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Glycinamide hydrochloride as a transient directing group: Synthesis of 2-benzylbenzaldehydes by C(sp^3)−H arylation

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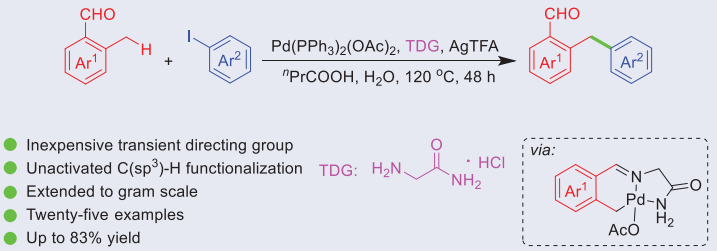
ABSTRACT

Glycinamide hydrochloride as an inexpensive and commercially available transient directing group for the C(sp^3)−H arylation of 2-methylbenzaldehydes is described. A series of practical 2-benzylbenzaldehydes bearing various functional groups are efficiently synthesized in satisfactory yield by this strategy. This method can also be extended to gram scale.

GRAPHICAL ABSTRACT



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KEYWORDS
Transient directing group; 2-benzylbenzaldehyde; glycinamide hydrochloride; C(sp^3)−H arylation; 2-methylbenzaldehyde

Introduction

In recent years, the transient directing group (TDG) strategy has attracted rising attention.[1–25] This strategy has become one of most efficient tools for transition-metal-catalyzed carbon-hydrogen bond functionalization. During this process (i) the transient directing group binds reversibly to the substrate; (ii) the conjunction of transient directing group and substrates coordinates with the transition metal to form the corresponding metallacycle; (iii) the expected product is furnished through the regeneration of transition-metal catalyst and the dissociation of transient directing group after reacting with the coupling partner. Compared with traditional carbon-hydrogen bond activation reactions,[26–31] the transient directing group assisted carbon-hydrogen activation reactions do not need covalent installation and removal of the stoichiometric directing groups. Therefore it can greatly improve the atom- and step-economy as well as the applicabilities.

The direct arylation of C(sp^3)−H with the transient directing group strategy is one of the most attractive reactions because it enables straightforward and economical

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syntheses of organic compounds containing aryl groups.[32–35] Recent years, this strategy has been used to the arylation of C(sp^3)−H in aliphatic aldehydes,[36,37] aliphatic ketones,[38] primary amines[39,40] and amino esters.[41]

2-Benzylbenzaldehydes are important structural scaffolds that can be converted into many fused rings,[42–45] natural products,[46,47] and biologically active compounds.[48,49] Due to the synthetic and biological importance of 2-benzylbenzaldehydes, much attention has been focused on the development of the related methodologies. Traditionally, the synthesis of 2-benzylbenzaldehydes largely rely on transformations of the regular functional groups, such as 2-benzylbenzyl alcohols,[50,51] *N*,*N*-dimethylcarboxamides,[52] and aromatic alcohols.[53] While these methods achieve satisfactory yield for 2-benzylbenzaldehydes, their cost-efficiency is hampered by the expensive and commercial unavailable starting materials. Other synthetic methods include *ortho*-site C(sp^2)−F,[54] C(sp^2)−O[55] benzylations of benzaldehydes with different benzyl reagents. However, prefunctionalized benzaldehydes must be prepared beforehand. After 2016, some transient directing groups, such as amino acids,[56,57] amino amides,[15,58,59] acetohydrazides[60] and semicarbazides,[61] were used to synthesize 2-benzylbenzaldehydes *via* C(sp^3)−H arylation of 2-methylbenzaldehydes, which represented a high-efficiency synthetic strategy. These successful examples verified that an effective transient directing group was the key for the synthesis of 2-benzylbenzaldehydes. Therefore, it is still necessary to explore novel and readily available transient directing group reagents and to expand the transient directing group reservoir for broad substrates.

In this paper, we report an efficient transient directing group reagent, glycinamide hydrochloride, which can be directly used without dehydrochlorination, for the C(sp^3)−H arylation of 2-methylbenzaldehydes to synthesize 2-benzylbenzaldehydes. To the best of our knowledge, glycinamide hydrochloride has never been described as a transient directing group reagent in C(sp^3)−H arylation of 2-methylbenzaldehydes.

Results and discussion

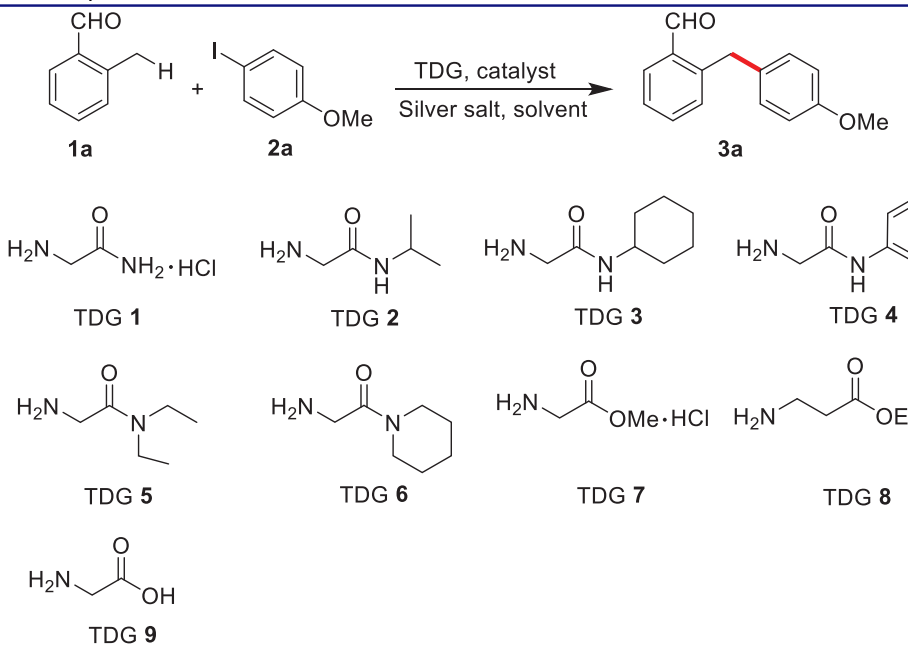
Initially, the reaction of 2-methylbenzaldehyde (**1a**) and 4-iodoanisole (**2a**) was selected as a model reaction to screen the optimal conditions. The model reaction was first tested in *n*-butyric acid using $Pd(PPh_3)_2Cl_2$ as a catalyst and stoichiometric amounts of AgTFA as an additive in the absence of a transient directing group reagent. However, no product was observed (Table 1, entry 1). When 0.4 equivalents of glycinamide hydrochloride (TDG **1**) as a transient directing group reagent was added, as expected, the desired product 2-(4-methoxybenzyl)benzaldehyde (**3a**) was obtained in 58% yield after the mixture was stirred at 120 °C for 48 h (Table 1, entry 2). In order to further improve the yield, the other palladium catalysts were also tested. $PdCl_2$, $Pd(OAc)_2$, $Pd(CH_3CN)_2Cl_2$, $Pd_2(dba)_3$ and $Pd(PPh_3)_2(OAc)_2$ could catalyze the reaction (Table 1, entries 3−7). However, only $Pd(PPh_3)_2(OAc)_2$ gave higher yield than $Pd(PPh_3)_2Cl_2$ (Table 1, entry 7). The other transition metal catalysts, such as $Cu(OAc)_2$, $FeCl_2$ and $Ni(OAc)_2$, were also checked but no catalytic effect was observed (Supporting information, Table S1). Decreased and increased amount of TDG **1** both could cause the apparent drop of the yield (Supporting information, Table S2). Compared with *n*-butyric acid, other solvents, such as isobutyric acid, acetic acid, formic acid, DMF, DMSO,

MeCN and DCE, were not applicable to the reaction (Table 1, entries 8, 9; Supporting information, Table S3). Water as an important additive could promote the decomposition of imine intermediates into aldehydes and glycinamide under acidic conditions. The amount of water had an impact on the yield. The reaction could achieve 75% yield of **3a** when the amount of water was increased to 100 μL from 50 μL (Table 1, entry 10). However more water or without water were unfavorable to the yield (Table 1, entries 11 − 13). The other silver compounds, such as AgOAc, Ag_2O and Ag_2CO_3 (Supporting information, Table S4), as additives did not give better yield than AgTFA (Table 1, entry 10). *N*-Monosubstituted glycinamides, such as *N*-isopropyl (TDG **2**), *N*-cyclohexyl (TDG **3**) and *N*-phenyl glycinamides (TDG **4**), and *N,N*-disubstituted glycinamides, such as *N,N*-diethyl glycinamides (TDG **5**) and 2-amino-1-(piperidin-1-yl)ethan-1-one (TDG **6**) as transient directing groups all afforded low yield because of the large steric hindrance (Table 1, entries 14 − 18). Methyl glycinate hydrochloride (TDG **7**) as a transient directing group could give the product in 69% yield (Table 1, entry 19). Inversely its analogue, ethyl 3-aminopropanoate hydrochloride (TDG **8**), could not produce **3a** at all (Table 1, entry 20). When glycine (TDG **9**) was used as a transient directing group, the moderate yield (47%) of **3a** was afforded (Table 1, entry 21). In addition, increase of the equivalents of AgTFA and **2a** could not improve the yield of **3a** (Supporting information, Table S7).

With the optimized conditions in hand, the generality of the protocol was first examined through the reactions of 2-methylbenzaldehyde (**1a**) with a wide array of iodobenzenes (**2**). As depicted in Table 2, both electron-donating and electron-withdrawing groups on the aromatic rings of iodobenzenes **2** could be directly coupled with 2-methylbenzaldehyde (**1a**) to afford the target products. In general, iodobenzenes **2** bearing electron-donating groups, such as MeO (**3a**) and Me (**3c**, **3d**), on the aromatic rings afforded the products in higher yields than those bearing electron-withdrawing groups, such as F (**3f**), Br (**3g**, **3h**), CF_3 (**3i**), NO_2 (**3j**) and COOMe (**3l**). Iodobenzenes **2** bearing *ortho*-substituted aromatic ring (**3e**) gave lower yield than those bearing *meta*- and *para*-substituted aromatic rings because of the large steric hindrance. Dichloro-substituted iodobenzene could furnish the corresponding product in good yield (**3m**). 1-Iodonaphthalene was also found to be compatible with the reaction and gave the corresponding product in 39% yield (**3n**). The reaction of 4-iodobenzoic acid with **1a** in acetic acid could give the product in 83% yield (**3k**). Heteroaromatic iodides, such as 4-iodopyridine and 2-iodothiophene, were not applicable to this reaction system, and the corresponding products and other by-products could not be observed (**3o**, **3p**). The possible reason is that the strong coordinating ability of heteroatoms can cause the deactivation of metal catalyst.

In addition, the scope of 2-methylbenzaldehydes (**1**) bearing different substituents was also examined by their reactions with 4-iodoanisole (**2a**) (Table 3). 2-Methylbenzaldehyde **1** bearing both electron-donating (**3q**−**3s**) and electron-withdrawing groups (**3t**−**3w**) on the aromatic rings could be directly coupled with 4-iodoanisole (**2a**) to afford the target products in satisfactory yields. The electronic effect of substituents of 2-methylbenzaldehydes **1** was not obvious in these reaction systems. 3-Methylthiophene-2-carbaldehyde was able to give the corresponding C(sp^3)−H arylation

Table 1. Optimization of reaction conditions[a].



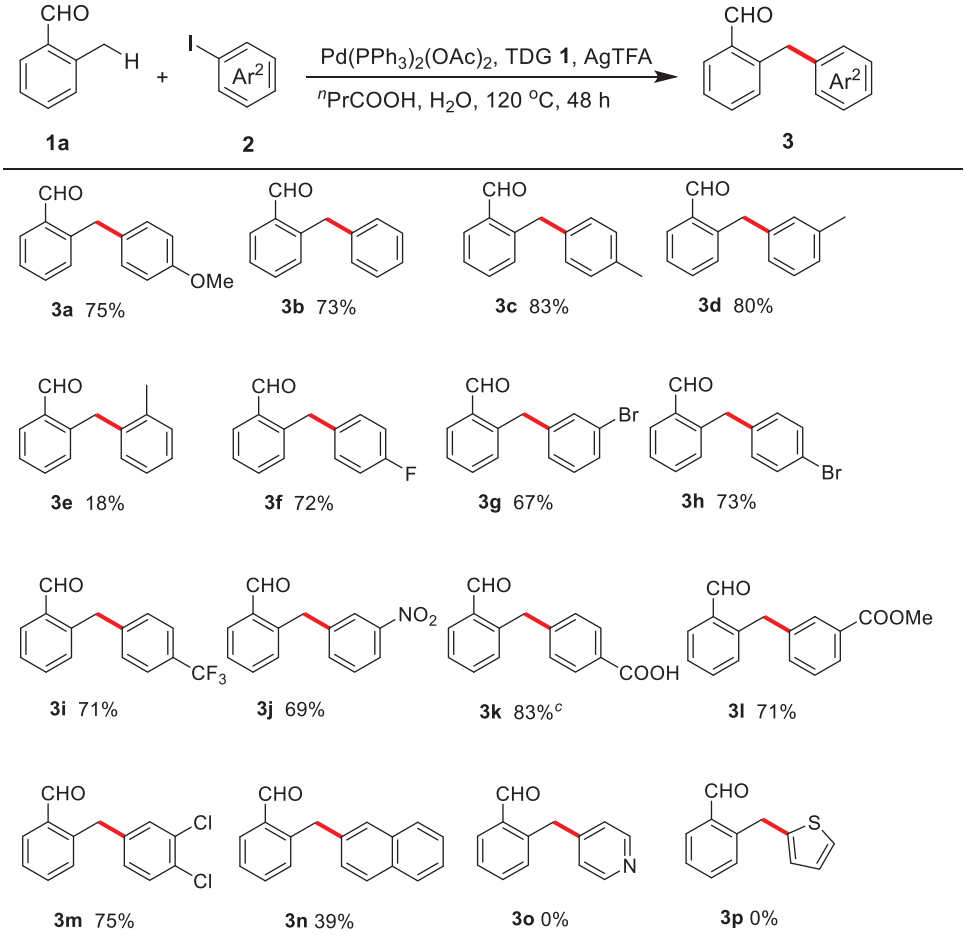
Entry	Catalyst	Silver salt (equiv)	Solvent	TDG (equiv)	Yield (%)[b]
1	$Pd(PPh_3)_2Cl_2$	AgTFA (2.0)	^{n}PrCOOH	None	0
2	$Pd(PPh_3)_2Cl_2$	AgTFA (2.0)	^{n}PrCOOH	TDG **1** (0.4)	58
3	$PdCl_2$	AgTFA (2.0)	^{n}PrCOOH	TDG **1** (0.4)	46
4	$Pd(OAc)_2$	AgTFA (2.0)	^{n}PrCOOH	TDG **1** (0.4)	42
5	$Pd(CH_3CN)_2Cl_2$	AgTFA (2.0)	^{n}PrCOOH	TDG **1** (0.4)	44
6	$Pd_2(dba)_3$	AgTFA (2.0)	^{n}PrCOOH	TDG **1** (0.4)	47
7	$Pd(PPh_3)_2(OAc)_2$	AgTFA (2.0)	^{n}PrCOOH	TDG **1** (0.4)	67
8	$Pd(PPh_3)_2(OAc)_2$	AgTFA (2.0)	^{i}PrCOOH	TDG **1** (0.4)	29
9	$Pd(PPh_3)_2(OAc)_2$	AgTFA (2.0)	HOAc	TDG **1** (0.4)	28
10	$Pd(PPh_3)_2(OAc)_2$	AgTFA (2.0)	^{n}PrCOOH	TDG **1** (0.4)	75[c]
11	$Pd(PPh_3)_2(OAc)_2$	AgTFA (2.0)	^{n}PrCOOH	TDG **1** (0.4)	69[d]
12	$Pd(PPh_3)_2(OAc)_2$	AgTFA (2.0)	^{n}PrCOOH	TDG **1** (0.4)	52[e]
13	$Pd(PPh_3)_2(OAc)_2$	AgTFA (2.0)	^{n}PrCOOH	TDG **1** (0.4)	38[f]
14	$Pd(PPh_3)_2(OAc)_2$	AgTFA (2.0)	^{n}PrCOOH	TDG **2** (0.4)	23[c]
15	$Pd(PPh_3)_2(OAc)_2$	AgTFA (2.0)	^{n}PrCOOH	TDG **3** (0.4)	7[c]
16	$Pd(PPh_3)_2(OAc)_2$	AgTFA (2.0)	^{n}PrCOOH	TDG **4** (0.4)	25[c]
17	$Pd(PPh_3)_2(OAc)_2$	AgTFA (2.0)	^{n}PrCOOH	TDG **5** (0.4)	6[c]
18	$Pd(PPh_3)_2(OAc)_2$	AgTFA (2.0)	^{n}PrCOOH	TDG **6** (0.4)	11[c]
19	$Pd(PPh_3)_2(OAc)_2$	AgTFA (2.0)	^{n}PrCOOH	TDG **7** (0.4)	69[c]
20	$Pd(PPh_3)_2(OAc)_2$	AgTFA (2.0)	^{n}PrCOOH	TDG **8** (0.4)	0[c]
21	$Pd(PPh_3)_2(OAc)_2$	AgTFA (2.0)	^{n}PrCOOH	TDG **9** (0.4)	47[c]

[a]Reaction condition: **1a** (0.2 mmol), **2a** (0.3 mmol), Ag salt (appropriate amount), TDG (appropriate amount), catalyst (0.02 mmol) and H_2O (50 μL) in 2 mL of solvent were stirred at 120 °C for 48 h.
[b]Isolated yield.
[c]H_2O (100 μL).
[d]H_2O (200 μL).
[e]H_2O (500 μL).
[f]Without H_2O.

product in 46% yield (**3x**). However, 3-methylpicolinaldehyde did not give the corresponding product possibly due to the strong coordination effect of pyridine ring (**3y**).

In addition, 2-ethylbenzaldehyde instead of 2-methylbenzaldehyde could be similarly arylated by 1-fluoro-4-iodobenzene to give 2-(1-(4-fluorophenyl)ethyl)benzaldehyde (**3z**)

Table 2. C(sp^3)−H arylation of 2-methylbenzaldehyde (**1a**) with various iodobenzenes **2**[a,b].



[a]Reaction conditions: 2-Methylbenzaldehyde **1a** (0.2 mmol), iodobenzenes **2** (0.3 mmol), AgTFA (0.4 mmol), glycinamide hydrochloride (TDG **1**) (0.08 mmol), $Pd(PPh_3)_2(OAc)_2$ (0.02 mmol) and H_2O (100 μL) in 2 mL of ^{n}PrCOOH were stirred at 120 °C for 48 h.
[b]Isolated yields.
[c]AcOH (2 mL) as solvent.

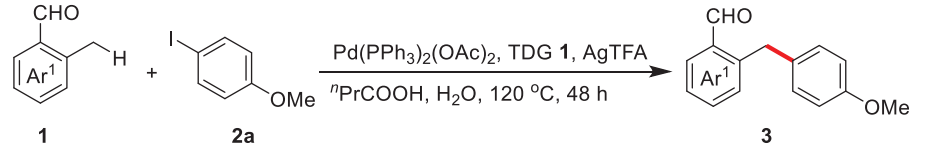
in 33% yield, indicating that the secondary C(sp^3)−H bond could also be functionalized, but the yield was low (Scheme 1).

In the same way, the C(sp^3)−H arylation of 2.6-dimethylbenzaldehyde with 4-iodoanisole (**2a**) was conducted under the standard conditions. The desired product **3aa** was afforded in moderate yield (Scheme 2).

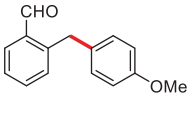
Similarly, the C(sp^3)−H arylation of 2-methylbenzaldehyde (**1a**) with 1.3-diiodobenzene was also tested. The target product **3ab** was obtained in 28% yield (Scheme 3).

With the success over generality of the protocol, the reaction of 2-methylbenzaldehyde (**1a**) with 4-iodoanisole (**2a**) was also performed on gram scale (Scheme 4). The reaction of 0.60g of 2-methylbenzaldehyde (**1a**) with 1.76 g of 4-iodoanisole (**2a**) in the presence of 2.21g of AgTFA, 0.22g of glycinamide hydrochloride (TDG **1**), 0.37g of $Pd(PPh_3)_2(OAc)_2$ and 2.5 mL of H_2O in ^{n}PrCOOH (50 mL) was performed under the

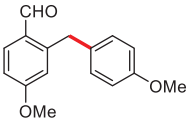
Table 3. C(sp^3)—H arylation of various 2-methylbenzaldehydes **1** with 4-iodoanisole (**2a**)[a,b].



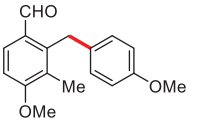
1 **2a** **3**



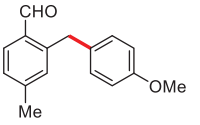
3a 75%



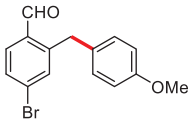
3q 71%



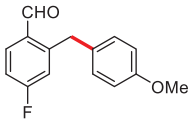
3r 71%



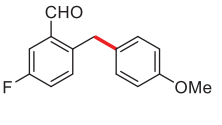
3s 48%



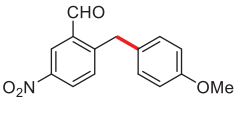
3t 67%



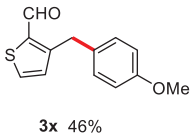
3u 69%



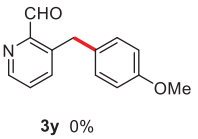
3v 72%



3w 69%

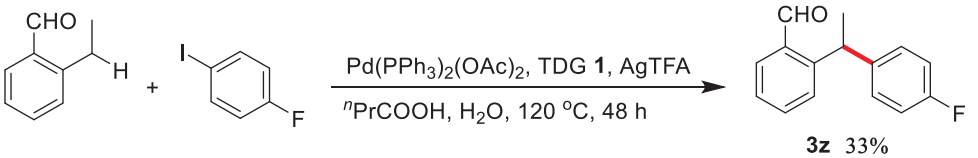


3x 46%



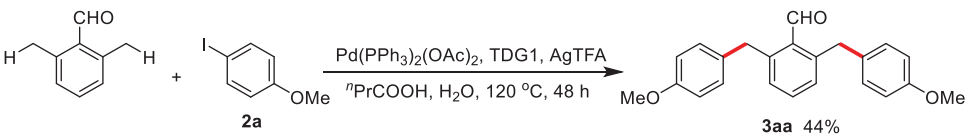
3y 0%

[a]Reaction conditions: 2-Methylbenzaldehydes **1** (0.2 mmol), 4-iodoanisole **2a** (0.3 mmol), AgTFA (0.4 mmol), glycinamide hydrochloride (TDG **1**) (0.08 mmol), $Pd(PPh_3)_2(OAc)_2$ (0.02 mmol) and H_2O (100 μL) in 2 mL of ^{n}PrCOOH were stirred at 120 °C for 48 h.
[b]Isolated yields.



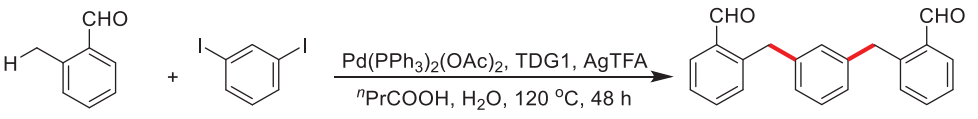
3z 33%

Scheme 1. C(sp^3)—H arylation of 2-ethylbenzaldehyde with 1-fluoro-4-iodobenzene.



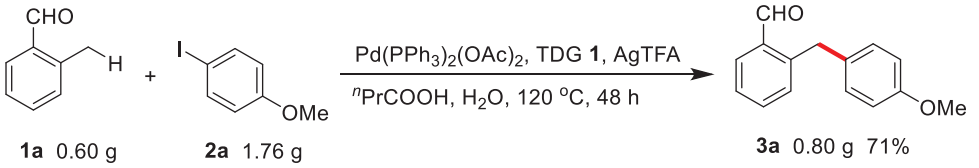
2a **3aa** 44%

Scheme 2. C(sp^3)—H arylation of 2.6-dimethylbenzaldehyde with 4-iodoanisole.

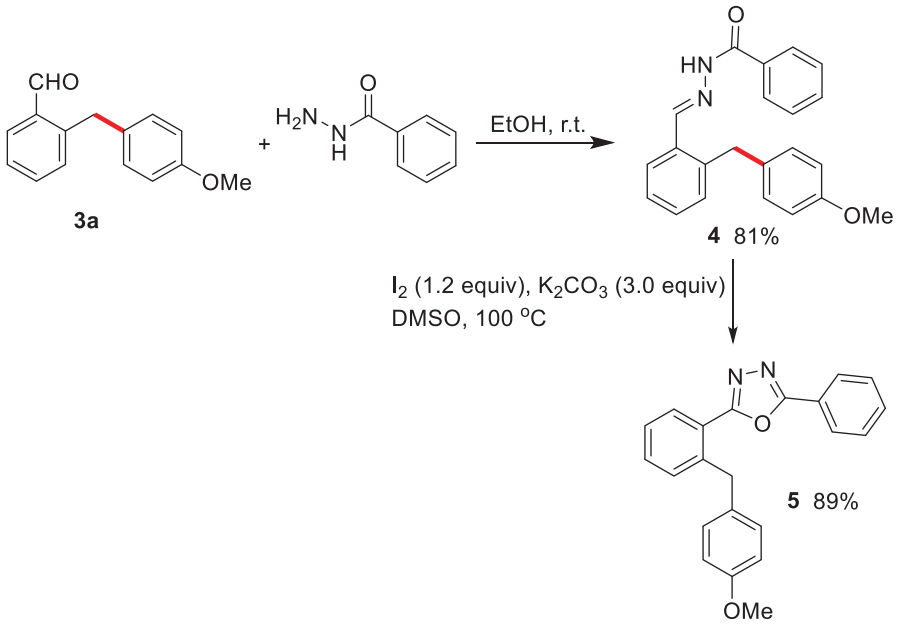


1a **3ab** 28%

Scheme 3. C(sp^3)—H arylation of 2-methylbenzaldehyde with 1,3-diiodobenzene.



Scheme 4. Gram-scale synthesis of **3a**.



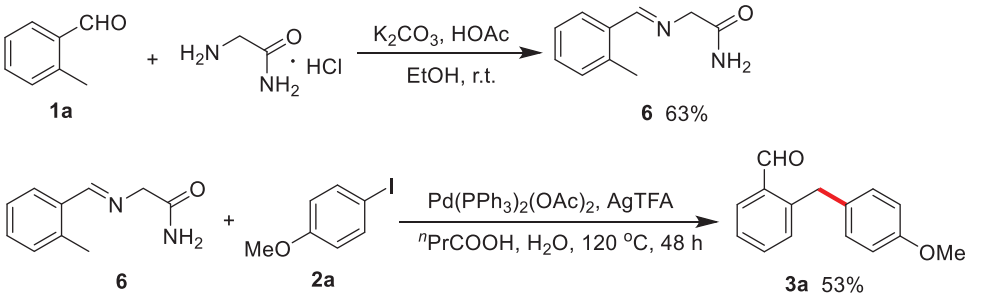
Scheme 5. Synthetic applications of **3a**.

optimized condition to give 0.80g of **3a** in 71% isolated yield. This success of gram scale reaction further showed the potency of optimized condition for the bulk processes.

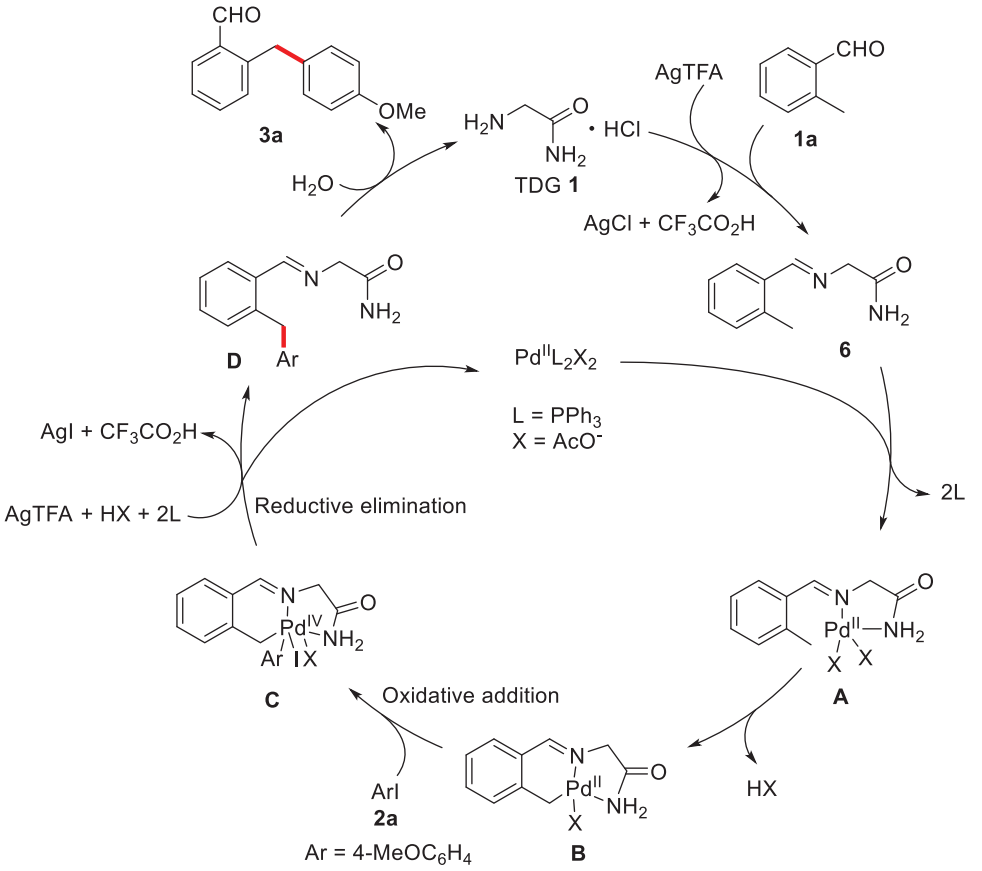
The synthesized products can be found many applications in organic synthesis. For example, the reaction of product **3a** with benzohydrazide in ethanol at room temperature could prepare corresponding acylhydrazone **4** in 81% yield,[62] which may be applied to pesticides, medicine and analytical reagents. Furthermore compound **4** could be further used to synthesize 1,3,4-oxadiazole **5** in 89% yield under iodine-mediated conditions,[63] which may be used in anti-inflammatory, anti-bacterial, anesthetic, analgesic and growth regulator fields (Scheme 5).

To gain insight into the reaction mechanism, some control experiments were carried out (Scheme 6). The reaction of 2-methylbenzaldehyde (**1a**) with glycinamide hydrochloride (TDG **1**) could first give (*E*)-2-((2-methylbenzylidene)amino)acetamide (**6**) in 63% yield. Compound **6** further reacted with 4-iodoanisole (**2a**) under standard reaction conditions (without TDG) to afford product **3a** in 53% yield. This result indicated that **6** might be the key intermediate for this reaction.

On the basis of the above control experiments, a plausible reaction mechanism is proposed for product **3a** (Scheme 7). The reaction of 2-methylbenzaldehyde (**1a**) with glycinamide hydrochloride (TDG **1**) first gives (*E*)-2-((2- methylbenzylidene)amino)acetamide



Scheme 6. Control experiments.



Scheme 7. The proposed reaction mechanism for **3a**.

(**6**) as an intermediate. Then two nitrogen atoms of **6** coordinate with palladium to produce active species **A.** This active species may be different from the literature method using aceto-hydrazide as a transient directing group, which uses one nitrogen and one oxgen as the coordinating atoms.[60] **A** undergoes a process of C−H bond activation forms [6,5]-bicyclic palladium intermediate **B**. Then the oxidative addition of intermediate **B** with 4-iodoanisole (**2a**) produces Pd(IV)-intermediate **C**. In the presence of AgTFA, Pd(IV)-intermediate **C** is then subjected to a reduction elimination process to produce intermediate **D** and release

catalyst Pd(II). At last, intermediate **D** is hydrolyzed to give the final product **3a** and release the transient directing group reagent TDG **1**.

Conclusion

In summary, an efficient method using inexpensive and commercially available glycinamide hydrochloride as a transient directing group for the practical synthesis of 2-benzylbenzaldehydes through C(sp^3)−H arylation of 2-methylbenzaldehydes has developed. The reactions can tolerate a variety of functional groups, and give 2-benzylbenzaldehydes in satisfactory yields. The method can also be extended to gram scale, and the resulting products can be found applications for the synthesis of important fine chemicals.

Experimental

Unless otherwise noted, all commercial materials were used without further purification. The reactions were monitored by TLC (thin layer chromatography) method; column and preparative TLC purification were carried out using silica gel. Melting points were uncorrected and recorded on X-4 melting point apparatus. ^{1}H NMR and ^{13}C NMR spectra were measured on 400/600 MHz and 100/150 MHz spectrometers, and ^{19}F NMR spectra was measured on 376/564 MHz spectrometers (NMR in $CDCl_3$ or DMSO-d_6 with TMS as an internal standard) respectively, and recorded as ppm. HRMS were measured with APEX II 47e mass spectrometer.

General procedure for the synthesis of 2-benzylbenzaldehydes (3a − 3z)

A reaction tube (15 mL) with magnetic stir bar was charged with 2-methylbenzaldehyde (0.2 mmol), aryl iodide (0.3 mmol), silver trifluoroacetate (88.4 mg, 0.4 mmol), $Pd(PPh_3)_2(OAc)_2$ (15.0 mg, 0.02 mmol), glycinamide hydrochloride (8.8 mg, 0.08 mmol), *n*-butyric acid (2 mL) and H_2O (100 µL) in air. The reaction tube was sealed and allowed to stir at ambient temperature for 30 min, then heated to 120 °C for 48 h. Upon completion, the reaction mixture was cooled to room temperature, filtered through a silica gel plug, and the filtrate was diluted with dichloromethane and washed with saturated sodium carbonate solution. The resulting organic phase was dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was isolated by column chromatography using petroleum ether and ethyl acetate or petroleum ether and dichloromethane as the eluent to give pure 2-benzylbenzaldehyde.

^{1}H NMR and ^{13}C NMR spectra for the products are available in the Supplementary information.

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