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Indirect *ortho* Functionalization of Substituted Toluenes through *ortho* Olefination of *N*,*N*-Dimethylbenzylamines Tuned by the Acidity of Reaction Conditions

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Abstract: Highly regioselective olefination of substituted *N*,*N*-dimethylbenzylamines was developed by tuning the acidity of reaction conditions based on analysis of their features. The *ortho*-functionalized *N*,*N*-dimethylbenzylamines were further transformed into 3-(2′-tolyl)propanoic acid and its derivatives under mild conditions. These two transformations could be combined into one pot, and 3-(2′-tolyl)propanoic acid and its derivatives were obtained in moderate to good yields. Mechanistic studies indicated that electrophilic attack on the phenyl ring by the Pd(II) ion assisted by the *N*,*N*-dimethylaminomethyl group was a key step during this catalytic transformation, which was controlled by the acidity of the reaction conditions.

Introduction

In the past several decades, many efforts have been made to direct functionalization of a variety of C−H bonds.[1] Aromatic C−H activation through different chemical processes has been studied.[2] Direct functionalization of aromatic C−H bonds by electrophilic attack of metal ions is one of the most important pathways.[3] Functional groups containing heteroatoms, such as acetamino, oxazolyl, pyridyl, and imino groups, have been broadly utilized to provide either stoichiometric or catalytic *ortho*-metalation of aromatic rings to construct C−C[4a−f] and C−X (X = halides, N, etc.) bonds.[4g−j]Previous synthetic work on functionalization of *N*,*N*-dimethylbenzylamine generally utilized *n*-BuLi to *ortho* lithiate the *N*,*N*-dimethylbenzylamine, which limited the tolerance of functional groups in the substrates.[5] Although the *N*,*N*-dimethylaminomethyl group has been used as a directing group to realize the *ortho*-metalation by transition metal complexes to form metallocycles and further construct C−C bonds in a stoichiometric manner under basic conditions,[6] the catalytic version of *ortho* functionalization of an aromatic C−H bond directed by an *N*,*N*-dimethylaminomethyl group has rarely been reported, except one case reported by Murai and co-workers, in which achieved *ortho* silylation catalyzed by Ru(0) was initiated through oxidative addition.[7]

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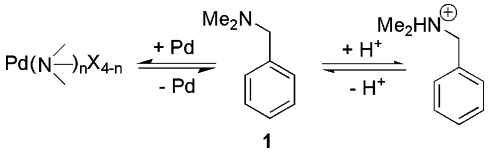
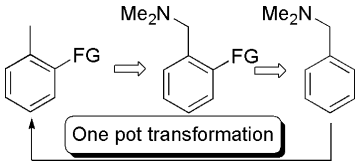
Scheme 1



Compared with other directing groups, the unique features of the *N*,*N*-dimethylaminomethyl group limited its utility as a directing group for catalytic C−H functionalization. First, the *N*,*N*-dimethylaminomethyl group is a very good σ-donor ligand, which binds to transition metal ions very well.[8] This binding not only occupies the chelating position but also increases the electron density of the metal ions. Thus, the electrophilic ability of transition metal ions is weakened. Second, acid can undoubtedly be employed to enhance the electrophilicity of transition metal ions to attack an aromatic ring.[3b] However, the dimethylamino group works as a relatively strong Brönsted base and is protonated under strong acidic conditions.[9] This protonation limits its ability to bind metal ions and work as a directing group. Thus, the selectivity of the reaction will be determined by the Friedel−Crafts pathway.[10] This contradiction makes selective *ortho* functionalization of arenes with an *N*,*N*-dimethylaminomethyl group as a directing group difficult, as indicated in Scheme 1. We envisioned that the difficulty of performing such a catalytic transformation directed by an *N*,*N*-dimethylaminomethyl group through electrophilic attack is to search for proper acidic reaction conditions.

On the other hand, the *N*,*N*-dimethylaminomethyl group of *N*,*N*-dimethylbenzylamines can be easily transformed to different functional groups in one or two steps, such as a methyl group,[11a−f] aldehyde,[11g,h] and alkene.[11i] Generally, with a methyl substituent, aromatic C−H bonds are functionalized in a Friedel−Crafts manner because the methyl group slightly activates the arene.[12] However, the methyl group cannot interact with most metal catalysts, and thus, the Friedel−Crafts functionalization of arenes with methyl substituent is not regiospecific. These potential utilities of functionalized *N*,*N*-dimethylbenzylamines made us search for the possibility to develop the highly selective functionalization of the aromatic C−H bond of *N*,*N*-dimethylbenzylamines under proper conditions. We herein demonstrate an *ortho* olefination of aromatic C−H bonds via a palladium-catalyzed Heck−Mizoroki-type process directed by the *N*,*N*-dimethylaminomethyl group. Further studies also offered a new useful indirect process to prepare the corresponding *ortho*-functionalized toluene and its derivatives through further transformation of the *ortho*-functionalized *N*,*N*-dimethylbenzylamine and its derivatives. With the combination of these two transformations, the desired *ortho*-functionalized toluene derivatives were easily afforded in good efficiency in one pot starting from *N*,*N*-dimethylbenzylamines in Scheme 2.

Scheme 2



Results and Discussion

Screening of Acidic Conditions of *ortho* Olefination of *N*,*N*-Dimethylbenzylamine. Heck−Mizoroki-type coupling via C−H functionalization with or without directing groups has been relatively less studied to construct C−C bonds in the past.[13] Our studies started from the *ortho* functionalization of *N*,*N*-dimethylbenzylamine by a Heck−Mizoroki-type coupling reaction. First, various neutral conditions were screened. A variety of solvents, either nonpolar or polar, such as toluene, dichloroethane (DCE), and DMF, could not support this *ortho* olefination. Further studies indicated that the reaction could not be performed in polar protic solvents such as methanol and 2,2,2-trifluoroethanol (TFEol), either. During all of the screenings, different organic and inorganic oxidants, such as $PhI(OAc)_2$ and $Cu(OAc)_2$, were tested in different systems. The failure implied that neutral conditions were not suitable for this transformation, perhaps arising from the inhibition of electrophilic attack by the tertiary amine as a strong σ-donor ligand to bind Pd(II) ion.

We then explored this transformation under acidic conditions. The first try was carried out in dichloromethane with trifluoroacetic acid (TFA), which is broadly used as a solvent system for electrophilic attack on arenes by transition metal cations.[3a,b] However, no desired product was observed. Further studies indicated that the transformation occurred when methanol and acetic acid (4:1) were utilized as cosolvents (entry 10, Table 1). Notably, the best solvent system for this transformation was 2,2,2-trifluoroethanol (TFEol) and AcOH, although this transformation could run in different solvents in the presence of AcOH (entry 6, Table 1). The quantity of acetic acid was also screened. The best ratio for this transformation was 16−32 equiv of acetic acid (based on tertiary amine). The conversion of this transformation decreased if the amount of acetic acid changed (comparing entry 6 to entries 7 and 8, Table 1). A decrease of the amount of acetic acid might affect both the concentration of tertiary amine and the electrophilicity of the metal ions. On the other hand, an increase of the amount of acetic acid also led to a decreased conversion, highlighting the importance of balancing the two factors shown in Scheme 1. Interestingly, when the same amount of a stronger trifluoroacetic acid (TFA) was used instead of acetic acid, the olefination was completely shut down. Strong acid may protonate the tertiary amine and terminate the metal binding.

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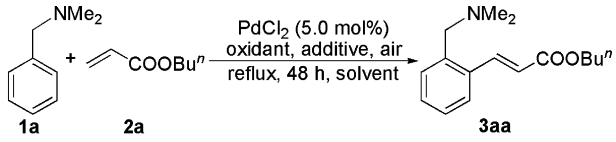
Table 1. *ortho* Olefination of **1a** under Various Conditions[a]



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

entry	oxidant (equiv)	additive (equiv)	solvent	**3aa** (%)[b]
1	$Cu(OAc)_2$ (1.0)	-	TFEol	<5
2	1,4-quinone (1.0)	AcOH (16)	TFEol	<5
3	$PhI(OAc)_2$ (1.0)	AcOH (16)	TFEol	9
4[c]	O_2	AcOH (16)	TFEol	7
5	$CuCl_2$ (1.0)	AcOH (16)	TFEol	25
6[d]	*$Cu(OAc)_2$ (1.0)*	*AcOH (16)*	*TFEol*	*86*
7	$Cu(OAc)_2$ (1.0)	AcOH (8)	TFEol	38
8	$Cu(OAc)_2$ (1.0)	AcOH (86)	-	64
9[c]	$Cu(OAc)_2$ (0.20), O_2	AcOH (16)	TFEol	66
10[e]	$Cu(OAc)_2$ (1.0)	AcOH (16)	MeOH	33
11[e]	$Cu(OAc)_2$ (1.0)	AcOH (16)	EtOH	27
12	$Cu(OAc)_2$ (1.0)	AcOH (16)	CH_3CN	53
13	$Cu(OAc)_2$ (1.0)	AcOH (16)	toluene	55
14	$Cu(OAc)_2$ (1.0)	AcOH (16)	DCE	66
15[f]	$Cu(OAc)_2$ (1.0)	AcOH (16)	TFEol	0

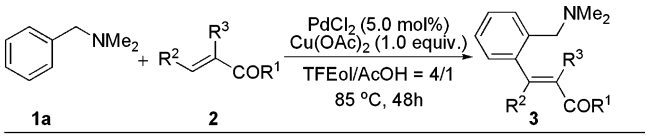
[a] The reactions were carried out in 0.5 mmol scale of **1a** in the presence of 1.0 mmol of **2a** and the proper catalyst in 2 mL of different solvents. [b] NMR yields with the use of CH_2Br_2 as internal standard. [c] The reactions were carried out under balloon pressure of O_2. [d] Isolated yields. [e] The products were obtained as a mixture accompanied with some ester exchanging products. [f] This reaction was carried out in the absence of palladium catalyst.

Different oxidants were explored in this system. Common organic oxidants, such as 1,4-quinone and $PhI(OAc)_2$, were not efficient for this transformation (entries 2 and 3, Table 1). Other copper salts, such as $CuCl_2$, could be employed as an oxidant with a very low efficiency (entry 5, Table 1). Dioxygen (O_2) could not play a role as a direct oxidant; however, it can be used as a co-oxidant in the presence of a catalytic amount of $Cu(OAc)_2$ with a relatively lower conversion (entry 9, Table 1). This transformation is not sensitive to Pd(II) species. According to all these studies, relatively cheap $PdCl_2$ was employed as a catalyst with 1 equiv of $Cu(OAc)_2$ in the presence of 16 equiv of AcOH in TEFol for this transformation.

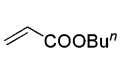
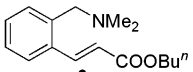
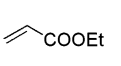
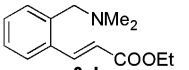
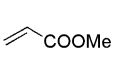
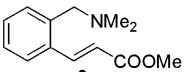
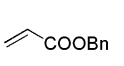
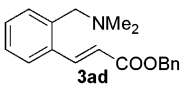
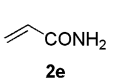
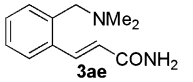
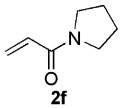
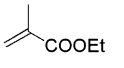
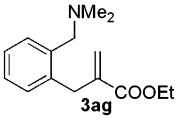
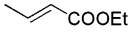
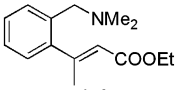
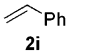
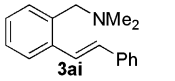
Evaluating the Reactivities of Different Alkenes. After screening the reaction conditions, the different alkenes were further explored (Table 2). We found that different acrylic acid esters were suitable substrates, whether methyl, ethyl, *n*-butyl, or benzyl was the protecting group (entries 1−4, Table 2). Free acrylamide and *N*,*N*-disubstituted amide could also be employed in this transformation to produce the desired *ortho*-olefinated products in moderate to good yields (entries 5 and 6, Table 2). It is noteworthy that the dynamic β-hydride elimination product was observed when the methyl group was present at the α-position of the acrylate (entry 7, Table 2). However, β-substituted ethyl acrylate was not suitable for this transformation (entry 8, Table 2). Furthermore, no desired product was obtained when styrene was subjected to these reaction conditions (entry 9, Table 2). This may arise from the alkylation of arenes in a Friedel−Crafts manner under the relatively strong acidic conditions.

Screening of Different Substituted Benzylamines. Different benzylamine derivatives were screened under the standard conditions (Table 3). Two methyl groups on nitrogen were necessary to complete this transformation (entry 1, Table 3). When either one methyl group or both of them were substituted by a proton, this transformation was completely terminated

Table 2. *ortho* Functionalization of *N*,*N*-Dimethylbenzylamine with Different Alkenes[a]

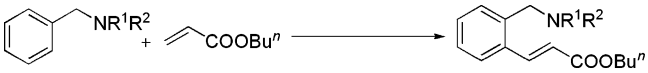


1a **2** **3**

entry	**2**	**3**	yield (%)[b]
1	 **2a**	 **3aa**	86
2	 **2b**	 **3ab**	85
3	 **2c**	 **3ac**	66
4	 **2d**	 **3ad**	86
5	 **2e**	 **3ae**	82
6	 **2f**	 **3af**	54
7	 **2g**	 **3ag**	53
8[c]	 **2h**	 **3ah**	< 10
9[c]	 **2i**	 **3ai**	< 5

[a] All the reactions were carried out in the scale of 0.5 mmol of **1a** and 1.0 mmol of **2** in 2.5 mL of solvent. [b] Isolated yields. [c] The yield was determined by ^1H NMR with the use of CH_2Br_2 as an internal standard.

Table 3. *ortho* Olefination of Different N-Substituted Benzylamines[a]



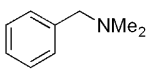
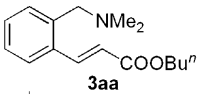
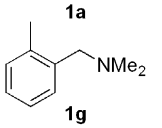
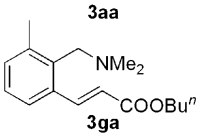
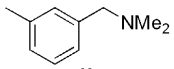
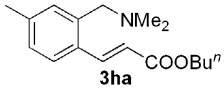
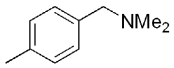
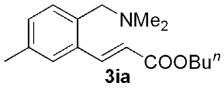
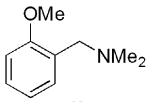
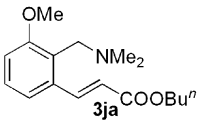
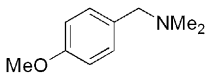
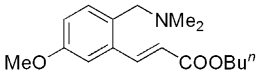
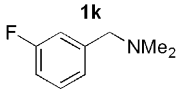
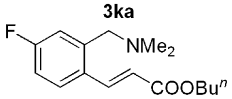
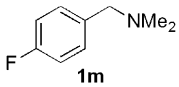
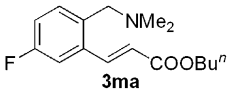
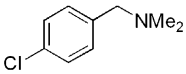
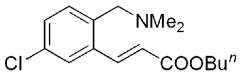
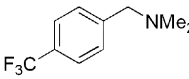
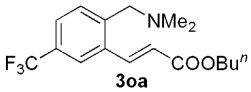
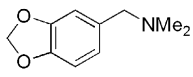
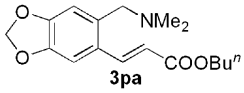
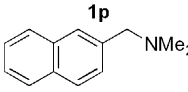
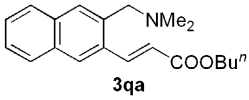
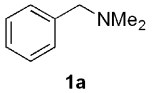
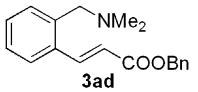
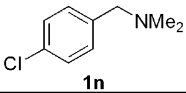
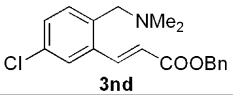
1 **2a** **3**

entry	R^1	R^2	**3** (%)[b]
1	Me	Me (**1a**)	**3aa** (86)
2[c]	Me	H (**1b**)	**3ba** (<5)
3[c]	H	H (**1c**)	**3ca** (<5)
4[d]	Me	Bn (**1d**)	**3da** (47)
5[c]	$CH_2CH_2CH_2CH_2$ (**1e**)		**3ea** (16)
6[c]	Me	Ac (**1f**)	**3fa** (<5)

[a] All the reactions were carried out in 0.5 mmol scale under standard conditions. [b] Isolated yields if without further notes. [c] NMR yield with the use of CH_2Br_2 as an internal standard. [d] Only one benzyl was olefinated.

(entries 2 and 3, Table 3). When *N*-methyldibenzylamine was employed as a substrate, only one phenyl ring was olefinated under this condition in a moderate isolated yield, which might be controlled by steric effects (entry 4, Table 3). Moreover, the isolated yield for the cyclic amine derivative was very low (entry 5, Table 3). An acetyl substituent on nitrogen instead of one of the methyl groups decreased the electron density of nitrogen;

Table 4. *ortho* Olefination of Differently Substituted Benzylamines with **2a** or **2d**[a]

entry	1	3	yield (%)[b]
1	 **1a**	 **3aa**	86
2	 **1g**	 **3ga**	75
3[c]	 **1h**	 **3ha**	75
4	 **1i**	 **3ia**	70
5	 **1j**	 **3ja**	75
6	 **1k**	 **3ka**	76
7[c]	 **1l**	 **3la**	86
8[d]	 **1m**	 **3ma**	76
9[d]	 **1n**	 **3na**	85
10[d]	 **1o**	 **3oa**	74
11[c]	 **1p**	 **3pa**	80
12[c]	 **1q**	 **3qa**	85
13	 **1a**	 **3ad**	86
14[d]	 **1n**	 **3nd**	82

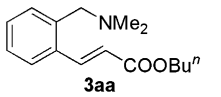
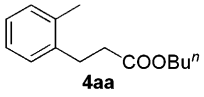
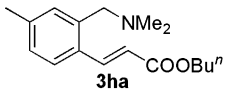
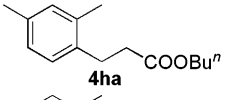
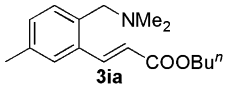
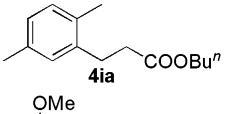
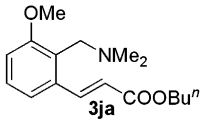
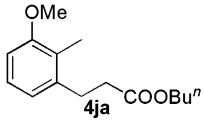
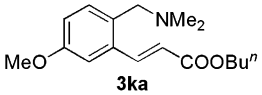
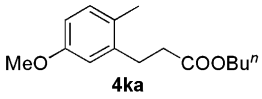
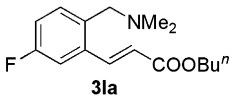
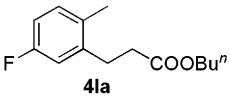
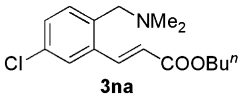
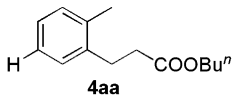
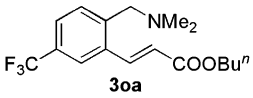
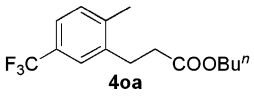
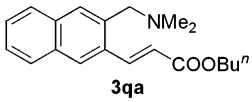
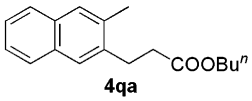
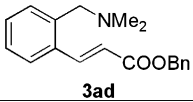
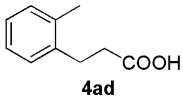
[a] All the reactions ran in the scale of 0.5 mmol of **1** and 1.0 mmol of **2** in 2.5 mL of solvent. [b] Isolated yields. [c] All the yields contained the minor products olefinated at the more hindered *ortho* position. The ratios of the two isomers are 4:1, 5:3, 12:1, and 11:1, respectively, which were determined by ^{1}H NMR analysis of crude products. [d] 10 mol % of $PdCl_2$ was used as catalyst.

thus the *ortho* olefination could not occur due to the low affinity of nitrogen to the Pd(II) catalyst (entry 6, Table 3).

The derivatives of *N*,*N*-dimethylbenzylamine with different substituents on the phenyl rings were further surveyed (Table 4). We found that (1) generally, electron-rich substituents were helpful for this *ortho* olefination (entries 2−6, Table 4); (2) electron-deficient groups decreased the reactivity of substrates, but high conversions and yields were also achieved with higher catalyst loading for *ortho* olefination (entries 8−10, Table 4); (3) it is important to note that the relatively stable C−Cl bond survived well under this transformation, which could be further transformed to different functionalities (entries 9 and 14, Table 4);[14] (4) the position of the substituents, an electron-rich group, or an electron-deficient group did not affect the reactivity obviously, and the selectivity was controlled by steric effects only when the substituent was at the *meso* position. The major products were produced by the olefination at the less hindered *ortho* position of the dimethylamino group, accompanied with

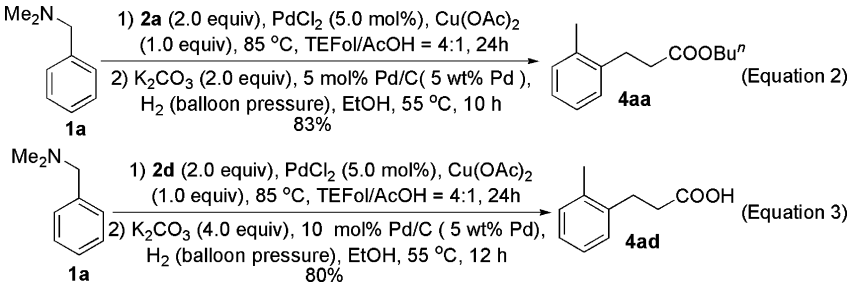
(14) Littke, A. F.; Fu, G. C. *Angew. Chem., Int. Ed.* **2002**, *41*, 4176.

Table 5. *ortho* Functionalization of Substituted Toluene **4** through *ortho* Olefination of Functionalized *N*,*N*-Dimethylbenzylamines **3**[a]

entry	3	4	yield (%)[b]
1	 **3aa**	 **4aa**	81
2[c]	 **3ha**	 **4ha**	90
3	 **3ia**	 **4ia**	90
4	 **3ja**	 **4ja**	89
5	 **3ka**	 **4ka**	82
6	 **3la**	 **4la**	67
7	 **3na**	 **4aa**	52
8	 **3oa**	 **4oa**	47
9	 **3qa**	 **4qa**	66
10	 **3ad**	 **4ad**	77

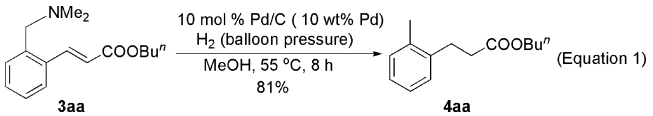
[a] All the reactions were carried out in the scale of 0.2−0.5 mmol of **3** in the presence of 10 mol % of Pd/C (10 wt % Pd) in 2−6 mL of methanol under balloon pressure of H_2. [b] Isolated yields. [c] The product with two isomers from olefination was submitted to this reduction, and the reduced product was obtained as a mixture in the same ratio.

Scheme 3. Transformation of Tertiary Amines to Functionalized Toluenes in One Pot



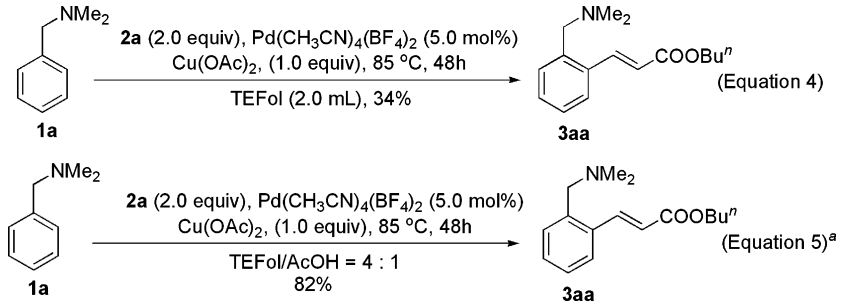
the minor products functionalized at the correspondingly more hindered *ortho* position (entries 3, 7, 11, and 12, Table 4).

Removal of the *N*,*N*-Dimethylamino Group and Reduction of the C═C Double Bond. With the development of *ortho* olefination of *N*,*N*-dimethylbenzylamine in hand, further transformation of this product to produce substituted toluenes was explored as we designed. The *N*,*N*-dimethylaminomethyl group could be converted into a methyl group under the reductive hydrogen atmosphere with Pd/C as a catalyst, acompanied with the reduction of the C═C double bond in excellent isolated yield (eq 1). Thus, the highly selectively *ortho*-functionalized toluene was produced indirectly through simple procedures based on the methodology we have developed.

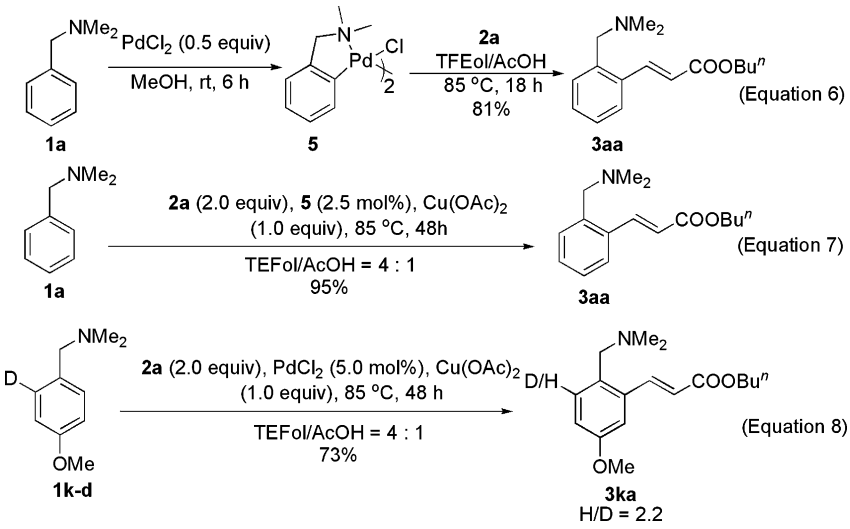


The corresponding derivatives of toluene were obtained after the hydrogenation of the *ortho*-olefinated products **3** (Table 5).

Scheme 4. *ortho* Olefination of *N,N*-Dimethylbenzylamine Catalyzed by Palldium Ion Species



Scheme 5. Mechanistic Studies on *ortho* Olefination of *N,N*-Dimethylbenzylamine



Most of the substituents except the C−Cl group were compatible with this reductive condition, and the products **4** were isolated in good to excellent yields. Under this reductive condition, the C−Cl bond was also transformed into a C−H bond in good efficiency (entry 7, Table 5). Similarly, electron-deficient groups decreased the reactivity of substrates during this reduction process (entry 8, Table 5). It is noteworthy that 3-substituted phenyl propanoic acids could be obtained under the same reaction condition with the use of a benzyl group as a protecting group for the ester (entry 10, Table 5).

One-Pot Transformation to Afford Toluene Derivatives. After the investigation of the hydrogenation, further studies to combine *ortho* olefination and hydrogenation into one pot were conducted. Since both of these two transformations were performed in polar protic solvent, Pd/C was directly added into the vessel with the change of atmosphere from air to hydrogen gas without any purification after the olefination. Gratifyingly, the desired product **4aa** was produced in good isolated yield in the presence of 2 equiv of K_2CO_3 as an additive and 2 mL of EtOH as a cosolvent (eq 2). This one-pot transformation also occurred in the absence of additional Pd/C with a much lower efficiency. The corresponding acid **4ad** was also produced under the same sequential reactions in 80% isolated yield (eq 3). This one-pot process offered a greener process to perform this two-step transformation by avoiding the purification.

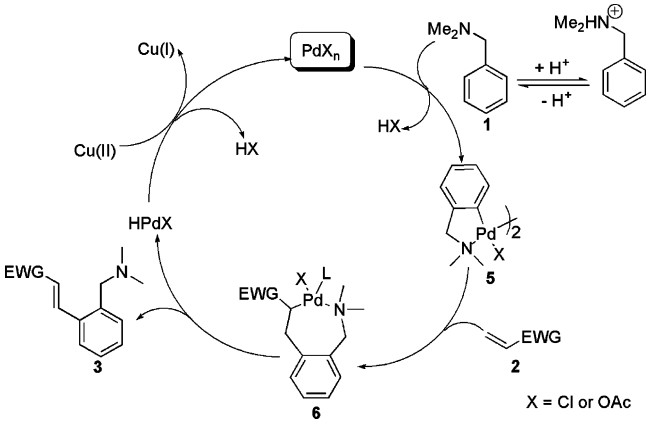
Mechanistic Studies. Noticeably, this reaction could not occur in the absence of Pd(II) salts. To investigate the role of acetic acid during this transformation, we first tested $Pd(CH_3CN)_4(BF_4)_2$ as a catalyst in the absence or presence of acetic acid (eqs 4 and 5, Scheme 4). The results indicated that both reactions could run, but the efficiency of the transformation was much lower in the absence of acetic acid. Thus, the role of the AcOH is most likely to tune the concentration of the free amine moiety so that the amine promotes directed, Pd-catalyzed C−H cleavage to realize this transformation.

To further understand the mechanism of this transformation, the palladacycle **5** was prepared according to ref 15. The palladacycle **5** could undergo *ortho* olefination stoichiometrically to form the desired product **3aa** in 81% yield (eq 6). It could also catalyze *ortho* olefination in excellent efficiency under the standard conditions (eq 7). Thus, the palladacycle **5** was proposed as a key intermediate during this catalytic cycle. Moreover, the 2-deuterium-substituted *N,N*-dimethyl-4-methoxylbenzylamine **1k**-*d*[16] was subjected to the standard conditions (eq 8). The observed intramolecular isotope effect H/D = 2.2 indicated that cleavage of the C−H bond at the *ortho* position was involved in the rate-determining step.

On the basis of these preliminary results, the catalytic cycle of this transformation was hypothesized as shown in Scheme 6. As we have mentioned, the proper acidic condition is critical for tuning the concentration of free tertiary amine. Free tertiary amine **1** could bind to the Pd(II) cation, which electrophilically attacks the aromatic ring regioselectively to form the key five-membered palladacycle **5**. After the insertion of the double bond of the acrylate into the C−Pd bond of **5**, the intermediate **6** was produced and underwent β-hydride elimination to form the

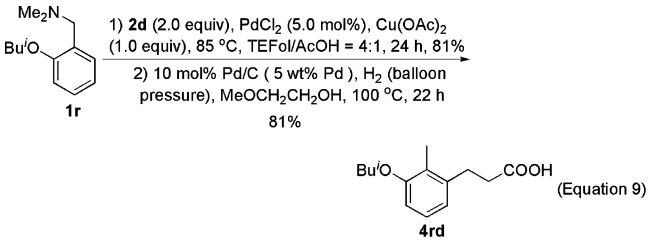
(15) (a) Cope, A. C.; Friedrich, E. C. *J. Am. Chem. Soc.* **1968**, *90*, 909. (b) Mentes, A.; Kemmitt, R. D. W.; Fawcett, J.; Russell, D. R. *J. Mol. Struct.* **2004**, *693*, 241.
(16) Jones, F. N.; Zinn, M. F.; Hauser, C. R. *J. Org. Chem.* **1963**, *28*, 663.

Scheme 6. Proposed Mechanism of *ortho* Olefination of *N*,*N*-Dimethylbenzylamine



final product **3**. The palladium hydride species was transformed to Pd(0) and further oxidized to Pd(II) by Cu(II) to finish this catalytic cycle.

Application of Developed *ortho* Olefination−Hydrogenation. 3-*o*-Tolylpropanoic acid and its derivatives have been utilized as a key structural unit in bioactive molecules.[17] According to this developed process, the compound **4rd** was synthesized by this transformation in excellent yield with short routes (eq 9).[17a] This process also offers a new method to quickly construct this type of compound in high efficiency and good diversity, which will be beneficial to further unveil new utilities of this unique scaffold.



(Equation 9)

Conclusions

Starting from the easily available *N*,*N*-dimethylbenzylamines, we have developed a novel method to achieve a regioselective functionalization via direct C−H functionalization by tuning the acidity of the reaction conditions. Although the acid has been applied to the C−H activation by electrophilic attack through enhancing the electrophilic ability of metal ions, the acid plays a much more important role to conduct this transformation. The acidity and quantity of the Brönsted acid remarkably controlled the efficiency of this *ortho* olefination. Starting from the corresponding functionalized tertiary amines, highly selectively *ortho*-functionalized toluene and its derivatives were synthesized by simple reduction. These two transformations could be combined in one vessel to offer a much more environmentally benign process. Besides *ortho*-functionalized *N*,*N*-dimethylbenzylamines,[18] 3-*o*-tolylpropanoic acid and its derivatives are also important units of synthetic molecules and show some biological activity.[17] Our development here advances a remarkable and useful method to construct both of these important scaffolds. Further study to apply these methods to organic synthesis is underway in our laboratory.

Experimental Section

General Methods. All the reactions were carried out in a stoppered Schlenk flask.[19] All the solvents were freshly distilled before use except CF_3CH_2OH. CF_3CH_2OH, anhydrous $Cu(OAc)_2$, Pd/C (5 wt % Pd), and $Pd(CH_3CN)_4(BF_4)_2$ were purchased from Acros. $PdCl_2$ was purchased from Zealand Co. Ltd., and Pd/C (10 wt % Pd) and *N*,*N*-dimethylbenzylamine were purchased from Sinopharm Chemical Reagent Co., Ltd. *N*,*N*-Dimethylbenzylamine was distilled under reduced pressure and stored under N_2 atmosphere. Other commercially available chemicals were directly used without further purification.

Physical Methods. ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) were registered on Varian 300M spectrometers with $CDCl_3$ as solvent and tetramethylsilane (TMS) as an internal standard. Chemical shifts were reported in units (ppm) by assigning the TMS resonance in the ^{1}H spectrum as 0.00 ppm and the $CDCl_3$ resonance in the ^{13}C spectrum as 77.0 ppm. All coupling constants (*J* values) are reported in hertz (Hz). Column chromatography was performed on silica gel 200−300 mesh. IR, GC, and MS were performed by the State-authorized Analytical Center in Peking University.

General Procedure for Preparation of Functionalized *N*,*N*-Dimethylbenzylamines 1. Functionalized *N*,*N*-dimethylbenzylamines were prepared by reductive amination according to the reported procedure.[20] To a solution of NEt_3 (4.2 mL, 30 mmol) in absolute EtOH (23 mL) was added dimethylamine hydrochloride (2.48 g, 30 mmol), Ti(*i*-PrO)$_4$ (9.0 mL, 30 mmol), and the corresponding aldehyde (15 mmol). The mixture was stirred at 25 °C for 12 h, $NaBH_4$ (0.86 g, 22.5 mmol) was added, and the resulting mixture was further stirred for 10 h at 25 °C. The reaction was quenched by pouring the mixture into aqueous ammonia (25 mL, 2 N) and filtered through a Celite pad, and the resulting inorganic solid was washed with CH_2Cl_2 (100 mL). The filtrate was washed with CH_2Cl_2 (3 × 50 mL), concentrated to about 30 mL, and washed with HCl (2 N, 3 × 10 mL). The solution was neutralized to pH = 9 with 10% aqueous NaOH and extracted with CH_2Cl_2 (3 × 50 mL). Additional NaOH was added to keep the inorganic phase basic. The organic phases were combined and dried over $MgSO_4$ and then evaporated to give the corresponding *N*,*N*-dimethylbenzylamine **1** without further purification.

General Procedure for the *ortho* Olefination of Tertiaryamines with Acrylic Esters. In a typical experiment, $PdCl_2$ (4.4 mg, 0.025 mmol), $Cu(OAc)_2$ (90.8 mg, 0.5 mmol), and CF_3CH_2OH (2 mL) were added into a Schlenk tube. Then *N*,*N*-dimethylbenzylamine **1** (0.5 mmol) was added, followed by **2** (1.0 mmol) and HOAc (0.5 mL, 8.0 mmol). The flask was stoppered and heated at 85 °C in an oil bath for 48 h. The mixture was made slightly alkaline with a saturated Na_2CO_3 solution (3 mL), and a light blue precipitate appeared. The suspension was filtered through a Celite pad and extracted with CH_2Cl_2 three times. The combined organic layers were dried over anhydrous Na_2SO_4 and evaporated in vacuo. The desired products **3** were obtained in the corresponding yields after purification by flash chromatography on silica gel with PE, EtOAc, and NEt_3.

(17) (a) Bohacek, R.; Boosalis, M. S.; McMartin, C.; Faller, D. V.; Perrine, S. P. *Chem. Biol. Drug Des.* **2006**, *67*, 318. (b) Frankish, N.; Farrell, R.; Sheridan, H. *J. Pharm. Pharmacol.* **2004**, *56*, 1423. (c) Burlingame, R. P.; Wyman, L.; Chapman, J. P. *J. Bacteriol.* **1986**, *168*, 55. (d) Kuhler, T. C.; Swanson, M.; Christenson, B.; Klintenberg, A.-C.; Lamm, B.; Fagerhag, J.; Gatti, R.; Ölwegard-Halvarsson, M.; Shcherbuchin,V.; Elebring, T.; Sjostrom, J.-E. *J. Med. Chem.* **2002**, *45*, 4282. (e) Conner, S. E.; Knobelsdorf, J. A.; Mantlo, N. B.; Schkeryantz, Jeffrey M.; Shen, Q.; Warshawsky, A. M.; Zhu, G. PCT Int. Appl. WO 2003072100 A1, 2003.

(18) (a) Fevig, J. M.; Cacciola, J.; Buriak, J.; Rossi, K. A.; Knabb, R. M.; Luettgen, J. M.; Wong, P. C.; Bai, S. A.; Wexler, R. R.; Lam, P. Y. S. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 3755. (b) Kung, H. F.; Newman, S.; Choi, S.-R.; Oya, S.; Hou, C.; Zhuang, Z.-P.; Acton, P. D.; Ploessl, K.; Winkler, J.; Kung, M.-P. *J. Med. Chem.* **2004**, *47*, 5258. (c) Hine, J.; Khan, M. N. *J. Am. Chem. Soc.* **1977**, *99*, 3847. (d) Nielsen, S. F.; Larsen, M.; Boesen, T.; Schonning, K.; Kromann, H. *J. Med. Chem.* **2005**, *48*, 2667.

(19) Safety note: CF_3CH_2OH is corrosive and H_2 is explosive. Thus, great caution should be exercised when handling them.

(20) Bhattacharyya, S. *J. Org. Chem.* **1995**, *60*, 4928.

General Procedures for the Reduction of Functionalized *N*,*N*-Dimethylbenzylamines to Corresponding *o*-Tolylpropanoic Acids and Their Derivatives 4. A mixture of the functionalized *N*,*N*-dimethylbenzylamine **3** (0.5 mmol) and Pd/C catalyst (10 wt % Pd, 106 mg, 10 mol %) in MeOH (6 mL) was stirred under H_2 at balloon pressure at 55 °C for 8 h. After the catalyst was filtered, the filtration was evaporated to get the crude product. Further purification by flash chromatography on silica gel with PE/EtOAc (10:1) afforded the corresponding product **4**. For the corresponding acid, the filtration was acidified with HCl (2 mol/L) to pH = 1, extracted with CH_2Cl_2 three times, and evaporated to give the product as white crystals in reported yields.

Procedures for the Transformation from *N*,*N*-Dimethylbenzylamine 1 to Functionalized Toluene 4 in One Pot. In a typical experiment, $PdCl_2$ (4.4 mg, 0.025 mmol), $Cu(OAc)_2$ (90.8 mg, 0.5 mmol), and CF_3CH_2OH (2 mL) were added into a Schlenk tube. Then *N*,*N*-dimethylbenzylamine **1** (0.5 mmol) was added, followed by **2** (1.0 mmol) and HOAc (0.5 mL, 8.0 mmol). The flask was stoppered and heated at 85 °C in an oil bath for 24 h. After that, the reaction mixture was cooled to room temperature and K_2CO_3 (1.0 mmol), Pd/C (5 wt % Pd, 53 mg, 0.025 mmol), and additional EtOH (2 mL) were added. The mixture was stirred at 55 °C under H_2 at balloon pressure for 10 h. The mixture was neutralized and the solid (Pd/C and Cu) was filtered. The inorganic phase was extracted by CH_2Cl_2 three times. The organic layers were combined, dried over Na_2SO_4, evaporated, and purified by flash chromatography (first PE and then PE/EtOAc = 10:1) to give the product **4aa**. For the *o*-tolylpropanoic acid **4ad**, the workup procedure was different. The reaction was quenched with water. The mixture was filtered and extracted with ether (Et_2O) three times. The combined ether extracts were dried over anhydrous $MgSO_4$ and concentrated in vacuo. Purification by flash chromatography (first PE/EtOAc = 10:1 and then PE/EtOAc = 3:1) gave the product.

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Supporting Information Available: Brief experimental details and other spectral data for products **3** and **4**. This material is available free of charge via the Internet at http://pubs.acs.org.

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