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Letter

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Borane Catalyzed Chemoselectivity-Controllable N-alkylation and ortho C-alkylation of Unprotected Arylamines Using Benzylic Alcohols

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KEYWORDS: Unprotected arylamine, N-alkylation, ortho C-alkylation, chemoselectivity-controllable, $B(C_6F_5)_3$.

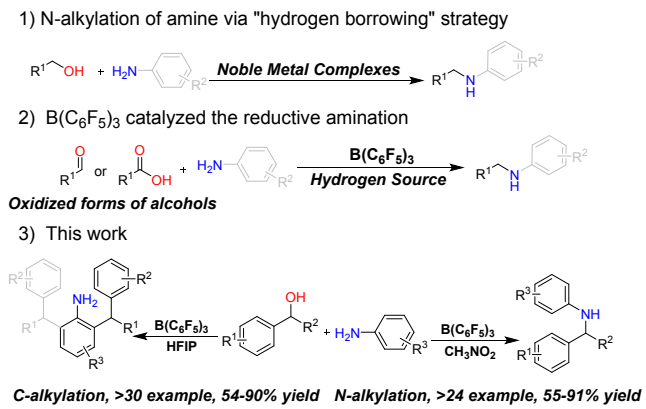
ABSTRACT: An unprecedented protocol for the efficient and highly chemoselective alkylation of unprotected arylamines using alcohols catalyzed by $B(C_6F_5)_3$ has been developed. The reaction gives N-alkylated products and ortho C-alkylated products in different solvents in good chemoselectivities and yields. Control experiments and DFT calculations indicated that the borane underwent alcohol/arylamine exchange to ensure catalytic activity, and a possible mechanism involving a carbocation is proposed.

Arylamines, which are important and fundamental compounds, have unique significance in industrial, agricultural and pharmaceutical chemistry.[1] Alkylation is one of the most direct and powerful tools for increasing the complexity of arylamines.[2] Numerous alkylating agents and methods have been developed to enable the N-alkylation of arylamines. However, traditional alkylating methods often generate stoichiometric amounts of waste and salt contaminants. Alcohols are a class of stable and widely available organic compounds with low toxicity, making them ideal alternatives to traditional alkylating agents. Since the first example of a transitional-metal catalyzed alkylation of aniline using an alcohol via the so-called "hydrogen borrowing" strategy was reported, this area has been intensely explored (Scheme 1).[3] However, this protocol has its natural limitations: 1) only primary alcohols have been thoroughly investigated, and 2) the alkylation is strictly limited to amino groups.

Using alcohols to obtain alkylated arylamines via nucleophilic substitution is another option.[4] Due to the poor leaving ability of hydroxyl groups and the incompatibility between catalysts and amines, few examples of such reactions have been reported. In 2011, Saito and coworkers developed a promising direct N-alkylation of amines with primary alcohols catalyzed by an Fe/amino acid system.[5] More recently, the Sweeney group reported an elegant N-allylation of amines catalyzed by nickel.[6] Despite these precedents, there are many problems in this area that must be addressed. N-Alkylations with bulky alcohols, e.g., secondary and tertiary alcohols, remain difficult.[4e] Moreover, to the best of our knowledge, the synthesis of *ortho* C-alkylated anilines, which are important motifs in ligands, still requires excess $ZnCl_2$/HCl and harsh reaction conditions.[7] Therefore, a catalytic, efficient and practical alkylation of arylamines using bulky alcohols is challenging yet highly appealing, and developing the catalytic alkylation with controllable chemoselectivity is also of interest.

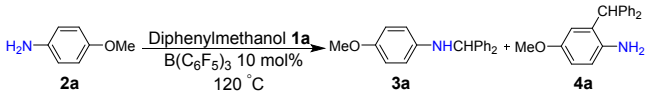
The main challenge in the direct catalytic alkylation of amines with alcohols is that an "off-cycle species" can form between the electron-rich arylamines and acidic catalysts.[4,5] To realize the alkylation, the catalyst must meet three basic conditions: 1) acidic enough to activate the hydroxyl group; 2) stable in wet and basic conditions; 3) able to dissociate from amines. $B(C_6F_5)_3$, a powerful nonmetallic Lewis acid catalyst, has been elegantly applied in "frustrated Lewis pair" catalysis.[8] Fu[9] and Ingleson[10] have both reported $B(C_6F_5)_3$ -catalyzed N-alkylations of amines using carboxylic acids or aldehydes in the presence of an organosilane. In their reports, the borane maintained its catalytic activity in the presence of arylamines (Scheme 1). $B(C_6F_5)_3$ has also been shown to activate hydroxyl groups for various transformations of alcohols.[11,12] The Li group developed a high *ortho*-selective alkylation of phenols using 1,3-dienes catalyzed by $B(C_6F_5)_3$ and studied the mechanism in great detail.[13] Zhang and Liu reported an elegant, chemoselective and *ortho*-selective substitution of phenols with diazoesters using the same catalyst.[14] However, *ortho*-selective alkylations of unprotected arylamines remain underdeveloped. Herein, we report an unprecedented protocol for practical and efficient N-alkylations and *ortho* C-alkylations of unprotected arylamines with bulky alcohols (secondary and tertiary alcohols) with controllable chemoselectivity catalyzed by $B(C_6F_5)_3$.

Scheme 1. The methods of catalytic alkylation of arylamines with alcohols.



The initial investigation with model substrates **1a** and **2a** revealed the successful N-alkylation in 63% yield using 10 mol% $B(C_6F_5)_3$ in toluene (Table 1, entry 1). The polar aprotic solvent CH_3NO_2 gave a higher yield of **3a** (entry 3), and an unexpected *ortho* C-alkylation product (**4a**) was also isolated. This exciting finding indicated that the challenging *ortho* C-alkylation of arylamines might be achievable with this catalytic system. The reaction did not proceed in ether or ester solvents (entries 4 and 5). To further improve the yield of the N-alkylation, the reaction was found to proceed smoothly under ambient atmosphere, generating **3a** in 86% yield after 48 h (entry 6). We wondered if a weakly acidic environment might promote the C-alkylation because the amino group would be protonated and thus less reactive. Polyfluorinated alcohols, which are protic nonnucleophilic solvents, have been utilized in functional reactions of aromatic rings in previous reports.[15] To our delight, an obvious increase in the yield of **4a** was observed when CF_3CH_2OH was used (entry 7). A perfluorinated alcohol, HFIP (1,1,1,3,3,3-hexafluoro-2-propanol), was found to be superior, giving 71% yield of **4a** with negligible N-alkylation product (entry 9).[16]

TABLES 1. Optimization of alkylation conditions.[a]

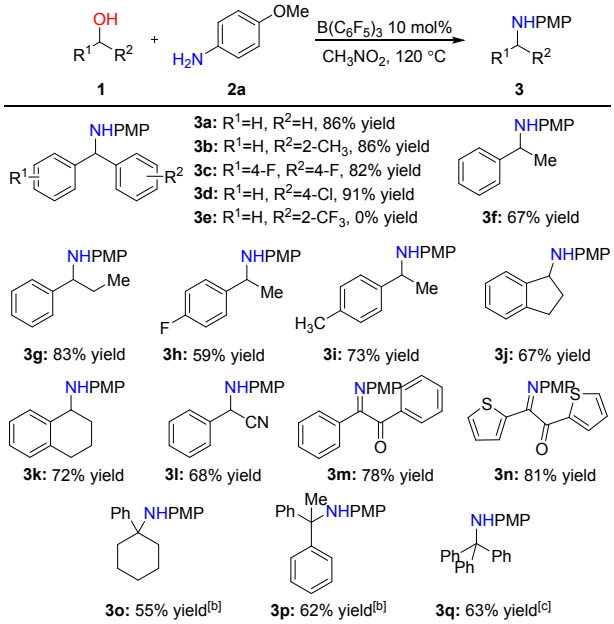


Entry	Solvent	yield%[b] (**3a**)	yield%[b] (**4a**)
1	toluene	63	<5
2	1,2-dichloroethane	62	<5
3	CH_3NO_2	71	12
4	THF	0	0
5	Ethyl acetate	0	0
6[c]	CH_3NO_2	86	<5
7	TFE	24	36
8	$CF_3CHOHCH_3$	27	30
9	HFIP	<5	71
10[c,d]	CH_3NO_2	67	<5

[a]Reaction conditions: **1a** (0.2 mmol), **2a** (0.4 mmol), $B(C_6F_5)_3$ (10 mol%), 15 ml sealed tube, 120 °C, 12h. [b]Isolated yield. [c]In 10 ml Schlenk tube with an air-balloon, 48h. [d]At 100 °C. HFIP=1,1,1,3,3,3-hexafluoro-2-propanol.

With the optimal conditions in hand, we decided to explore the alcohol scope of this N-alkylation. Diphenylmethanols with electron-neutral and electron-donating groups were suitable for the reaction (**3b-d,** 82-91%, Scheme 2). However, the desired reaction did not occur for the alcohol with a strong electron-withdrawing group (**3e**). For less reactive alcohols, 1-phenylethan-1-ol and 1-phenylpropan-1-ol, the N-alkylation still provided satisfactory results (**3f-i,** 59%-83%). Cyclic alcohols were smoothly transformed into the corresponding amines (**3j** 73%, **3k** 67%). The functional group tolerance of this system was also investigated (**3l-n**, 68-81%), and the products were further oxidized to imines under the reaction conditions (**3m**, **3n**). α-Tertiary amines always attract considerable interest due to their unique properties.[17] However, the catalytic alkylation of amines using tertiary alcohols is rarely achieved because of the low reactivity of tertiary alcohols and the elimination of the hydroxyl group. Luckily, the desired transformations proceeded with satisfactory efficiencies with little optimization of the conditions (**3o-q,** 55-63%).

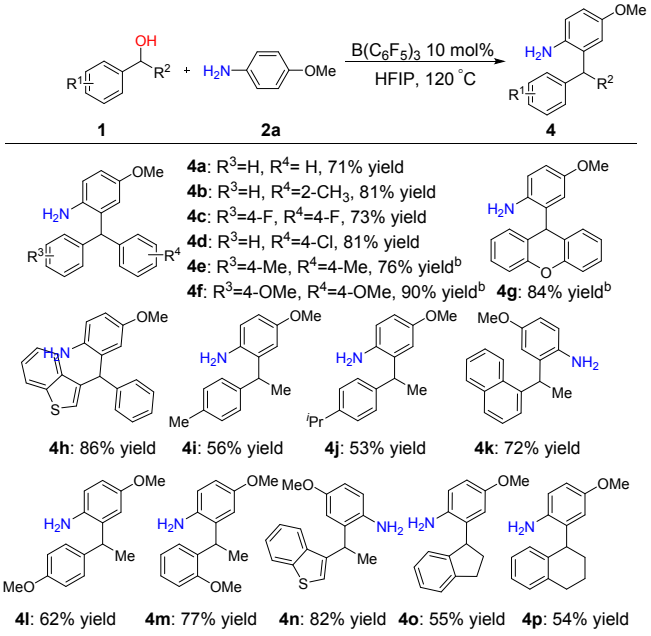
Scheme 2. The alcohol scope of N-alkylation.[a]



[a]Reaction conditions: **1** (0.2 mmol), **2a** (0.4 mmol), $B(C_6F_5)_3$ (10 mol%), CH_3NO_2 (1 ml), 120 °C, 10 ml Schlenk tube, 24-48h. Isolated yield. [b]CH_3NO_2 (0.5 ml), 85 °C. [c]DCE (0.5 ml), 85 °C.

A series of alcohols was examined under the *ortho* C-alkylation conditions (Scheme 3). Substituted benzhydrols gave the *ortho* C-alkylated arylamines in HFIP (**4a-4d**, 71%-81%); strangely, the C-alkylation with benzhydrols bearing electron-donating groups was more efficient in CH_3NO_2 than in HFIP (**4e-4g**). The electronic properties of the alcohol substrate is a key factor in the *ortho* C-alkylation. The H-substituted and F-substituted benzyl alcohols did not give the desired products, but even the very weak electron-donating group CH_3 could facilitate the C-alkylation, generating the corresponding product in moderate yield (**4i,** 56%). Other electron-rich benzyl alcohols efficiently produced *ortho*-alkylation amines under the optimal conditions (**4j-4p**, 53%-82%).

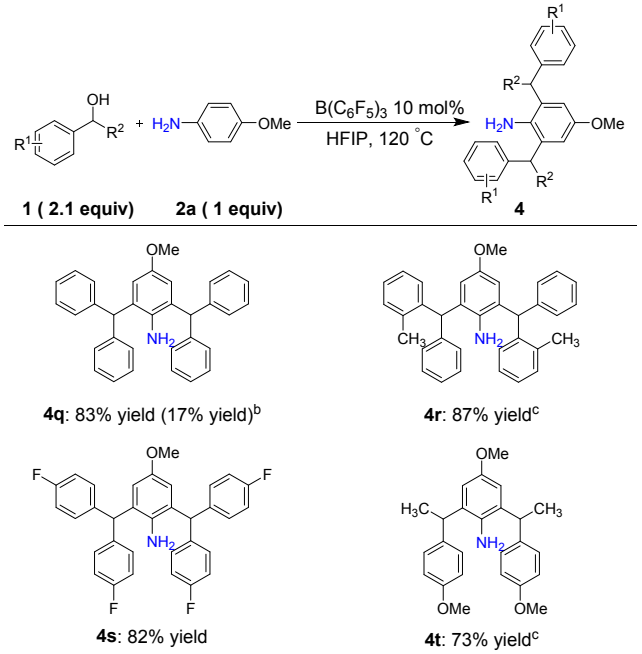
Scheme 3. The alcohol substrate of *ortho*-selective C-alkylation.[a]



[a]Reaction conditions: **1** (0.2 mmol), **2a** (0.4 mmol), $B(C_6F_5)_3$ (10 mol%), HFIP (1 ml), 15 ml sealed tube, 120 °C, 12h. Isolated yield. [b]CH_3NO_2 (1 ml).

Trisubstituted aromatics, which are important frameworks, appear frequently in organic ligands, functionalized organometallic compounds and polymeric materials.[18] The appealing bis C-alkylation products could be isolated in high yields (Scheme 4, **4q**-**4t**, 73%-87%) from this C-alkylation system when the ratio of alcohols to amines was changed to 2.1:1.

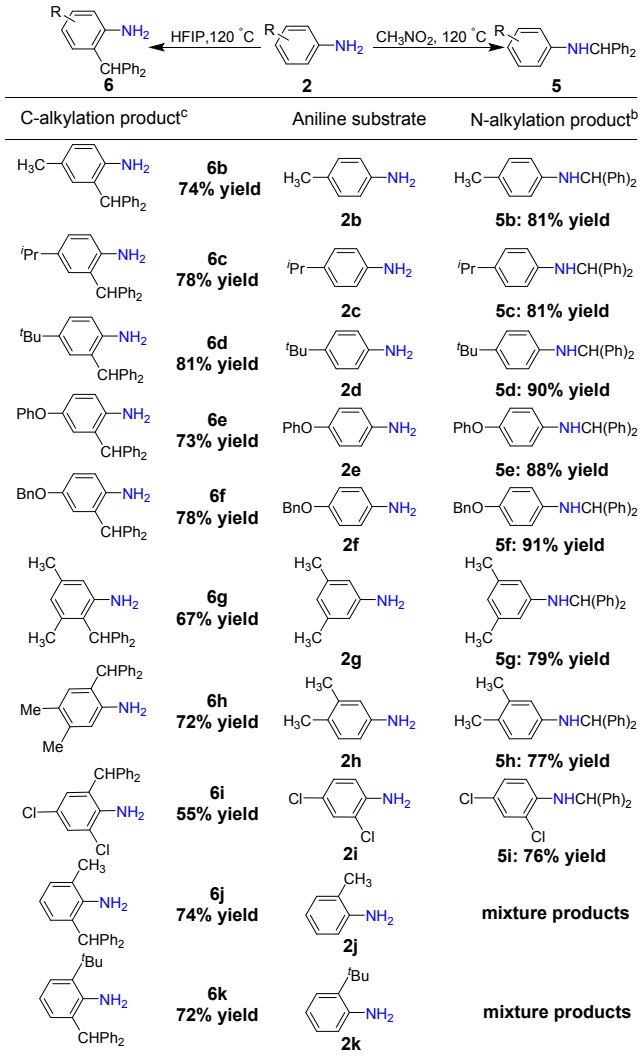
Scheme 4. The alcohol substrate of *ortho, ortho'* bis C-alkylation.[a]



[a]Reaction conditions: **1** (0.42 mmol), **2a** (0.2 mmol), $B(C_6F_5)_3$ (10 mol%, 0.02 mmol), HFIP (1 ml), 15 ml sealed tube, 120 °C, 12h. Isolated yield. [b]The ratio between **1a** and **2a** was 1:1. [c]dr = 1:1.

Different arylamines gave both the desired N-alkylation and C-alkylation products in high yields (Scheme 5). Different electron-neutral and electron-donating substituents at the 4-position were well tolerated (**5b**-**5f**, 81%-91%; **6b**-**6f**, 73%-81%). To ensure that the C-alkylation is *ortho*-selective, 3,5-dimethylaniline was evaluated and generated **6g** in high yield and excellent site selectivity. The *ortho*-alkylation was more likely to occur at a less hindered position (**6h**). 2-Substituted arylamines also gave excellent *ortho* selectivity in the C-alkylation under the optimal conditions (**6j**, 74%; **6k**, 72%); however, a mixture of unknown compounds was generated when the reactions were conducted under the N-alkylation conditions.

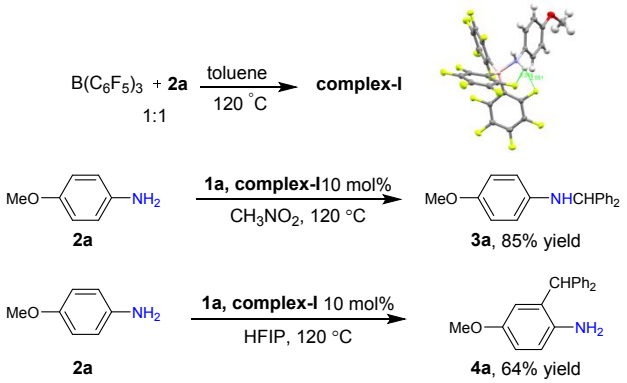
Scheme 5. The scope of arylamines.[a]



[a]The reaction was carried out under the specified conditions. Isolated yield. [b]Reaction conditions: **1** (0.2 mmol), **2a** (0.4 mmol), $B(C_6F_5)_3$ (10 mol%), CH_3NO_2 (1 ml), 120 °C, 10 ml Schlenk tube. [c]Reaction conditions: **1** (0.2 mmol), **2a** (0.4 mmol), $B(C_6F_5)_3$ (10 mol%), HFIP (1 ml), 15 ml sealed tube, 120 °C.

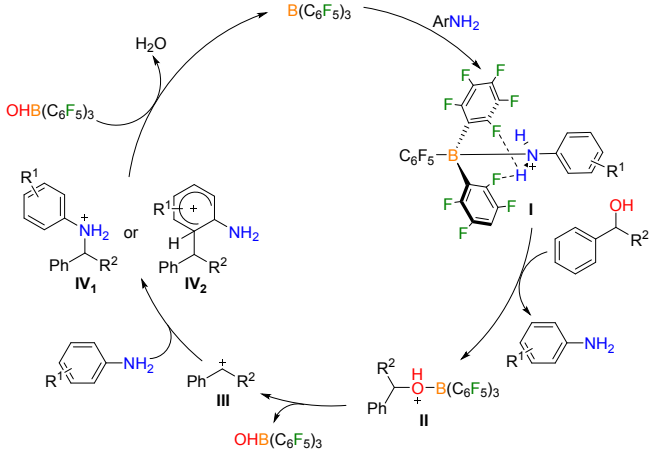
To provide more insight into the reaction, complex **I** ($B(C_6F_5)_3$-NH_2PMP) was synthesized, and the structure was confirmed by single-crystal X-ray analysis (Scheme 6). In a previous report, the generation of an "off-cycle species" between the amine and Lewis catalyst would limit the reaction,[4,5] but in our system, the N-alkylation and C-alkylation could be catalyzed by complex **I,** and similar results were achieved. Control experiments indicated that a S_N1 pathway was more reasonable in the alkylated reaction (see Supporting Information).

Scheme 6. The reaction catalyzed by complex I.



The $B(C_6F_5)_3$-catalyzed alkylation of arylamines with alcohols is assumed to proceed through four steps as shown in Figure 1: (1) alcohol/amine exchange of complex **I** generates catalyst-alcohol complex **II**; (2) dissociation of complex **II** delivers the carbocation; (3) nucleophilic attack of the carbocation by the arylamine produces the N-/C-alkylation intermediates; (4) protolysis of the σ-complex intermediates produces the final N-/C-alkylation products and regenerates $B(C_6F_5)_3$. To verify the feasibility of our proposed catalytic cycle, density functional theory (DFT) calculations with the M06-2X[19] functional were conducted to evaluate the energy profile and configurational information of the catalytic process. The reaction between model substrates diphenylmethanol (**1a**) and p-anisidine (**2a**) in toluene was chosen as the model reaction. Moreover, the temperature was set to 393.15 K, which is consistent with the actual reaction conditions. More computational details are described in the Supporting Information.

Figure 1. Plausible mechanism of the alkylation.



The free energy profile and pivotal transition states along the proposed reaction path are shown in Figure 2, and all structures involved in the catalytic cycle are shown in Figure S1 (see the Supporting Information). The coordination of $B(C_6F_5)_3$ and **2a** is highly exothermic by 16.9 kcal/mol, while the coordination with **1a** is slightly endergonic by 2.4 kcal/mol. This suggests that amine-coordinated catalyst complex **I** is thermodynamically stable; nevertheless, alcohol-amine exchange is also feasible. The subsequent alcohol activation is still endergonic by 11.2 kcal/mol with a barrier of 12.7 kcal/mol, indicating that intermediate complex **III** is metastable and that the formation of the carbocation is the rate-limiting step. In the initial stage of the arylamine alkylation, the carbocation is stabilized by the p-π conjugated system of **2a** via a cation-π interaction. The atom distances involved with the following nucleophilic attack are 3.48 Å for C-N and 3.09 Å for C-C, which are consistent with the both the N-alkylation and C-alkylation occurring simultaneously. However, the free energy profile of the two alkylation steps indicates that N-alkylation is absolutely favored over the C-alkylation both thermodynamically and kinetically. The N-alkylation is highly exothermic by 20.8 kcal/mol and was shown to be barrierless by our potential energy surface scan (Figure S2, see the Supporting Information), while the C-alkylation is slightly exothermic by 8.7 kcal/mol with a barrier of 5.2 kcal/mol. It seems that the N-alkylation could be the sole dominant pathway in our system. In the latter stage of the catalytic cycle, proton transfer from ammonium N-alkylation intermediate $\mathbf{IV_1}$ to $\mathbf{B_2}$ is endergonic by 2.0 kcal/mol without a reaction barrier; conversely, a rearomatization process involving a proton transfer from C-alkylation intermediate $\mathbf{IV_2}$ to $\mathbf{B_2}$ is highly exothermic by 16.4 kcal/mol with a negligible barrier of 0.1 kcal/mol. These significant thermodynamic differences facilitate the C-alkylation pathway. After the proton transfer process, hydroxide-coordinated catalyst $\mathbf{B_2}$ is reverted to water-coordinated complex $\mathbf{B_3}$. The coordinating free energy of the water molecule and $B(C_6F_5)_3$ is -6.0 kcal/mol, indicating that thermodynamically favored complex **I** can be generated rapidly via an exchange of arylamine **1a** and water. To further illuminate the chemoselectivity in different solvents, the interactions of **2a** with solvent molecules are investigated[10a,20] and the electrostatic potential surfaces of HFIP-**2a**, **2a** and CH_3NO_2-**2a** complex are displayed in Figure 2C. The arylamine **2a** is hydrogen-bonding acceptor in solvent HFIP making the amine group electron-deficient, which can be a severe obstacle for N-alkylation, and the reaction is more likely to undergo C-alkylation pathway. But in CH_3NO_2, the arylamine **2a** turns into hydrogen-bonding donor and the amine group is much more electron-rich, which enhances the N-alkylation giving a higher yield of N-alkylated product.

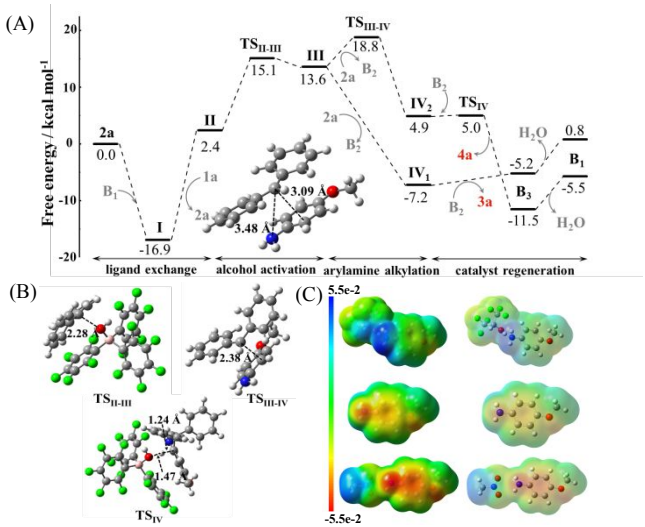


Figure 2. (A) Gibbs free energy profile of $B(C_6F_5)_3$-catalyzed alkylation of **2a** with **1a**. (B) 3D-structures of the transition states involved in the reaction process. (C) Electrostatic potential surfaces of HFIP-**2a**, **2a** and CH_3NO_2-**2a** complex.

In conclusion, efficient N-alkylations and ortho C-alkylations of arylamines with controllable chemoselectivity catalyzed by $B(C_6F_5)_3$ using alcohols has been developed. The

chemoselectivity is controlled by the solvent; CH_3NO_2 gives N-alkylation products, while HFIP, which is protic, is essential for C-alkylation. The reaction features a wide substrate scope and provides convenient access to advanced arylamines. Mechanistic studies and DFT calculations suggest that the reaction might proceed through a four-step mechanism, and the feasibility of N-alkylation and ortho C-alkylation is well demonstrated.

ASSOCIATED CONTENT

The Supporting Information is available free of charge on the ACS Publications website.
Experimental details, GCMS, and NMR spectra of products (PDF)
Crystallographic data for Complex **I** (CIF)

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Author Contributions

The manuscript was written through contributions of all authors. / All authors have given approval to the final version of the manuscript. / ‡ S.-S. Meng and X. Tang contributed equally.

Notes

The authors declare no competing financial interests.

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