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Directed Amination of Aryl Methyl Ethers Mediated by $Ti(NMe_2)_4$ at Room Temperature

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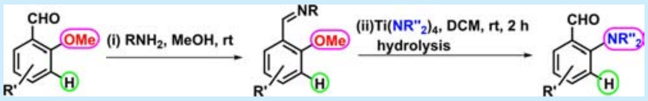
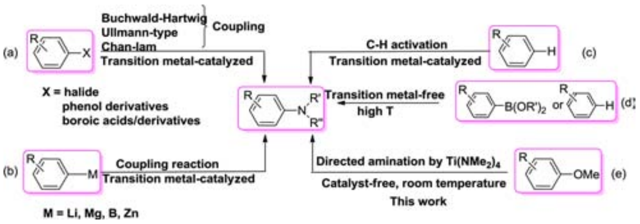
Supporting Information

ABSTRACT: An efficient C−O amination of aryl methyl ethers has been achieved. This transformation proceeds via imine-directed Ti(IV)-mediated cross-coupling reactions between aryl methyl ethers and $Ti(NR_2)_4$ at room temperature, straightforwardly leading to a series of arylamines. This protocol features a wide substrate scope, exclusive regioselectivity, and mild reaction conditions.



Aromatic amines are a valuable class of compounds that have numerous applications in pharmaceutical, agrochemical, dye, and polymer industrial.[1] Traditionally, arylamines are prepared by metal-catalyzed hydrogenation of aromatic nitro compounds.[2] Since the pioneering work by Migita and co-workers,[3] who established an effective palladium-catalyzed synthesis of arylamines via coupling reactions, spectacular advancements have been made in the efficient constructions of C_{aryl}−N bonds by metal-catalyzed coupling reactions. The important methodologies include: (i) Buchwald−Hartwig[4] or Ullmann-type,[5] and Chan−Lam[6] coupling reactions by employing palladium,[7] nickel,[8] copper,[9] and cobalt[10] as catalysts (Scheme 1a); (ii) metal-catalyzed amination of organometallic reagents (e.g., B, Zn, Mg, etc.)[11] (Scheme 1b); (iii) direct C−H amination of aromatic compounds[12] (Scheme 1c). More recently, transition-metal-free amination of aryl boronic acids and derivatives has emerged as an attractive strategy due to being devoid of metal catalysts (Scheme 1d).[13]

Scheme 1. Synthesis of Arylamines via Coupling Reactions



Due to the high bond dissociation energy of C−O bond, the phenol derivatives have been previously considered poor electrophiles in cross-coupling reactions. However, Wenkert,[14] Dankwardt,[15] Shi,[16] Chatani,[17] Kwong,[18] Garg,[19] Itami,[20] Martin,[21] Cook,[22] Han,[23] and other groups[24] reported that phenol derivatives could be applied as the electrophiles to the Kumada−Tamao−Corriu, Suzuki−Miyaura, Negishi, and other coupling reactions. Chatani[25] reported that Buchwald−Hartwig type amination could be accomplished by employing fused aromatic ethers and *N*-heteroaryl methyl ethers as electrophiles (Scheme 1a).

The above-mentioned precedents can provide an efficient and facile route to the arylamines. However, these coupling reactions were accomplished at a price. They rely on both noble palladium or other late transition metal catalysts, and specific phosphine-, carbene-, or phenolic ligands. Moreover, most of organometallic compounds are air and moisture sensitive. For metal-free reactions, drastic conditions are usually required to achieve high conversions. Hence, the development of a new protocol that provides amines without using any ligands and under mild conditions is in high demand and also poses an actual challenge.

Herein, we demonstrate a new strategy that involves imine-directed, Ti(IV)-mediated amination of aryl methyl ether by $Ti(NR_2)_4$, achieving arylamines at room temperature without using ligands and noble or late transition metals (Scheme 1e). This is the first time that an early transition metal was employed to mediate the amination reaction.

Recently, we disclosed that the NMe_2 group of $Ti(NMe_2)_4$ could activate the C−H bond.[26] We reasoned that the C−O bond of a phenol derivative might be activated by $Ti(NR_2)_4$. Encouraged by our previous success and also inspired by the literature reports that phenol derivatives could be aminated by the cleavage of aryl C−O bonds,[25] we postulated that readily available $Ti(NR_2)_4$ might be used both as a C−O bond activator and as an amination partner with phenol derivatives, giving arylamines straightforwardly via coupling reactions. Thus, we began our investigation by testing the reaction of $Ti(NMe_2)_4$ and a Schiff base *N*-(2-methoxybenzylidene)-1-(1*H*-pyrrol-2-yl)-methanamine (**3a**), which was formed by the condensation reaction between (1*H*-pyrrol-2-yl)methanamine (**1a**) and 2-methoxybenz-aldehyde (**2a**). In **3a**, an imine group is attached to the ortho position of a methoxy group as a directing group since imines have been previously employed as directing groups for amination reactions.[27] To our delight, an aminated product 2-

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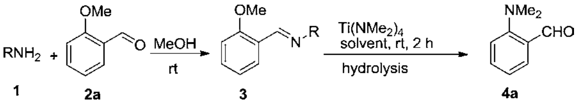
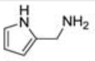
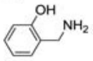
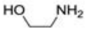
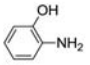
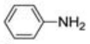
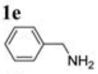
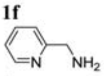
(dimethylamino)benzaldehyde (**4a**) (Table 1, entry 1) is obtained in high yield (92%) after hydrolysis. Intrigued by this harvest observation, we endeavored to investigate this directed amination more thoroughly by performing extensive screening of the directing groups, solvents, and loadings of $Ti(NMe_2)_4$.

Table 1. Discovery and Evaluation of Reaction Conditions

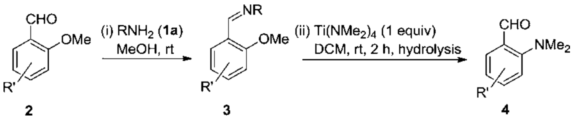


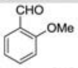
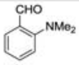
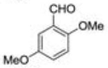
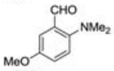
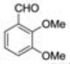
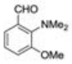
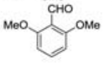
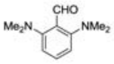
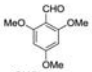
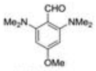
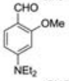
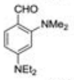
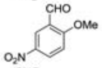
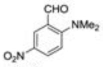
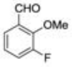
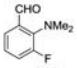
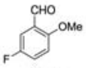
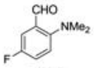
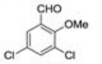
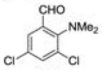
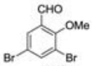
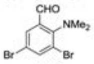
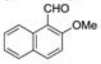
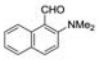
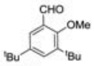
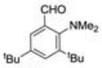
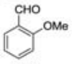
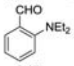
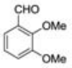
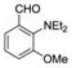
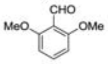
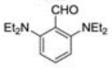
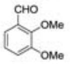
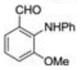
entry[a]	amine[b]		solvent	$Ti(NMe_2)_4$	yield of **4a**[%][c]
1		**1a**	DCM	1.0 equiv	92
2	**1a**		DCM	0.5 equiv	25
3		**1b**	DCM	1.0 equiv	31
4	**1b**		DCM	0.5 equiv	75
5	**1b**		THF	1.0 equiv	28
6	**1b**		THF	0.5 equiv	74
7		**1c**	DCM	0.5 equiv	27
8		**1d**	DCM	1.0 equiv	5
9	**1d**		DCM	0.5 equiv	3
10		**1e**	DCM	1.0 equiv	0
11	**1e**		THF	1.0 equiv	0
12		**1f**	DCM	1.0 equiv	0
13	**1f**		THF	1.0 equiv	0
14		**1g**	DCM	1.0 equiv	0
15	**1g**		THF	1.0 equiv	0

[a]Reaction conditions: **3** (0.5 mmol), solvent (5 mL), $Ti(NMe_2)_4$ (0.5 or 0.25 mmol), room temperature, 2 h. [b]Amines used for the synthesis of the directing imine groups of **3**. The loadings of **1** and **2** and the detailed preparations of **3** are provided in the Supporting Information. [c]Yield of the isolated product.

After the amine employed to prepare the directing group was switched to 2-(aminomethyl)phenol (**1b**), the desired product **4a** was obtained in good (Table 1, entries 4 and 6) and relatively lower (Table 1, entries 3 and 5) yields, showing **1a** and **1b** are good amine substrates for the directing group. Other amines are also tested, and none of them showed better yields than **1a** and **1b** (Table 1, entries 7−15). 2-Aminoethanol (**1c**) afforded **4a** in low yield, 2-aminophenol (**1d**) gave trace amount of the product, and no products were detected for **1e**, **1f**, and **1g**. Solvents did not show the remarkable effect on the yields. The yields of **4a** in THF and DCM were almost the same. We found that the loadings of $Ti(NMe_2)_4$ were crucial to the yields of **4a**. When **1a** was used as the directing amine group, excellent yield of **4a** was afforded for 1 equiv of $Ti(NMe_2)_4$. Nevertheless, 0.5 equiv of $Ti(NMe_2)_4$ was the better choice as **1b** was used for constructing the directing group.

Table 2. Ti(IV)-Mediated Amination of Aryl Methyl Ether by $Ti(NMe_2)_4$



entry[a]	aryl methyl ether		product		yield[%][b]
1		**2a**		**4a**	87%
2		**2b**		**4b**	88%
3		**2c**		**4c**	81%
4		**2d**		**4d**	78%
5		**2e**		**4e**	75%
6		**2f**		**4f**	83%
7		**2g**		**4g**	78%
8		**2h**		**4h**	81%
9		**2i**		**4i**	70%
10		**2j**		**4j**	65%
11		**2k**		**4k**	87%
12		**2l**		**4l**	82%
13		**2m**		**4m**	Trace[c]
14		**2a**		**4n**	80%[d]
15		**2c**		**4o**	81%[d]
16		**2d**		**4p**	74%[d]
17		**2c**		**4q**	20%[e]

[a]Reaction conditions: **1a** (0.5 mmol), **2** (0.5 mmol), solvent (5 mL), $Ti(NMe_2)_4$ (0.5 mmol), room temperature, 2 h. [b]Isolated yield. [c]**1a** and **1b** were employed to synthesize the directing imine group. [d]$Ti(NEt_2)_4$ was used as amination partner. [e]$Ti(HNPh)_4$ was used as coupling partner. A mixture of **4q** and 2-methoxy-*N*-phenyl-6-((phenylimino)methyl)aniline (**4q-1**) was obtained. See Supporting Information for the details.

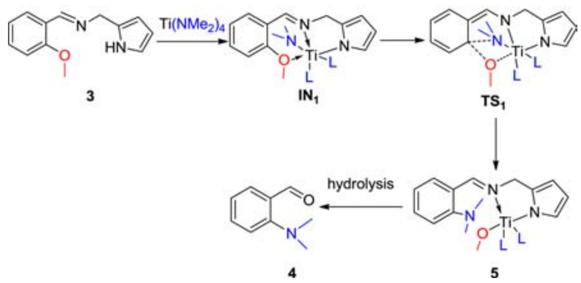
With these optimized reaction conditions in hand, we endeavored to expand the scope and generality of this directed amination reaction (Table 2). To simplify the reaction, the starting substrates (**3**) were changed to the substituted methoxybezealdehydes (**2**) and amines (**1a** or **1b**) since the directing imine groups could be generated *in situ* via the condensation reaction of **2** and amines (**1a** or **1b**). When 2-methoxybezealdehyde (**2a**) was used as the substrate, 87% yield of the amination product was afforded, which is slightly lower than that of straightly employing imine as the directing group (Table 1, entry 1). Electron-rich methoxybenzaldehydes with another one methoxy group at either the para or ortho position, or other two methoxy groups at the meta position, of the OMe group of methoxybenzaldehydes were proved to be good substrates for this transformation, producing the corresponding aminated products in good yields (Table 2, **2a**−**2e**). 4-(Diethylamino)-2-methoxybenzaldehyde (**2f**), albeit also effective, furnished the product in good yield. Having an electronwithdrawing NO_2 substituent at the para position, methoxybenzaldehyde **2g** gave excellent coupling product. Remarkably, the fluoro, chloro, and bromo moieties in methoxybenzaldehydes **2h**−**2k** were all tolerated under this novel transformation and afforded the targeted products in moderate to good yields, making further elaborations of the corresponding aminated products possible. 2-Methoxy-1-naphthaldehyde (**2l**) was found to couple with $Ti(NMe_2)_4$ efficiently and afforded the desired product in good yield. The bulky substituents on the phenyl ring of the methoxybenzaldehyde derivative **2m** affected the efficiency of the coupling reaction, and trace amount of the aminated product was obtained. When $Ti(NEt_2)_4$ was used as the coupling partner (Table 2, entries 14−16), good yields of the targeted products (**4n**−**4p**) were also obtained.

Importantly, exclusive regioselectivity was observed in all cases, and the methoxy group at the ortho position was aminated only. With two ortho positions of the aldehyde group being occupied by methoxy groups, doubly aminated products were produced (**4e** and **4p**).

The generality of this process was expanded by conducting coupling reaction between **2c** and $Ti(HNPh)_4$. It was found that $Ti(HNPh)_4$ could be employed in this transformation. Two products 3-methoxy-2-(phenylamino)benzaldehyde (**4q**) and 2-methoxy-*N*-phenyl-6-((phenylimino)methyl)aniline (**4q-1**) were determined. For the convenience of purification, **4q-1** was further reduced to 2-methoxy-*N*-phenyl-6-((phenylamino)-methyl)aniline (**4q-2**). Compounds **4q** and **4q-2** were fully characterized. Unfortunately, −H^{t}NBu and $-NPh_2$ could not be introduced into the products by using this methodology.

A proposed mechanism for the amination process is outlined in Scheme 2. Initially, the condensation reaction between **1a** and **2** generates the imine substrate **3**. Next, the reaction of $Ti(NMe_2)_4$ with **3** gives titanium complex **IN1** in which the metal center may adopt a pseudo octahedral geometry. The nitrogen atom of a NMe_2 group, which is cis to the methoxy oxygen atom, might be quite close to the carbon atom bearing the methoxy group. After dearomatization process, the interactions of C, N, O, and Ti atoms may give a four-membered ring transition state **TS1**, which subsequently undergoes a C−O bond-cleavage and a C−N bond-forming process to give complex **5**. Hydrolysis of **5** affords the aminated product **4**. For the methoxy group being meta to the imine directing group, greatly enlarged Ti−O and C−N distances are resulted. Thus, the expected four-membered Ti−N−C−O ring could not be generated, and no amination occurs for the meta C−O bond, elucidating the regioselectivity of the reactions.

Scheme 2. Postulated Mechanism for the Formation of the Aminated Product



One of the titanium complexes $[Ti(C_{15}H_{18}N_3O)_2(OMe)(NMe_2)](hex)_{0.125}(tol)(H_2O)_{0.25}$ (**5ac**) was isolated from the reaction between $Ti(NMe_2)_4$ and *N*-(2,3-dimethoxybenzylidene)-1-(1*H*-pyrrol-2-yl)methane amine (**3ac**) in THF at room temperature (Figure 1). X-ray quality crystals of **5ac** were grown from solvent mixture of toluene and hexane. The titanium center of **5ac** displays distorted octahedron geometry and is chelated by two aminated ligand sets, suggesting the amination occurs via an imine-directed Ti(IV)-mediated process.

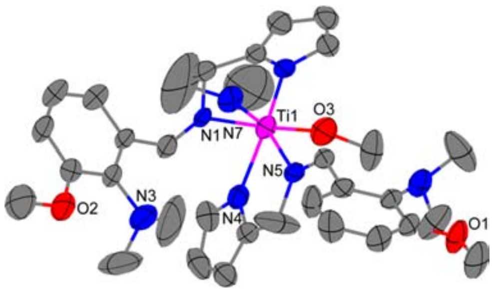


Figure 1. Solid state structure of **5ac** with thermal ellipsoids drawn at 50%. Hydrogen atoms have been omitted for clarity.

In light of the observations that one equivalent of $Ti(NMe_2)_4$ gave lower yields of **4a** while 0.5 equiv of $Ti(NMe_2)_4$ resulted in good yields of **4a** (Table 1, entries 3−6) when **1b** was used as the amine source for the directing group, we attempted to explore if the substrate 2-(((2-methoxybenzylidene)amino) methyl)-phenol (**3ba**), which was generated by the condensation reaction between **1b** and **2a**, was consumed by some unexpected side reactions. To this end, we tried to isolate the intermediate of the reaction between **3ba** and $Ti(NMe_2)_4$. A titanium compound Ti_2[2-((2-(2-(dimethylamino)benzylamino)-1-(2-(dimethylamino)phenyl)-2-(2-hydroxyphenyl)ethylimino)methyl)-phenol]$(NMe_2)_4$ (OMe) (**6ba**) was generated and its crystal structure was determined (Figure S2). Complex **6ba** is dinuclear and is chelated by an *in situ* formed molecule 2-((2-(2-(dimethylamino)benzyl-amino)-1-(2-(dimethylamino)pheny)-2-(2-hydroxyphenyl)ethyl-imino)ethyl) phenol. It is obvious that C−C coupling[28] and C−O amination reaction occurred simultaneously, as the bulky molecule 2-((2-(2-(dimethylamino)benzylamino)-1-(2-(dimethylamino)pheny)-2-(2-hydroxyphenyl)ethylimino)ethyl)phenol was produced by C−C coupling of 2-((2-(dimethylamino)benzyl-amino)methyl)-phenol and 2-((2-(dimethylamino)benzylimino)methyl)phenol. The formation of **6ba** suggests that some of $Ti(NMe_2)_4$ reagents were consumed by the side reaction, giving the target products with lower yields.

In summary, we have developed a general, mild and experimentally simple method for the amination of aryl methyl ethers. This transformation proceeds via imine-directed Ti(IV)-mediated cross-coupling reactions between aryl methyl ethers and $Ti(NR_2)_4$ at room temperature. A variety of aryl methyl ethers can participate in the process with good yields. The room temperature reaction coupled with a broad substrate scope render this method particularly attractive for the preparation of arylamines.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Details of the synthesis of the complexes, the characterizations of the compounds, and X-ray crystallographic data of **5ac** and **6ba**. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01229.

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Notes

The authors declare no competing financial interest.

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