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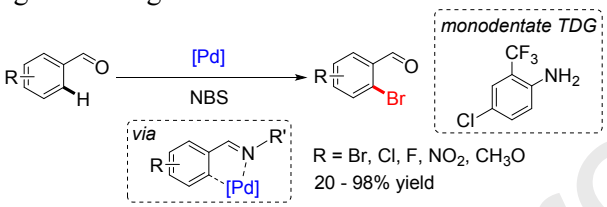

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Palladium-catalyzed *ortho*-C(sp^2)−H bromination of benzaldehydes *via* a monodentate transient directing group strategy

Qiyun Yong,[a] Bing Sun[a,] ∗ and Fang-Lin Zhang[a,] ∗

[a] *School of Chemistry, Chemical Engineering and Life Sciences, Wuhan University of Technology, Wuhan 430070, PR China*

ARTICLE INFO

∗ Corresponding author. e-mail: bing.sun@whut.edu.cn (B. Sun)

∗ Corresponding author. e-mail: fanglinzhang@whut.edu.cn (F.-L. Zhang)

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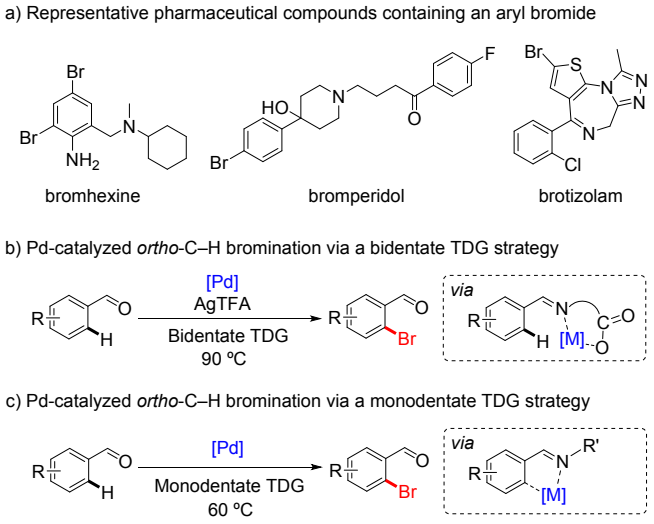
ABSTRACT

A facile and efficient monodentate transient directing group strategy was developed to enable the palladium-catalyzed *ortho*-C(sp^2)–H bromination of benzaldehydes. A broad scope of benzaldehydes were transformed into the desired products by employing 2-amino-5-chlorobenzotrifluoride as a monodentate transient directing group, demonstrating good functional group tolerance. Mild reaction conditions and no requirement for a silver salt are also features of this strategy.

1. Introduction

Aryl halides are widely utilized as important precursors for organometallic reagents as well as transition-metal-catalyzed cross-coupling partners.[1] In addition to these general features, aryl bromides are considered as building blocks for valuable classes of pharmaceutical compounds. Bromhexine, bearing an aryl dibromide subunit, is well known as an expectorant in the treatment of respiratory disorders and mucus.[2] Bromperidol is a bromine analog of haloperidol hydrochloride, which acts as an antipsychotic in the treatment of schizophrenia.[3] Brotizolam is a sedative-hypnotic drug with a thienodiazepine bromide pharmacophore (Scheme 1a).[4] The growing practical value of aryl bromides has attracted extensive attention toward their efficient synthesis.[5]

In recent years, transition-metal-catalyzed transient-directing-group (TDG)-mediated C−H functionalization has emerged as a powerful tool to access complex molecules.[6] Pioneering work by the Yu group disclosed that amino acids could be employed as bidentate TDGs for the Pd-catalyzed C(sp^3)−H arylation of *o*-alkyl benzaldehydes and ketones, featuring no auxiliary installation and the removal of stoichiometric directing groups.[7] Subsequently, a set of nitrogen-based small molecules were reported as suitable bidentate TDGs for diverse C–H functionalizations.[Error! Reference source not found.] However, the transition metal-catalyzed bromination of C(sp^2)–H bonds *via* bidentate TDG remains rare.



Scheme 1. Representative pharmaceuticals containing aryl bromides (a), the previously reported synthetic approach (b),[9] and the present work (c).

An example was demonstrated in a collaborative report by Yu and our group, where the *ortho*-C(sp^2)−H bromination of a broad scope of benzaldehydes were catalyzed by Pd with 4-nitroanthranilic acid as a bidentate TDG (Scheme 1b).[8] Nevertheless, this bidentate TDG pattern typically requires an *in situ* formed neutral imine coordinating site and a second coordinating site on the directing group to form the reactive metallocycle species. Meanwhile, the addition of a silver salt reduced the atom-economy of this strategy. Alternatively, the monodentate TDG strategy, where an *in situ* formed imine could be directly coordinated to transition metals to access the

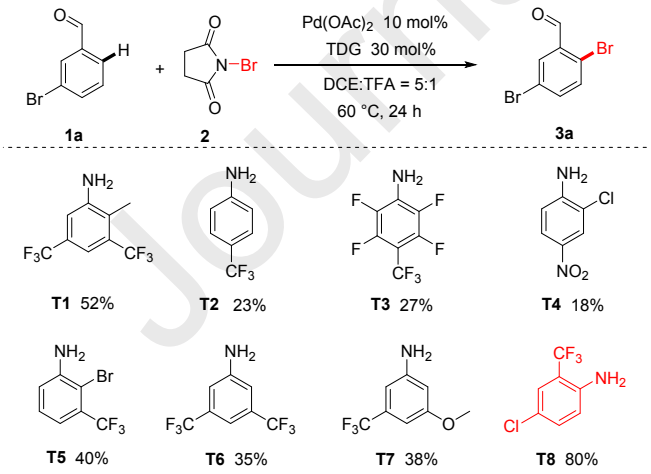
meta
H functionalization. Recently, we reported the Pd-catalyzed *ortho*-C−H methoxylation and chlorination of benzaldehydes by employing 3-(trifluoromethyl)-aniline as a monodentate TDG, either with or without the assistance of an external ligand, where a broad product scope was obtained with moderate to excellent yields.[10] To the best of our knowledge, there are no reports covering Pd-catalyzed C–H bromination *via* monodentate TDG strategies. Therefore, in this work we report the facile and efficient Pd-catalyzed *ortho*-C(sp²)–H bromination of benzaldehydes *via* a monodentate TDG strategy under mild reaction conditions without the addition of silver salts or an external ligand (Scheme 1c).

2. Results and Discussion

We initiated our investigation by screening various monodentate TDGs for the model reaction of *m*-bromobenzaldehyde **1a** (1.0 eq.) with *N*-bromosuccinimide **2** (NBS, 1.5 eq.) to afford 2,5-dibromobenzaldehyde **3a** (Table 1). The initial experiments were conducted with 10 mol% $Pd(OAc)_2$ as catalyst and 30 mol% ligand in a mixed solvent of DCE and TFA (v:v = 5:1) at 60 °C for 24 h. A series of anilines with different substituents were tested as monodentate TDGs. 2-Amino-5-chlorobenzotrifluoride (**T8**) proved to be the best TDG for this reaction, affording the brominated product **3a** in 80% yield.

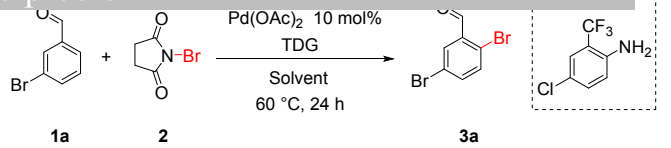
Next, optimization of the reaction conditions was carried out. As summarized in Table 2, the solvent screening showed that the presence of TFA was essential to trigger the reaction, albeit excess TFA inhibited the yields (Table 2, entries 1-7). A maximum yield of 80% was obtained in the mixed solvent of DCE and TFA (v:v = 5:1). Next, the amount of NBS was examined to improve the yield. Gratifyingly, lowering the amount of NBS to 1.2 eq. was beneficial to the reaction (Table 2, entry 9). However, lowering the amount of NBS (1.0 eq.) sharply decreased the yield (Table 2, entry 8). Finally, we optimized the amount of TDG (**T8**) and observed that 20 mol% gave the best yield (Table 2, entry 11). More or less **T8** was unfavorable to promoting the reaction (Table 2, entries 10 and 12).

Table 1. Transient directing group screening.[a]



[a] Reagents and conditions: **1a** (0.1 mmol), **2** (1.5 eq.), $Pd(OAc)_2$ (10 mol%), TDG (30 mol%), DCE (1 mL), TFA (0.2 mL), 60 °C, 24 h. Isolated yield after column chromatography.

Table 2. Optimization of the reaction conditions.[a]



Entry	Solvent (v:v)	NBS	**T8** (mol%)	Yield **3a** (%)
1	DCE	1.5 eq.	30%	NR
2	DCE:TFA=10:1	1.5 eq.	30%	77%
3	DCE:TFA=5:1	1.5 eq.	30%	80%
4	DCE:TFA=4:1	1.5 eq.	30%	74%
5	DCE:TFA=1:1	1.5 eq.	30%	71%
6	TFA	1.5 eq.	30%	68%
7	DCE:HOAc=5:1	1.5 eq.	30%	NR
8	DCE:TFA=5:1	1.0 eq.	30%	62%
9	DCE:TFA=5:1	1.2 eq.	30%	83%
10	DCE:TFA=5:1	1.2 eq.	10%	37%
11	**DCE:TFA=5:1**	**1.2 eq.**	**20%**	**86%**
12	DCE:TFA=5:1	1.2 eq.	40%	78%

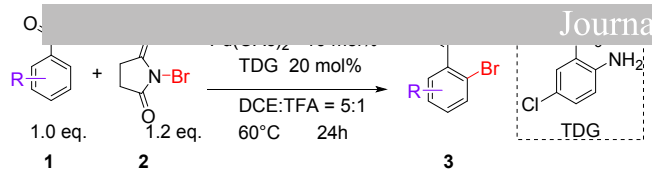
[a] Reagents and conditions: **1a** (0.1 mmol), $Pd(OAc)_2$ (10 mol%), solvent, 60 °C, 24 h. Isolated yield after column chromatography.

With the optimized reaction conditions in hand, the substrate scope was examined (Table 3). First, we evaluated the compatibility of this strategy with various electron-donating or electron-withdrawing mono-substituents at different positions of the benzaldehydes, such as halogen (**3a-e**), methyl (**3f**), methoxy (**3g**) and nitro (**3h**) groups at the *ortho* or *meta* sites. Generally, moderate to good yields were obtained, except for the methoxy and nitro groups which led to lower yields (**3g-h**). Additionally, the position of the halogen substituent has no significant effect. Good yields were obtained for disubstituted benzaldehydes with different halogen groups (**3i-l**). For disubstituted benzaldehydes containing both halogen and methyl groups, moderate yields were obtained (**3m-p**). Dimethyl benzaldehyde substituted at different positions gave moderate yields (**3q-r**), and trimethyl benzaldehyde gave a low yield due to steric hindrance (**3s**). For benzaldehydes with methoxy groups, moderate yields were obtained (**3t-w**). 2-Naphthylbenzaldehyde also gave an excellent yield (**3x**). The thiophene aldehyde underwent bromination in an acceptable yield (**3y**), providing a potential candidate for the synthesis of benzothiophene carboxamide derivatives for application as inhibitors of plasmodium falciparum enoyl-ACP reductase.[11]

Next, we examined the utility of the monodentate TDG strategy in the dibromination of benzaldehydes, which can be potentially applied for diverse late-stage functionalizations to access complex bioactive molecules.[12] As shown in Table 4, a low yield (29%) was obtained for dibromination product **5a** when 1.5 eq. NBS was used (Table 4, entry 1). When the amount of NBS was increased to 2.5 eq., an excellent yield of 73% was obtained (Table 4, entry 4).

Under the optimal reaction conditions, the substrate scope for dibromination was examined to introduce two bromine atoms at *ortho* positions (Table 5). For benzaldehydes bearing methyl (**5a**), benzyl (**5b**) and methyl 4-methylbenzoate (**5c**) substituents at the *para* position, the electronic properties exerted negligible effects on the reactivity and selectivity. The desired products were afforded with good to excellent yields (67-82%).

Table 3. Scope of the *ortho*-C(sp²)−H bromination of benzaldehydes.[a]



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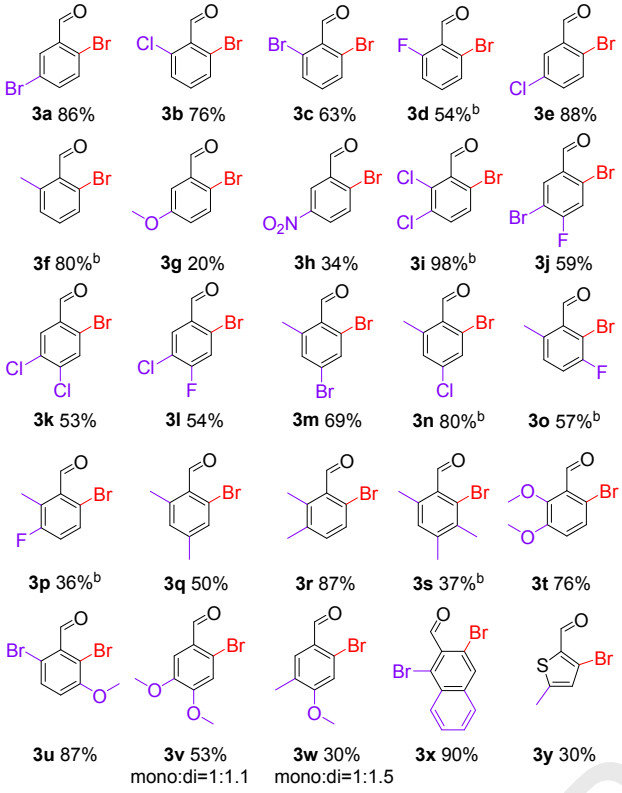
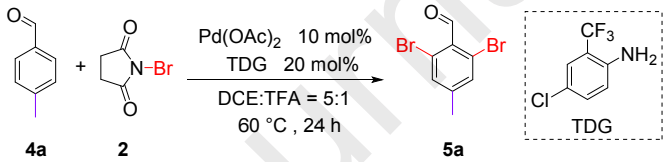


[a] Reagents and conditions: **1** (0.4 mmol), **2** (1.2 eq.), $Pd(OAc)_2$ (10 mol%), TDG (20 mol%), DCE (2.5 mL), TFA (0.5 mL), 60 °C, 24 h. Isolated yield after column chromatography. [b] **1** (0.2 mmol), **2** (1.2 eq.), $Pd(OAc)_2$ (10 mol%), TDG (20 mol%), DCE (1 mL), TFA (0.2 mL), 60 °C, 24 h.

Table 4. Optimization of the reaction conditions.[a]



4a 2 5a

Entry	NBS	Yield **5a** (%)
1	1.5 eq.	29%
2	2.0 eq.	42%
3	2.3 eq.	65%
4	**2.5 eq.**	**73%**

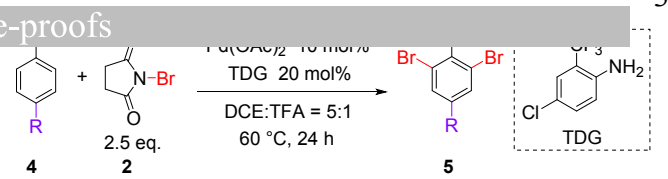
[a] Reagents and conditions: **4a** (0.1 mmol), **2**, $Pd(OAc)_2$ (10 mol%), TDG (20 mol%), DCE (1 mL), TFA (0.2 mL), 60 °C, 24 h. Isolated yield after column chromatography.

3. Conclusion

We have developed an efficient Pd-catalyzed *ortho*-C(sp^2)–H bromination of benzaldehydes *via* a monodentate TDG strategy which proceeds under mild conditions without the addition of silver salts or an external ligand.

Table 5.

Scope of the *ortho*-C(sp^2)−H dibromination of benzaldehydes[a]



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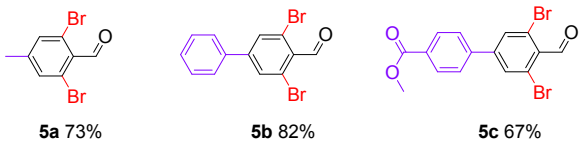

[a] Reagents and conditions: **4** (0.4 mmol), **2** (2.5 eq.), $Pd(OAc)_2$ (10 mol%), TDG (20 mol%), DCE (2.5 mL), TFA (0.5 mL), 60 °C, 24 h. Isolated yield after column chromatography.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found in the online version containing experimental procedures and characterization data for all new compounds.

- An efficient monodentate transient directing group strategy was developed.
- *Ortho*-C–H bromination of benzaldehydes was catalyzed by Pd via Monodentate TDG.
- Mild reaction conditions and no addition of silver salt are featured.

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