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Acetohydrazone: A Transient Directing Group for Arylation of Unactivated C(sp^3)−H Bonds

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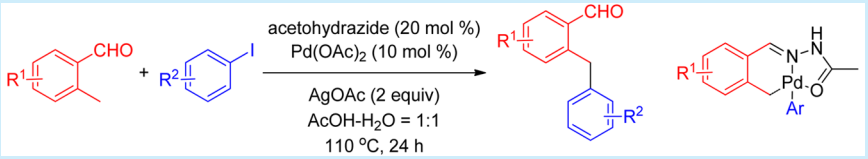
Supporting Information



ABSTRACT: A straightforward and efficient method has been developed for the synthesis of 2-benzylbenzaldehyde derivatives from 2-methylbenzaldehyde and iodobenzene via a C(sp^3)−H activation process. In the course of the activation reaction, acetohydrazone is formed between 2-benzylbenzaldehyde and acetohydrazine as a transient directing group. As a new kind of transient directing group, acetohydrazone exhibits a remarkable directing effect to give corresponding products in good to excellent yields.

2-Benzylbenzaldehyde derivatives are an important intermediate which are used widely for the synthesis of fused ring compounds,[1] spiro compounds,[2] natural products,[3] and biologically active compounds.[4] Due to the importance of these compounds, a lot of methods for the synthesis of them have been reported: (i) oxidation of 2-benzylbenzyl alcohol;[3b,4a,5] (ii) Suzuki cross-coupling reaction;[1a,6] (iii) Vilsmeier reaction;[7] (iv) Kumada−Tamao−Corriu reaction;[8] (v) C−F[9] or C−H[10] activation reaction. Although a number of modified methods under improved conditions have been reported, many of them suffer from drawbacks such as unsatisfactory yields, poor substrate tolerance, difficult-to-obtain starting materials, and the use of stoichiometric and/or relatively expensive reagents. Therefore, searching for more facile and practical synthetic routes to 2-benzylbenzaldehyde derivatives is still highly desirable work.

During the past decades, C−H activation reactions have become powerful tools in modern organic synthesis.[11] In general, a directing group is required to covalently bind to substrates and then form a bidentate coordination with a transition metal to control selectivity and facilitate reactivity in C−H activation reaction.[12] However, these processes have two significant shortcomings: (i) a directing group must be introduced to the substrate in advance which dramatically increased the workload; (ii) the removal of the directing groups from product always needs harsh reaction conditions. In this paper, in order to solve the problems mentioned above, a transient directing group is put forward which includes three processes: (i) the formation of a transient directing group; (ii) the C−H activation process; (iii) the removal of the directing group.

As shown in Figure 1, we tried to introduce acetohydrazone to the substrate as a transient directing group.[13] After

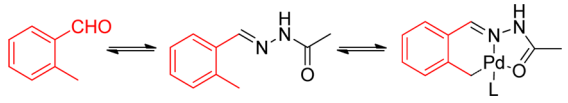


Figure 1. Acetohydrazone as transient directing group.

completion of the C−H activation reaction, the transient directing group was removed by hydrolysis. To verify our idea, the reaction of 2-methylbenzaldehyde (**1a**) and 1-iodo-4-methoxybenzene (**2a**) was carried out using Pd(OAc)$_2$ as the catalyst, AgOAc as the oxidant, and acetohydrazide as the additive in AcOH. The mixture was stirred at 120 °C for 24 h, and the desired product 2-(4-methoxybenzyl)benzaldehyde (**3a**) was obtained in 64% yield. This result clearly indicated that introducing acetohydrazone as the transient directing group was a feasible route. To improve the yield and optimize the reaction conditions, this model reaction was carried out under different conditions, and the results are summarized in Table 1.

Preliminary experiments suggested that the solvents had a significant impact on the model reaction. Hence, various solvents, such as toluene, 1,4-dioxane, DMF, DMSO, MeCN, EtOH, and AcOH, were applied to promote this coupling reaction. As shown in Table 1, the reaction could not proceed smoothly to obtain the corresponding product **3a** except for

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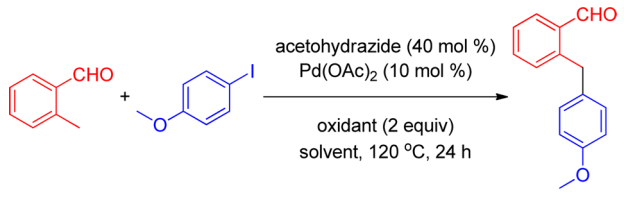
Table 1. Optimization of the Reaction Conditions[a]



1a 2a 3a

entry	solvent	oxidant	yield[b] (%)
1	toluene	AgOAc	0
2	1,4-dioxane	AgOAc	0
3	DMF	AgOAc	0
4	DMSO	AgOAc	0
5	MeCN	AgOAc	0
6	EtOH	AgOAc	0
7	AcOH	AgOAc	64
8	AcOH−H_2O = 2:3	AgOAc	81
9	AcOH−H_2O = 1:1	AgOAc	85
10	AcOH−H_2O = 2:1	AgOAc	80
11	AcOH−H_2O = 4:1	AgOAc	80
12	AcOH−H_2O = 8:1	AgOAc	77
13	AcOH−H_2O = 1:1	Ag_2O	75
14	AcOH−H_2O = 1:1	Ag_2CO_3	59
15	AcOH−H_2O = 1:1	AgTFA	62
16	AcOH−H_2O = 1:1	$CuSO_4$	39
17	AcOH−H_2O = 1:1	$Cu(OAc)_2$	45
18	AcOH−H_2O = 1:1	$Cu(TFA)_2{\cdot}nH_2O$	70
19	AcOH−H_2O = 1:1	$PhI(OAc)_2$	0
20	AcOH−H_2O = 1:1	$K_2S_2O_8$	15
21	AcOH−H_2O = 1:1	1,4-BQ	0

[a]Reaction conditions: **1a** (1.2 mmol), **2a** (1.0 mmol), $Pd(OAc)_2$ (10 mol %), acetohydrazide (40 mol %), oxidant (2.0 mmol, 2 equiv), solvent (10 mL), 120 °C, 24 h. [b]Isolated yields.

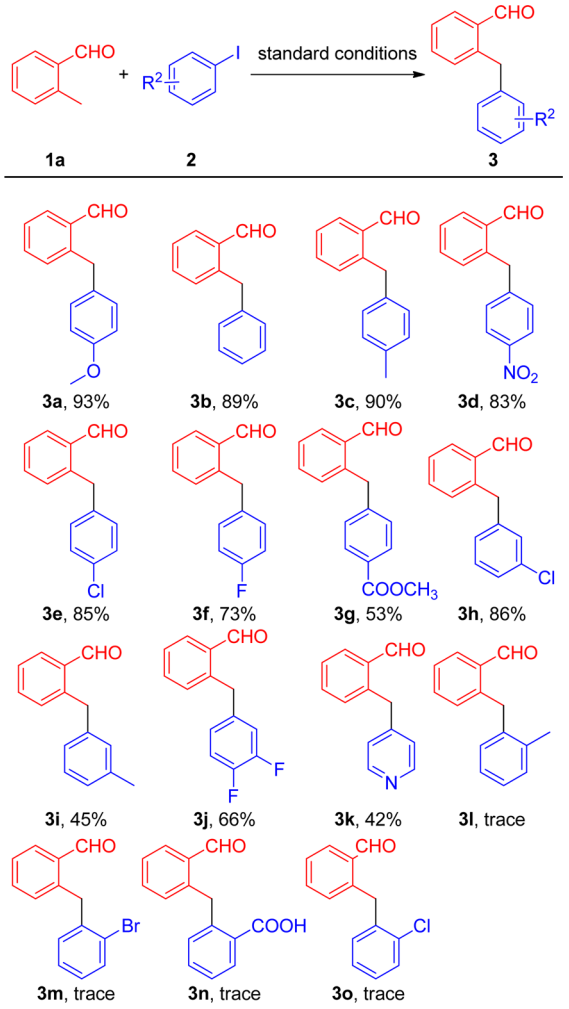
AcOH as solvent (Table 1, entries 1−7). One possible reason for these results was that acid could promote the reaction of **1a** and acetohydrazide to form acetohydrazone. Furthermore, we found the hydrolysis of acetohydrazone was incomplete after the C(sp^3)−H activation reaction, which led to only a moderate yield of **3a** (64%). Inspired by this phenomenon, we thought that adding an appropriate amount of water might promote the hydrolysis of acetohydrazone to increase the yield of **3a**. Therefore, the model reaction was carried out under similar conditions in AcOH−H_2O as a mixed solvent. The results presented in Table 1 showed that the yields of **3a** were increased greatly (77−85%) when using AcOH−H_2O as solvent (Table 1, entries 8−12), and AcOH−H_2O (v/v, 1:1) proved to be effective (Table 1, entry 9).

Then, a series of oxidants, such as Ag-salts, Cu-salts, $PhI(OAc)_2$, $K_2S_2O_8$, and 1,4-BQ, were examined for this model reaction. By a screening of oxidants, AgOAc was found to be optimal to obtain **3a** in 85% isolated yield (Table 1, entry 9). Therefore, AgOAc was chosen as the oxidant for all further reactions.

In addition, the other factors, such as the Pd-catalyst and the amount of acetohydrazide and temperature, were also investigated and these contents are provided in the Supporting Information. Then, optimal reaction conditions were obtained by using $Pd(OAc)_2$ (10 mol %), acetohydrazide (20 mol %), AgOAc (2 equiv), and AcOH−H_2O (v/v, 1:1) to afford desired product **3a** in 91% yield. Furthermore, we also carried out the reaction under the optimal conditions using aromatic compounds with different leaving groups, such as Br-, Cl-, TsO-, and TfO-, as substrates to replace **2a**. In these cases, the results showed that the reaction could not take place, and the desired **3a** was not formed (see Supporting Information).

In order to gauge the scope of the C(sp^3)−H activation arylation process, reaction of various aryl iodides and 2-methylbenzaldehyde (**1a**) was carried out under the optimized conditions (Scheme 1). As shown in Scheme 1, *para*, *meta*, and

Scheme 1. C(sp^3)−H Arylation of Aryl Iodides (2) with 2-Methyl-benzaldehyde (1a)[a,b]



[a]Standard conditions: **1a** (1.2 mmol), **2** (1.0 mmol), $Pd(OAc)_2$ (10 mol %), acetohydrazide (20 mol %), AgOAc (2.0 mmol, 2 equiv), AcOH−H_2O (10 mL, v/v, 1:1), 110 °C, 24 h. [b]Isolated yields.

ortho substituted substrates were chosen to examine the effect of steric hindrance on this reaction. The results clearly indicated that both *para* and *meta* substituted aryl iodides could react smoothly to obtain the corresponding products **3a−j** in good yields (45−93%). In contrast, *ortho* substitued aryl iodides failed to yield desired product **3l−o**. These results suggested that steric hindrance could significantly effect this reaction. Moreover, a heterocyclic substrate (4-iodopyridine) was applied for this C(sp^3)−H activation arylation reaction, and the desired product **3k** was obtained in 42% yield.

We further investigated the reactions of 1-iodo-4-methoxybenzene (**2a**) with substituted 2-methylbenzaldehydes (Scheme 2). All of the aryl 2-methylbenzaldehydes were

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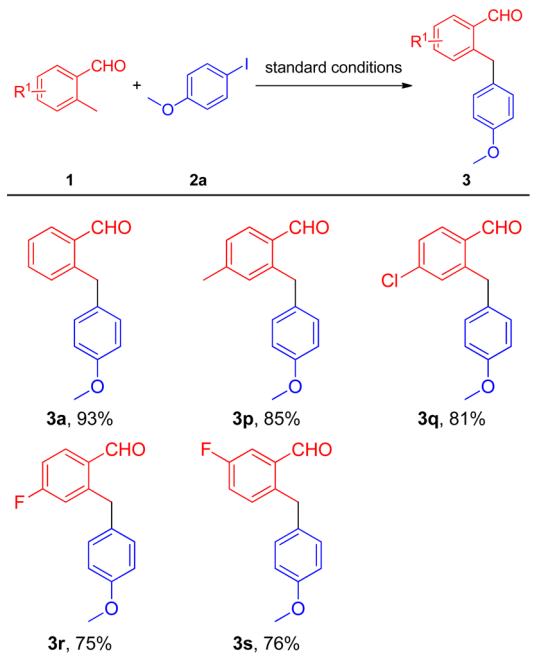
coupled with iodobenzene to afford the products **3a**, **3p**–**s** in good yields (75–93%).

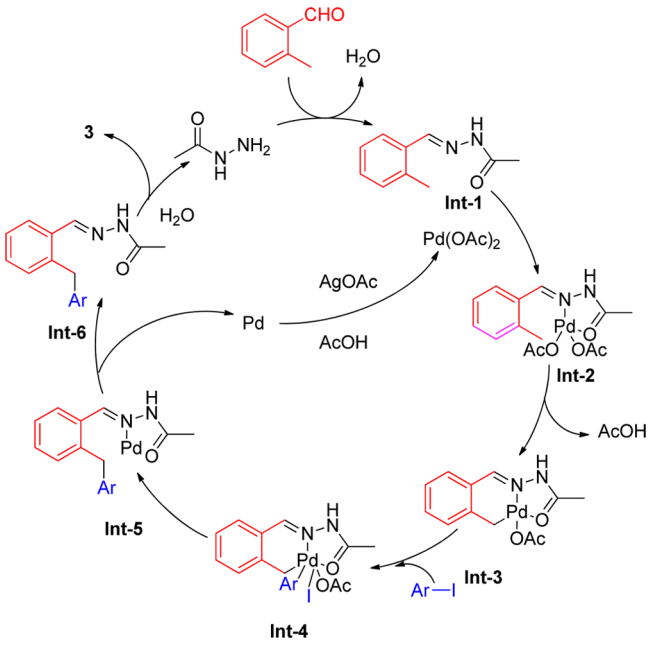
Scheme 2. C(sp^3)–H Arylation of 1-Iodo-4-methoxybenzene (2a) with Aldehyde (1)[a,b]



[a]Standard conditions: **1** (1.2 mmol), **2a** (1.0 mmol), $Pd(OAc)_2$ (10 mol %), acetohydrazide (20 mol %), AgOAc (2.0 mmol, 2 equiv), AcOH–H_2O (10 mL, v/v, 1:1), 110 °C, 24 h. [b]Isolated yields.

On the basis of the experimental results, a possible mechanism for the C(sp^3)–H activation arylation reaction is presented in Scheme 3. Initially, aldehyde reacts with acetohydrazide to form acetohydrazone (**Int-1**), which serves as a directing group in the next step. Then, bidentate coordination of the acetohydrazone moiety in **Int-1** to the $Pd(OAc)_2$ species occurs to form the chelated cyclometalated Pd-complex **Int-2**, followed by formation of **Int-3**. Then, oxidation–addition of **Int-3** and aryl iodide takes place to form **Int-4**, which undergoes reductive elimination to obtain **Int-5**. Subsequently, **Int-5** is decomposed to **Int-6** along with the Pd^0 species. **Int-6** is hydrolyzed to the desired product **3** and acetohydrazide. The catalytic cycle is completed by the AgOAc/AcOH-promoted reoxidation of Pd^0 into the starting $Pd(OAc)_2$ species.

Scheme 3. Proposed Mechanism



In conclusion, we have demonstrated a straightforward and efficient procedure for the synthesis of 2-benzylbenzaldehyde derivatives from 2-methylbenzaldehyde and iodobenzene via a C(sp^3)–H activation process. In the course of the activation reaction, acetohydrazone serves as a transient directing group which has several main advantages: (i) the directing group need not be introduced to substrate in advance; (ii) bidentate coordination of the acetohydrazone moiety is an efficient directing group; (iii) the directing group is easy to remove from the intermediate to obtain the desired product.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01170.

Experimental procedures and spectral data for all compound (PDF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Yu, X.; Lu, X. *Adv. Synth. Catal.* **2011**, *353*, 569. (b) Kuninobu, Y.; Tatsuzaki, T.; Matsuki, T.; Takai, K. *J. Org. Chem.* **2011**, *76*, 7005. (c) Hussain, A.; Parrick, J. *Tetrahedron Lett.* **1983**, *24*, 609. (d) Rafiq, S. M.; Sivasakthikumaran, R.; Karunakaran, J.; Mohanakrishnan, A. K. *Eur. J. Org. Chem.* **2015**, *2015*, 5099.

(2) Bhattacharya, A.; Miller, B. *J. Am. Chem. Soc.* **1980**, *102*, 2450.

(3) (a) Charlton, J. L.; Plourde, G. L.; Koh, K.; Secco, A. S. *Can. J. Chem.* **1990**, *68*, 2022. (b) Durst, T.; Kozma, E. C.; Charlton, J. L. *J. Org. Chem.* **1985**, *50*, 4829.

(4) (a) Runyon, S. P.; Peddi, S.; Savage, J. E.; Roth, B. L.; Glennon, R. A.; Westkaemper, R. B. *J. Med. Chem.* **2002**, *45*, 1656. (b) Patel, B. A.; Ashby, C. R., Jr.; Hardej, D.; Talele, T. T. *Bioorg. Med. Chem. Lett.* **2013**, *23*, 5523. (c) Runyon, S. P.; Mosier, P. D.; Roth, B. L.; Glennon, R. A.; Westkaemper, R. B. *J. Med. Chem.* **2008**, *51*, 6808. (d) Hagishita, S.; Yamada, M.; Shirahase, K.; Okada, T.; Murakami, Y.; Ito, Y.; Matsuura, T.; Wada, M.; Kato, T.; Ueno, M.; Chikazawa, Y.; Yamada, K.; Ono, T.; Teshirogi, I.; Ohtani, M. *J. Med. Chem.* **1996**, *39*, 3636. (e) Gribble, A. D.; Dolle, R. E.; Shaw, A.; McNair, D.; Novelli, R.;

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Org. Lett. XXXX, XXX, XXX–XXX

Novelli, C. E.; Slingsby, B. P.; Shah, V. P.; Tew, D.; Saxty, B. A.; Allen, M.; Groot, P. H.; Pearce, N.; Yates, J. *J. Med. Chem.* **1996**, *39*, 3569.
(5) (a) Wang, F.; Ueda, W. *Appl. Catal., A* **2008**, *346*, 155. (b) Ganesamoorthy, S.; Shanmugasundaram, K.; Karvembu, R. *Catal. Commun.* **2009**, *10*, 1835.
(6) Kuninobu, Y.; Tatsuzaki, T.; Matsuki, T.; Takai, K. *J. Org. Chem.* **2011**, *76*, 7005.
(7) Nakamura, Y.; O-kawa, K.; Minami, S.; Ogawa, T.; Tobita, S.; Nishimura, J. *J. Org. Chem.* **2002**, *67*, 1247.
(8) Cong, X.; Tang, H.; Zeng, X. *J. Am. Chem. Soc.* **2015**, *137*, 14367.
(9) Sun, A. D.; Leung, K.; Restivo, A. D.; LaBerge, N. A.; Takasaki, H.; Love, J. A. *Chem. - Eur. J.* **2014**, *20*, 3162.
(10) Zhang, F.-L.; Hong, K.; Li, T.-J.; Park, H.; Yu, J.-Q. *Science* **2016**, *351*, 252.
(11) (a) He, G.; Zhao, Y.; Zhang, S.; Lu, C.; Chen, G. *J. Am. Chem. Soc.* **2012**, *134*, 3. (b) Nadres, E. T.; Daugulis, O. *J. Am. Chem. Soc.* **2012**, *134*, 7. (c) Sun, W.-W.; Cao, P.; Mei, R.-Q.; Li, Y.; Ma, Y.-L.; Wu, B. *Org. Lett.* **2014**, *16*, 480. (d) Zheng, L.; Hua, R. *Chem. - Eur. J.* **2014**, *20*, 2352. (e) Jun, C.-H.; Lee, H.; Hong, J.-B. *J. Org. Chem.* **1997**, *62*, 1200.
(12) (a) Zaitsev, V. G.; Shabashov, D.; Daugulis, O. *J. Am. Chem. Soc.* **2005**, *127*, 13154. (b) Takamatsu, K.; Hirano, K.; Satoh, T.; Miura, M. *J. Org. Chem.* **2015**, *80*, 3242. (c) Wei, Y.; Tang, H.; Cong, X.; Rao, B.; Wu, C.; Zeng, X. *Org. Lett.* **2014**, *16*, 2248. (d) McGowan, M. A.; Henderson, J. L.; Buchwald, S. L. *Org. Lett.* **2012**, *14*, 1432.
(13) (a) Bedford, R. B.; Coles, S. J.; Hursthouse, M. B.; Limmert, M. E. *Angew. Chem., Int. Ed.* **2003**, *42*, 112. (b) Piou, T.; Rovis, T. *Nature* **2015**, *527*, 86. (c) Mo, F.; Dong, G. *Science* **2014**, *345*, 68.

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