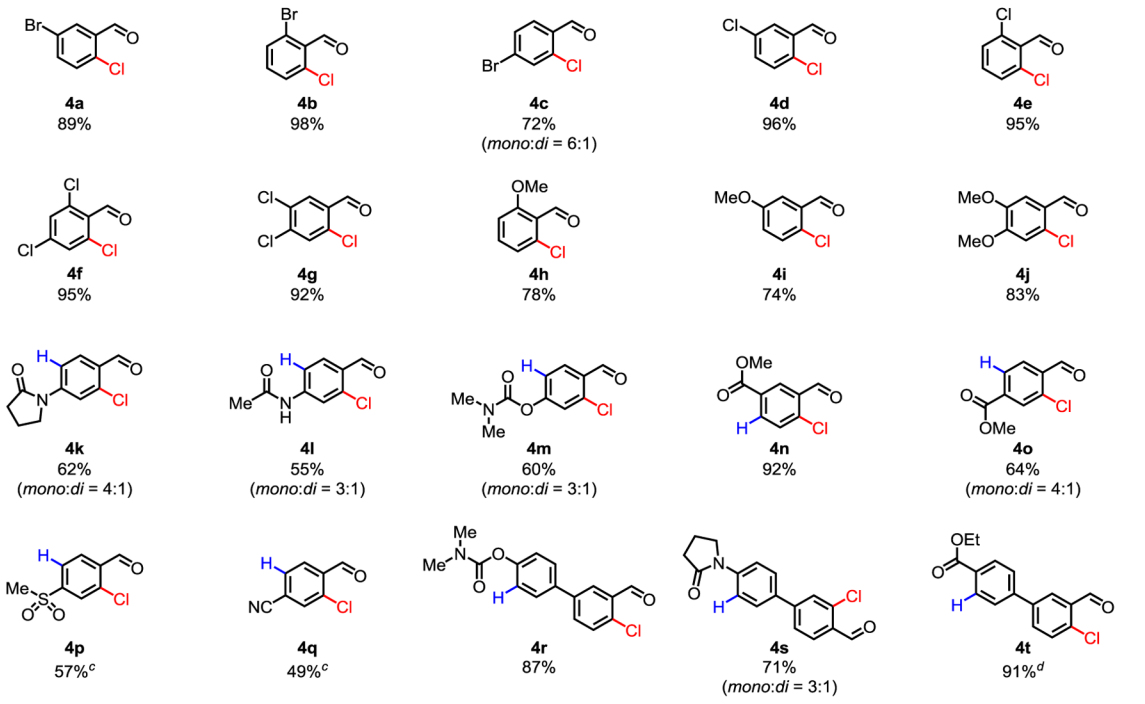
anthranilic acid derivatives led us to identify the electron-deficient 4-nitroanthranilic acid **T10** as the best transient DG, and 1 equiv of *p*-TsOH as a beneficial additive providing 85% NMR yield of **5a**. It was crucial to optimize the concentration of acid and transient DG, as these factors directly affect the equilibrium of the imine formation and catalytic turnover of the transient DG. The detrimental effect of a −OMe group in both chlorination and bromination implies the importance of weak coordination in achieving C−H functionalization reactivity.[13] Control experiments for both chlorination and bromination without using the transient DGs gave trace amounts of product formation.

We first examined the scope of benzaldehydes for the *ortho*-C(sp^2)−H chlorination reaction (Table 5). Benzaldehydes bearing different halogen substitutions (**4a**−**4g**), electron-donating groups (**4h**−**4m**), and electron-withdrawing groups (**4n**−**4q**) all underwent smooth chlorination to provide the corresponding products in moderate to excellent yields. Using transient DG, we were able to obtain exquisite site-selectivity *ortho* to the aldehyde group for substrates containing functional groups that are known to direct transition-metal catalysts for *ortho*−C-H activation, including ester (**4n**, **4o**), sulfone (**4p**), amide (**4k**, **4l**), carbamate (**4m**), and nitrile (**4q**). The high site-selectivity and efficiency were also pertained in biaryl substrates, where the aldehyde can override carbamate (**4r**), amide (**4s**), and ester (**4t**) that are placed on the different aryl ring. Next, we discovered that we can further push the reaction toward dichlorination when excess NCS was used under slightly more acidic condition (**4u**−**4y**). Both electron-donating and electron-withdrawing groups at the *para* position or the second aryl ring

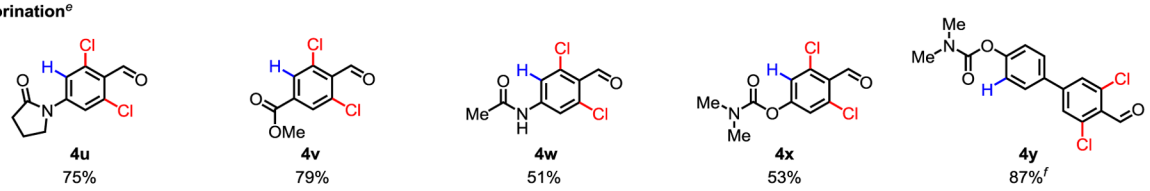
DOI: 10.1021/jacs.6b11188
J. Am. Chem. Soc. 2017, 139, 888−896

Table 5. Scope of *ortho*-C(sp^2)−H Chlorination of Benzaldehydes[a,b]





Dichlorination[e]



[a]Reaction conditions: substrate **1** (0.3 mmol, 1.0 equiv), NCS (1.5 equiv), Pd(OAc)$_2$ (10 mol%),**T7** (30 mol%), Ag(TFA) (10 mol%), TFA (10 equiv), DCE (3.0 mL), 60 °C, 24 h. [b]Isolated yields. [c]2.5 equiv of NCS was used. [d]4.0 mmol scale. [e]2.5 equiv of NCS, DCE:TFA = 4:1 (3.0 mL) were used. [f]5.0 mmol scale.

can be tolerated to give the dichlorinated product in moderate to good yields with complete site-selectivity. Also, the scalability of this transformation was demonstrated by gram-scale preparation of **4t** and **4y**.

Next, we evaluated the scope of the *ortho*-C(sp^2)−H bromination reaction (Table 6). Substrates with halogen substitutions at different position underwent bromination to give the corresponding products (**5a**−**5f**) in excellent to moderate yields. Both electron-donating groups (**5g**−**5i**) and electron-withdrawing groups (**5j**−**5m**) were tolerated as well, providing moderate yields of the products. Interestingly, we could carry out bromination on a thiophene ring (**5n**), showing the compatibility with heterocyclic substrates. Bromination was also achieved with biaryl substrates that contain coordinating functionalities on the other aryl ring (**5o**−**5q**). Indeed, in all of the above cases the transient imino acid directing group can completely override other directing functional groups such as ester, carbmate, amide, nitrile, and sulfone. Also, dibromination can be achieved when excess NBS was used (**5r**).

2.3. Amidation. Aromatic amines are widespread in pharmaceuticals and natural products.[14] Accordingly, a number of catalytic C(sp^2)−H amination/amidation reactions were reported in the past decade using different transition-metal species.[15] Among those methods, Ir(III)-catalyzed amidation using organic azides as nitrogen source has a number of advantages, including mild reaction condition (as low as room temperature), no byproduct except N_2, and no requirement for external oxidants.[16] Therefore, we decided to investigate whether our transient DG strategy could also be applied to C−H amidation reaction using Ir(III) catalysis.[17] After extensive screening, we found that anilines can serve as effective transient DGs for Ir-catalyzed amidation reaction with tosyl azide (Table 7). It is important to note that unlike the previous Pd-catalyzed reactions where bidentate amino acid-type transient DGs were used, a monodentate transient DG is utilized in this reaction. Next, the effect of substitution on the aniline transient DG was evaluated. With simple aniline **T14**, we observed 23% formation of the product **6**. When *p*-methoxy

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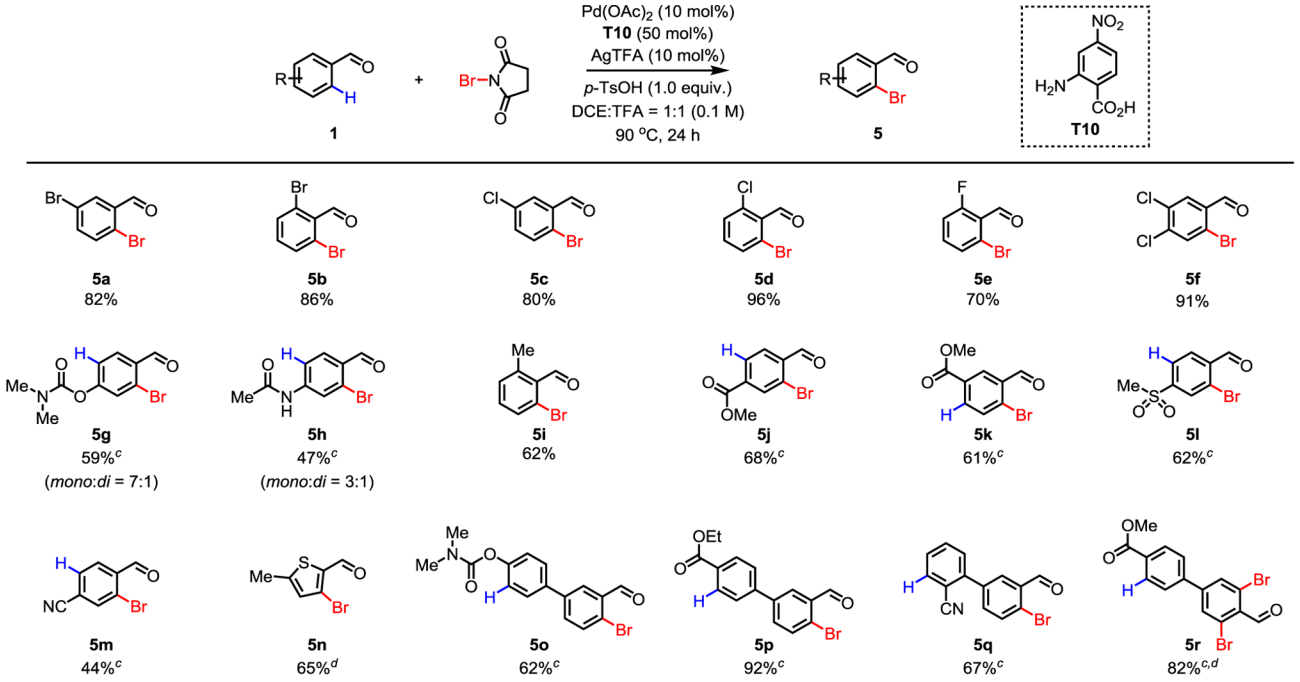
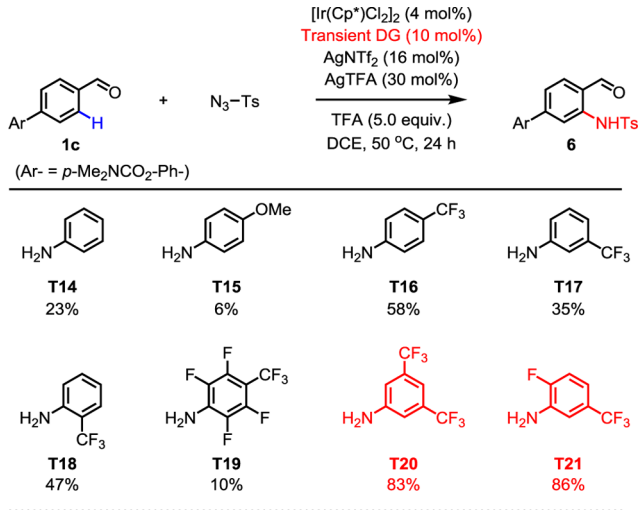
Table 6. Scope of *ortho*-C(sp^2)−H Bromination of Benzaldehydes[a,b]



[a]Reaction conditions: substrate **1** (0.3 mmol, 1.0 equiv), NBS (1.2 equiv), Pd(OAc)$_2$ (10 mol%), **T10** (50 mol%), Ag(TFA) (10 mol%),*p*-TsOH (1 equiv), DCE:TFA = 1:1 (3.0 mL), 90 °C, 24 h. [b]Isolated yields. [c]Substrate **1** (0.3 mmol, 1.0 equiv), NBS (1.5 equiv), Pd(OAc)$_2$ (10 mol%), **T10** (50 mol%), Ag(TFA) (10 mol%), TfOH (0.5 equiv), DCE (3.0 mL), 90 °C, 24 h. [d]2.0 equiv of NBS was used.

Table 7. Optimization of *ortho*-C(sp^2)−H Amidation of Benzaldehyde[a,b]



[a]Reaction conditions: substrate **1** (0.1 mmol, 1.0 equiv), TsN_3 (1.5 equiv), $[Ir(Cp^*)Cl_2]_2$ (4 mol%), transient DG (10 mol%), $Ag(NTf_2)$ (16 mol%), Ag(TFA) (30 mol%), TFA (5 equiv), DCE (1.0 mL), 50 °C, 24 h. [b]The yield was determined by ^{1}H NMR analysis of the crude product using CH_2Br_2 as the internal standard.

group is present (**T15**), the reaction only gave 6% of product, implying a similar trend with the previous halogenation reactions. Indeed, the yield was improved when electron-withdrawing CF_3 group was introduced at the *para* (**T16**), *meta* (**T17**), or *ortho* (**T18**) position. On the other hand, perfluorinated aniline (**T19**) was not effective, presumably due to the weak nucleophilicity of the aniline. These results led us to fine-tune the electronics of the aniline, and the optimal results were obtained with 3,5-bis(trifluoromethyl)aniline (**T20**) and 2-fluoro-5-(trifluoromethyl) aniline (**T21**), affording 83% and 86% of the amidation product, respectively. Under optimized conditions, the NMR yield drops to 16% when TFA is omitted, indicating the crucial effect of the acid. Most likely, the acid promotes the catalytic turnover of the transient DG. While the role of Ag(TFA) is currently unclear, it was not as crucial for the reaction to proceed (45% NMR yield without Ag(TFA)). Finally, a control experiment without using the transient DG gave no product formation.

Based on this optimized condition, we examined the scope of the amidation reaction (Table 8). Benzaldehydes with electron-donating carbamates (**6a**, **6b**), amides (**6c**), and sulfonamide (**6h**) smoothly reacted with tosyl azide to provide the amidated products in moderate to good yields with complete site-selectivity. Electron-withdrawing esters (**6d**, **6e**) and nitriles (**6f**, **6g**) were also well-tolerated to give moderate yields of the products. It is noteworthy that functional groups such as amide[16b] and ester[16c] groups are known to direct Ir-catalyzed amidation reaction, which clearly demonstrates the effectiveness of the transient DG strategy in overriding selectivity. As shown before, we also applied this system toward biaryl substrates with multiple coordinating groups. The transient DG can override the *ortho*-directing effect of carbamate (**6i**−**6k**), amide (**6l**−**6n**), and ester (**6o**, **6p**) groups on the different aryl ring.

2.4. Application. One of the key features we have shown in the above transformations is that we can selectively functionalize the C−H bond *ortho* to the aldehyde in the presence of a functional group that is also known to direct C−H functionalization. Accordingly, we can selectively synthesize multi-substituted aryl/biaryl compounds with our new C−H functionalization methods using transient DG in conjunction with previously known methods. In Scheme 4, we synthesized a

DOI: 10.1021/jacs.6b11188
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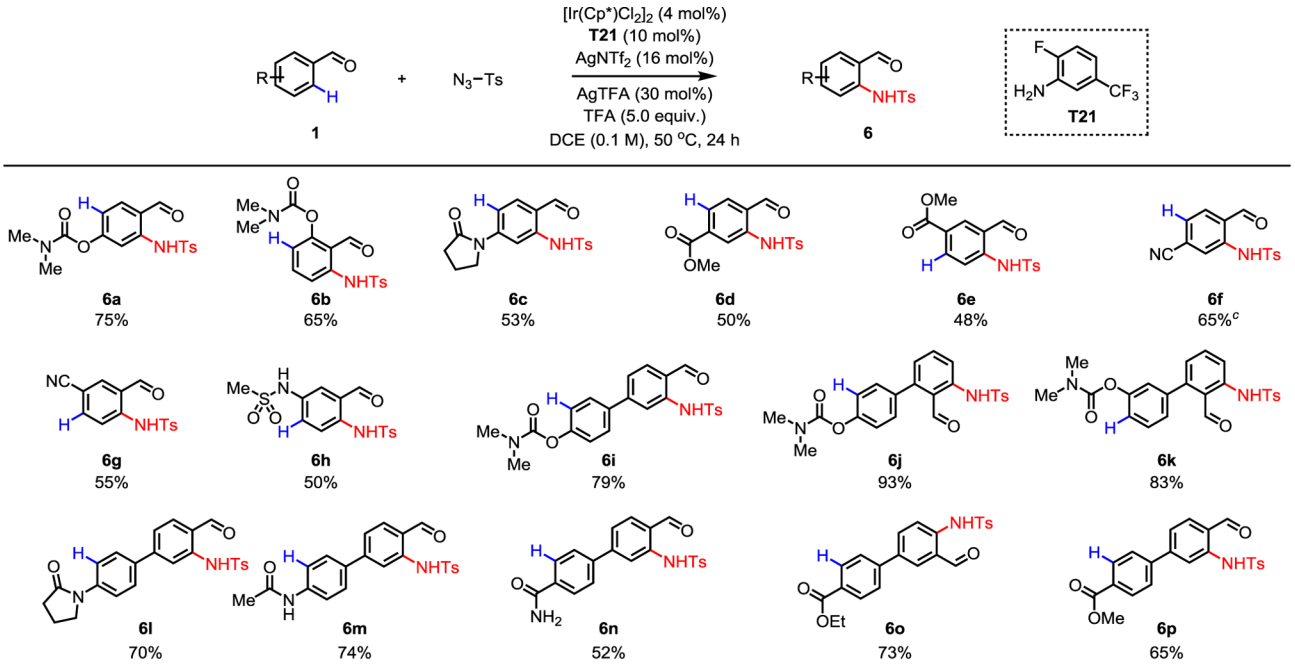
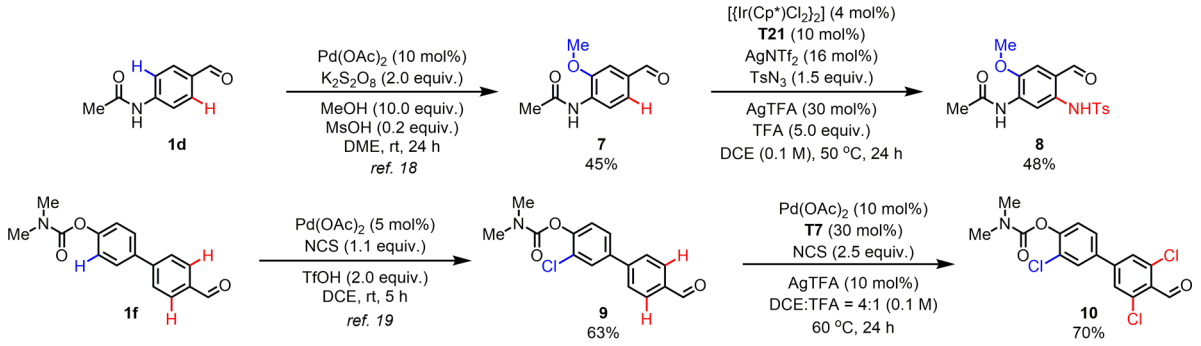
Table 8. Scope of *ortho*-C(sp^2)–H Amidation of Benzaldehydes[a,b]



[a]Reaction conditions: substrate **1** (0.2 mmol, 1.0 equiv), TsN_3 (1.5 equiv), $[Ir(Cp^*)Cl_2]_2$ (4 mol%), **T21** (10 mol%), $Ag(NTf_2)$ (16 mol%), Ag(TFA) (30 mol%), TFA (5 equiv), DCE (1.0 mL), 50 °C, 24 h. [b]Isolated yields. [c]**T20** was used instead of **T21**.

Scheme 4. Multi-substituted Arene Synthesis via Sequential C–H Functionalizations



tetra-substituted arene and penta-substituted biaryl compound via sequential C–H functionalization. In the first functionalization step without using any transient DG, Pd is directed toward the *ortho*-position of the anilide[18] and carbamate[19] group with complete site-selectivity. In the second functionalization step with transient DG, Pd is directed toward the *ortho*-position of the aldehyde group. Thus, an aldehyde group can be utilized as a latent directing group that is functional only in the presence of a transient DG.

Next, we sought to apply our methods to the late-stage diversification of drug molecules. Our group has reported a diverse set of C–H functionalizations on a celecoxib analogue, directed by an acidic sulfonamide group.[20] Here, we performed C–H chlorination, bromination, and amidation on a celecoxib analogue **11** using our newly developed transient DGs (Scheme 5). Remarkably, the transient DG can override the directing ability of both sulfonamide and pyrrazole with complete site-selectivity, allowing C–H functionalization on the other aryl ring. The versatility of aryl halides and anilines imply an additional element for diversification of this drug scaffold. Also, this example clearly demonstrates how transient DG-mediated C–H functionalization methods could potentially be utilized in pharmaceuticals containing multiple coordinating sites including heterocycles.

Lastly, in an attempt to demonstrate the synthetic utility of our new C–H functionalization methods, the *ortho*-functionalized benzaldehyde products were subjected to various annulation reactions to form valuable heterocyclic scaffolds. First, *ortho*-chlorobenzaldehydes were reacted with thioglycollic acid ethyl ester to form diverse benzothiophenes (Table 9).[21] Both electron-donating and electron-withdrawing substituents were well-tolerated, giving the desired benzothiophenes in moderate to good yields. Interestingly, the celecoxib analogue **11-Cl** also underwent smooth annulation, generating an additional heterocycle on its structure. Next, *ortho*-aminobenzaldehydes were reacted with nitroalkene **13**, to form *N*-Ts-1,2-dihydroquinolines with different substitutions in excellent to moderate yields (Table 10).[22] Again, the annulation was performed on the amidated celcoxib analogue **11-NHTs** which provided the corresponding product in excellent yield.

DOI: 10.1021/jacs.6b11188
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Scheme 5. Diversification of Celecoxib Analogue Using Transient DG Strategy

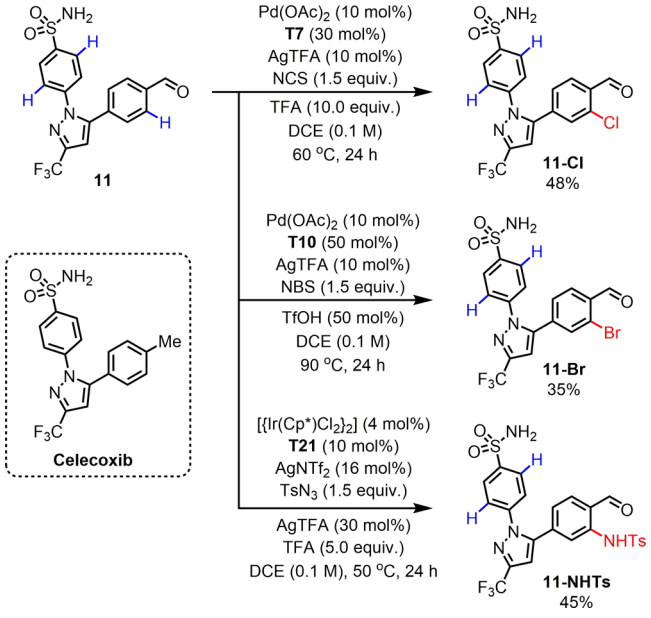
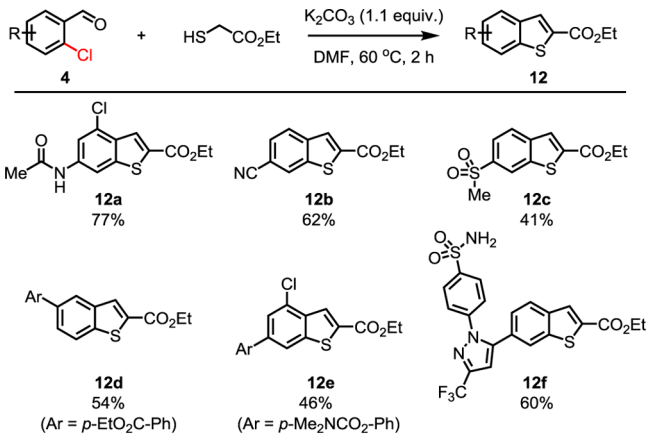


Table 9. Benzothiophene Synthesis from *o*-Chlorobenzaldehydes[a,b]

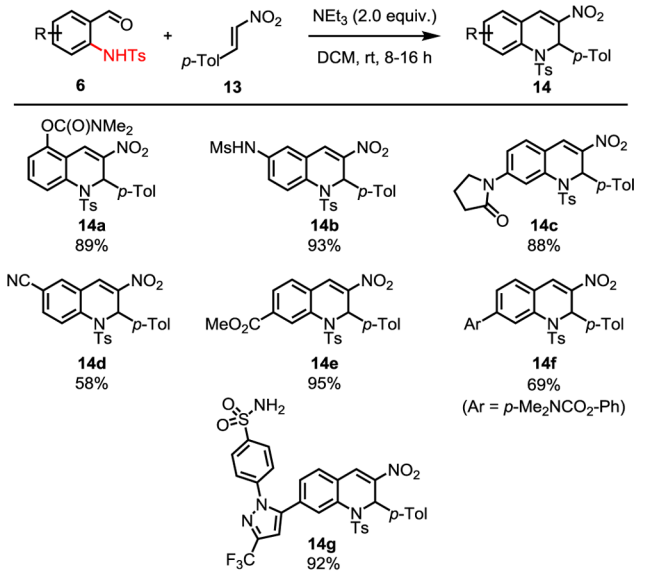


[a]Reaction conditions: **4** (0.2 mmol, 1.0 equiv), ethyl thioglycolate (1.0 equiv), K_2CO_3 (1.1 equiv), DMF (2.0 mL), 60 °C, 2 h. [b]Isolated yields.

3. CONCLUSION

In summary, a set of *ortho*-C(sp^2)−H functionalization methods of benzaldehydes using transient DG strategy has been disclosed. We developed Pd(II)-catalyzed arylation, chlorination, bromination, and Ir(III)-catalyzed amidation, indicating that a ubiquitous and versatile aldehyde group can also function as a competent directing group for various transformations. The transiently formed imino acid or imine directing group can override other directing functionalities such as amide, ester, carbamate, sulfonamide, and heterocycle, allowing a broad range of benzaldehyde substrates to undergo site-selective C−H functionalization. The selective syntheses of multi-substituted aryl/biaryl compounds via sequential C−H functionalization have been demonstrated. Also, our reaction conditions were directly applicable to a celecoxib analogue, allowing a late-stage diversification on a drug molecule. Finally,

Table 10. *N*-Tosyl-1,2-dihydroquinoline Synthesis from *o*-Aminobenzaldehydes[a,b]



[a]Reaction conditions: substrate **6** (0.1 mmol, 1.0 equiv), nitroalkene **13** (2.0 equiv), NEt_3 (2.0 equiv), DCM (2.0 mL), room temperature. [b]Isolated yields.

we demonstrated that our *ortho*-functionalization products can be readily transformed into valuable heterocycles, such as benzothiophenes and 1,2-dihydroquinolines.

4. EXPERIMENTAL SECTION

General Procedure for *ortho*-C−H Arylation of Benzaldehydes Using Bidentate Transient DG. A sealed tube with magnetic stir bar was charged with substrate **1** (0.10 mmol), $Pd(OAc)_2$ (0.01 mmol, 2.2 mg), **T5** (0.04 mmol, 4.1 mg), AgTFA (0.10 mmol, 22.1 mg), and **2a** (0.20 mmol, 52.4 mg) in air. Then, a premixed solution of HFIP:TFA = 9:1 (0.5 mL) was added. The reaction mixture was stirred at room temperature for 10 min, then at 100 °C for 24 h. Upon completion, the reaction mixture was cooled to room temperature, diluted with EtOAc, filtered through a silica gel plug, and concentrated *in vacuo*. The crude reaction mixture was purified by preparative TLC on silica gel using hexanes/EtOAc as the eluent to afford the desired products.

Full experimental details and characterization of new compounds can be found in the Supporting Information.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.6b11188.

Detailed experimental procedures and characterization of new compounds (PDF)

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DOI: 10.1021/jacs.6b11188
J. Am. Chem. Soc. 2017, 139, 888−896

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We gratefully acknowledge The Scripps Research Institute, Wuhan University of Technology, and the National Science Foundation (CHE-1465292) for financial support. We also thank Bristol-Meyers Squibb for financial support and providing chemicals. H.P. thanks the Korea Foundation for Advanced Studies for a predoctoral fellowship.

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DOI: 10.1021/jacs.6b11188
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