

Tungsten-Catalyzed Direct *N*-Alkylation of Amines with Alcohols

Xiao-Bing Lan,^{†, §} Zongren Ye,^{†, §} Weikang Li,[†] Jiaohao Liu,[†] Ming Huang,[†] Yan Liu,^{‡,*} and Zhuofeng Ke^{†,*}

[†] School of Materials Science & Engineering, PCFM Lab, Sun Yat-sen University, Guangzhou 510275, P. R. China

[‡] School of Chemical Engineering and Light Industry, Guangdong University of Technology, Guangzhou 510006, P. R. China

Supporting Information Placeholder

ABSTRACT: The implementation of earth-abundant metals mediated chemistry is a major goal in homogeneous catalysis. Borrowing hydrogen/hydrogen autotransfer (BH/HA) reaction, as a straightforward and sustainable synthetic method, has attracted considerable attention in the development of earth-abundant metal catalysts. Herein, we report a tungsten-catalyzed *N*-alkylation reaction of amines with primary alcohols via BH/HA. This phosphine-free W(phen)(CO)₆ (phen=1,10-phenanthroline) system was demonstrated as a practical and easily accessible *in-situ* catalysis for a broad range of amines and alcohols (up to 49 examples, including 16 previously undisclosed products). Notably, this tungsten system can tolerate numerous functional groups, especially the challenging substrates with sterically hindered substituents, or heteroatoms. Mechanistic insights based on experimental and computational studies are also provided.

Green and sustainable synthesis using alcohols as starting materials have attracted considerable attention because of their easy availability from renewable feedstock and nontoxic nature.¹ Thus, there is a high demand for practical reactions that utilize renewable alcohols and convert them into fine chemicals. To this end, the borrowing hydrogen/hydrogen autotransfer (BH/HA) has become one of the most important strategies for the green or sustainable formation of C–N bond directly from alcohols.² Different from traditional C–N bond formation methods like classic nucleophilic substitutions, hydroaminations,³ Buchwald-Hartwig reactions,⁴ and Ullmann reactions,⁵ the BH/HA *N*-alkylation reactions using unactivated renewable alcohols as a nucleophile and generate water as the byproduct, thus making the overall process atom-economical and sustainable (Scheme 1a).

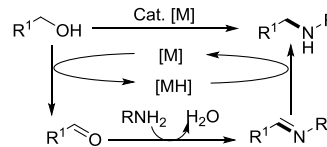
Since the earliest reports of homogeneous catalysts for the *N*-alkylation of amines by alcohols in 1932,⁶ various transition metal catalytic systems have been developed (Scheme 1a, top right). The traditional ones are usually based on precious metals such as Ir, Ru, Rh, and others.⁷ However, due to concerns regarding the cost, limited availability, and toxicity of precious-metal catalysts, numerous efforts have been devoted to developing non-noble metal catalysts⁸ with Fe,^{8a, 8b} Co,^{8c} as well as recently developed Mn,^{8d, 8e} and Ni,^{8f} for the *N*-alkylation of amines with alcohols. Very recently, Kempe and coworkers reported a chromium-catalyzed alkylation of amines with primary alcohols.⁹ Thus, to extend the scope and potential of the BH/HA transformation, developing new types of catalytic systems using alternative earth-abundant metals for BH/HA application is highly desirable.

Driven by previous studies in BH/HA reactions that earlier transition metal manganese incorporated with strong donor ligands showed advantages in reactivity and mild reaction

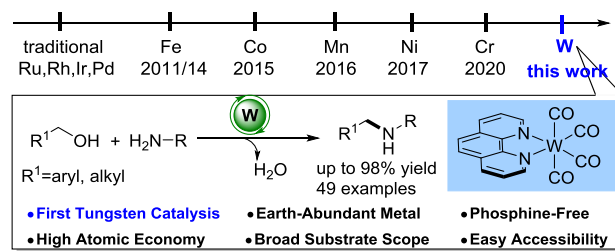
conditions,¹⁰ and encouraged by our theoretical understanding,¹¹ we envision the tungsten, which is an earlier transition metal than manganese, as well as a third-row transition metal with much higher earth abundance with respect to noble metals,¹² could be an appealing candidate in the design of new type of earth-abundant metal catalysts for BH/HA reactions. As part of our ongoing efforts, herein, we would like to disclose the first W-catalyzed direct *N*-alkylation of amines with alcohols. This tungsten system may be a potential alternative to previous systems, as a practical and easily accessible catalysis, showing tolerance to challenging substrates with sterically hindered substituents or heteroatoms, especially sulfur, via BH/HA methodology (Scheme 1b).

Scheme 1. Exploration and development of direct *N*-alkylation of amines with alcohols via BH/HA strategy

a) BH/HA-Mediated *N*-Alkylation of Anilines with Alcohols



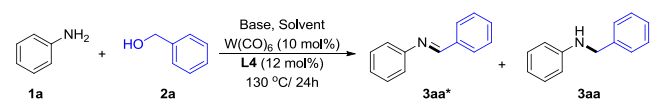
b) This Work: Tungsten-Catalyzed *N*-Alkylation of Anilines with Alcohols



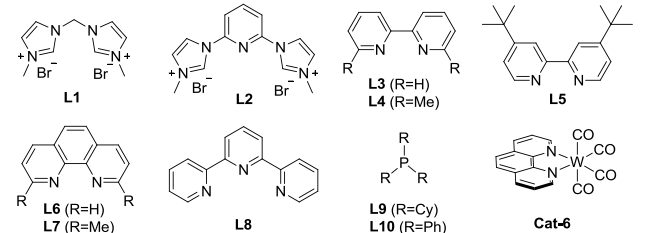
The alkylation of aniline (1a) with benzyl alcohol (2a) to *N*-benzylaniline (3aa) was selected as the model reaction to optimize reaction conditions (Table 1, top). After finding initial reaction conditions applying complex W(CO)₆, different easily available ligands (L1-L10) were tested to find the most suitable ligand for the catalysis, among which 1,10-phenanthroline (phen, L6) gave the highest conversion (90%) of 3aa (entries 1-11, Table 1). With this gratifying result in mind, optimization of other reaction parameters (such as solvent, base, and pre-catalyst loading, etc.) were evaluated. We observed the conversion of product 3aa was suppressed significantly when base other than KO^tBu, such as NaO^tBu, KOH, NaOH, Cs₂CO₃, K₂CO₃, or Na₂CO₃, was used (entries 12-17, Table 1). Optimally, product 3aa was obtained in 98% conversion and 94% isolated yield when 1,4-dioxane was used as the solvent (entry 18, Table 1). However, other solvents

such as DMF, DMSO, DMAc, CH₃CN, THF, *t*-AmOH, were found to be less suitable (entries 19-24, Table 1). Further reduction of the pre-catalyst loading resulted in decreased product conversion (entry 25, Table 1). The complex Cat-6 is expected to be *in-situ* formed for the catalysis. To confirm the participation of Cat-6, the synthesized complex Cat-6¹³ was employed in the reaction, which could give 3aa in 98% conversion and 95% isolated (entry 26, Table 1). Decreasing the amount of complex Cat-6 to 5 mol% also resulted in a reduced yield of 3aa (entry 27, Table 1). Control experiments suggest that both the complex and the base are essential for the success of the reaction (entry 28-29, Table 1).

Table 1. Optimization of the reaction conditions^a



| Entry | Ligand | Base | Solvent | Conversion ^b (%) | |
|-----------------|--------|---------------------------------|--------------------|-----------------------------|--------|
| | | | | 3aa* | 3aa |
| 1 | --- | KO ^t Bu | toluene | 16 | 40 |
| 2 | L1 | KO ^t Bu | toluene | 33 | 58 |
| 3 | L2 | KO ^t Bu | toluene | 19 | 62 |
| 4 | L3 | KO ^t Bu | toluene | 1 | 74 |
| 5 | L4 | KO ^t Bu | toluene | 1 | 75 |
| 6 | L5 | KO ^t Bu | toluene | 1 | 71 |
| 7 | L6 | KO ^t Bu | toluene | 0 | 90 |
| 8 | L7 | KO ^t Bu | toluene | 3 | 62 |
| 9 | L8 | KO ^t Bu | toluene | 3 | 63 |
| 10 | L9 | KO ^t Bu | toluene | 1 | 68 |
| 11 | L10 | KO ^t Bu | toluene | 4 | 44 |
| 12 | L6 | NaO ^t Bu | toluene | 28 | 47 |
| 13 | L6 | KOH | toluene | 15 | 8 |
| 14 | L6 | NaOH | toluene | 18 | 22 |
| 15 | L6 | Cs ₂ CO ₃ | toluene | 20 | 2 |
| 16 | L6 | K ₂ CO ₃ | toluene | 0 | 0 |
| 17 | L6 | Na ₂ CO ₃ | toluene | 0 | 0 |
| 18 | L6 | KO ^t Bu | 1,4-dioxane | 0 | 98(94) |
| 19 | L6 | KO ^t Bu | DMF | 34 | 35 |
| 20 | L6 | KO ^t Bu | DMSO | 0 | 5 |
| 21 | L6 | KO ^t Bu | DMAc | 0 | 44 |
| 22 | L6 | KO ^t Bu | CH ₃ CN | 0 | 0 |
| 23 | L6 | KO ^t Bu | THF | 1 | 89 |
| 24 | L6 | KO ^t Bu | <i>t</i> -AmOH | 20 | 45 |
| 25 ^c | L6 | KO ^t Bu | 1,4-dioxane | 0 | 71 |
| 26 ^d | Cat-6 | KO ^t Bu | 1,4-dioxane | 0 | 98(95) |
| 27 ^e | Cat-6 | KO ^t Bu | 1,4-dioxane | 0 | 68 |
| 28 ^f | --- | KO ^t Bu | 1,4-dioxane | 0 | 27 |
| 29 | L6 | ----- | 1,4-dioxane | 0 | 0 |

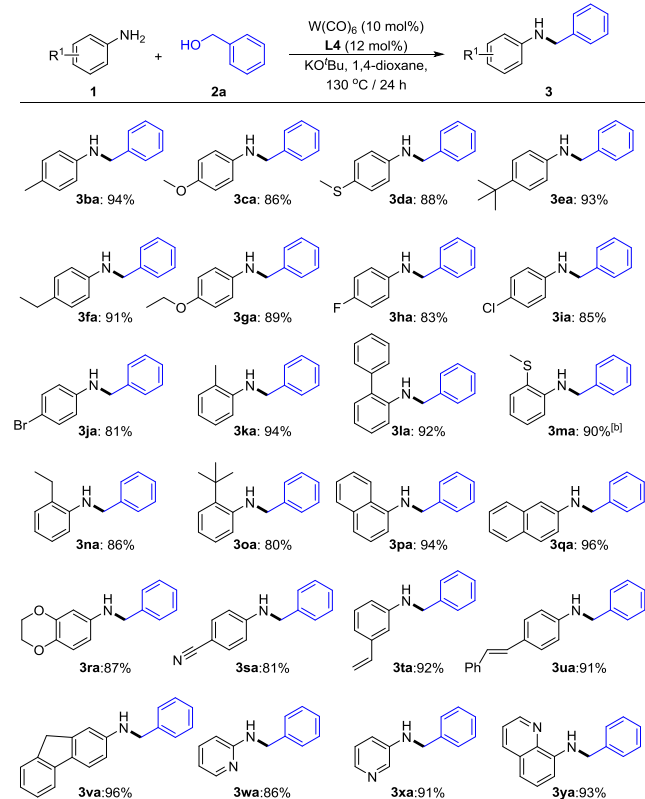


^a Reaction conditions: 1a (0.5 mmol), 2a (0.6 mmol), W(CO)₆ (0.05 mmol), Ligand (0.06 mmol), KO^tBu (0.5 mmol) and solvent (1 mL), at 130 °C for 24 h. ^b Conversion was determined by GC analysis (isolated yield in parentheses). ^c W(CO)₆ (0.025 mmol), L6 (0.03 mmol). ^d 1a (0.5 mmol), 2a (0.6 mmol), Cat-6

(0.05 mmol), KO^tBu (0.5 mmol) and 1,4-dioxane (1 mL), at 130 °C for 24 h. ^e Cat-6 (0.025 mmol). ^f No W(CO)₆ was added.

After the optimized reaction conditions were established, we next examined the versatility with various substituted anilines. As shown in Scheme 2, the reactions of anilines with electron-donating and electron-withdrawing groups all proceeded smoothly to deliver the desired products 3ba-3ga in good yields. Halogen substituents including F, Cl, and Br were also well tolerated, providing corresponding products 3ha-3ja in high yields. Delightedly, anilines with sterically hindered groups at 2-position were well tolerated (3ka-3oa), even the highly sterically hindered substrate 2-(*tert*-butyl)aniline reacted smoothly to afford the desired product 3oa in a good yield of 80%. 1-Naphthylamine and 2-naphthylamine reacted with 2a to desired products (3pa and 3qa) in high yields, 94% and 96%, respectively. Important building blocks for pharmaceuticals, such as aminobenzodioxane derivatives 3ra, was also efficiently obtained by the alkylation of 1,4-benzodioxan-6-amine with 2a. This catalytic system was also compatible with amines containing the C≡N or C=C bonds, which gave 3sa-3ua in 81-92% yields. Notably, heteroaromatic amines led to the compounds 3wa-3ya in good isolated yields (86-93%). Even the challenging sulfur-containing substrates can lead to desired products in good yields (3da and 3ma, 90% and 90%, respectively).

Scheme 2. Reaction scope of amines^a

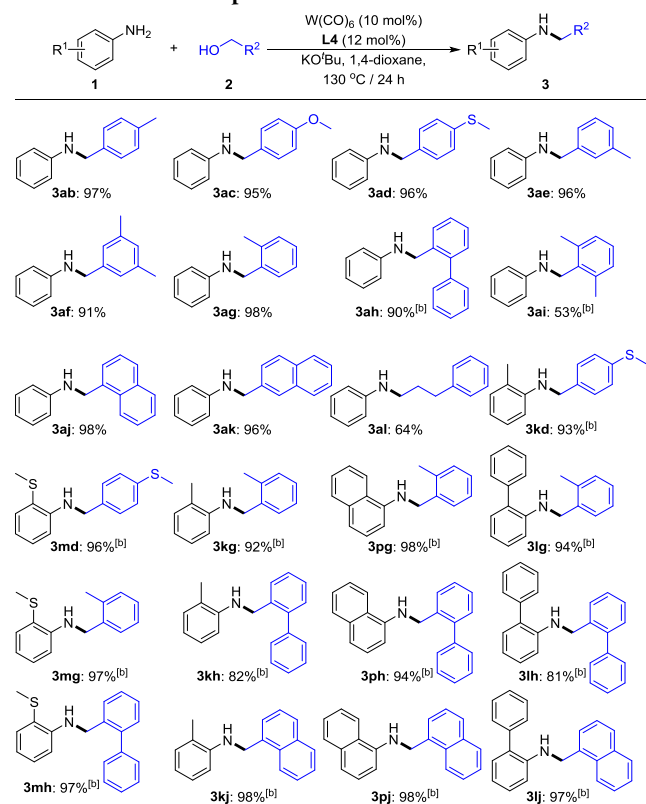


^a Reaction conditions: 1 (0.5 mmol), 2a (0.6 mmol), W(CO)₆ (0.05 mmol), L6 (0.06 mmol), KO^tBu (0.5 mmol) and 1,4-dioxane (1 mL), at 130 °C for 24 h, isolated yield. ^b New compound.

Having demonstrated that this protocol is compatible with various amines, we subsequently investigated the scope of alcohols

(Scheme 3). Benzylic alcohols with varying electronic and bulky substituents on the phenyl ring are viable for this *N*-alkylation reaction (3ab-3ai). Noticeably, the sterically hindered 2-methylbenzyl alcohol and 2-biphenylmethanol were compatible, generating 3ag and 3ah in yields of 98% and 90%, respectively. More hindered (2,6-dimethylphenyl)methanol made the transformation a little sluggish and gave 3ai in moderate yield (53%). 1-Naphthylethanol and 2-naphthylethanol reacted with 1a to desired products 3aj-3ak in high yields, 98% and 96%, respectively. Notably, more challenging sterically hindered coupling partners were also compatible and furnished the products in good yields (3kd-3lg), which are previously undisclosed. Surprisingly, alkylthio substrates that are usually challenging were demonstrated to be excellently compatible in this *W*-catalyzed system (93-97% yields).

Scheme 3. Reaction scope of alcohol^a

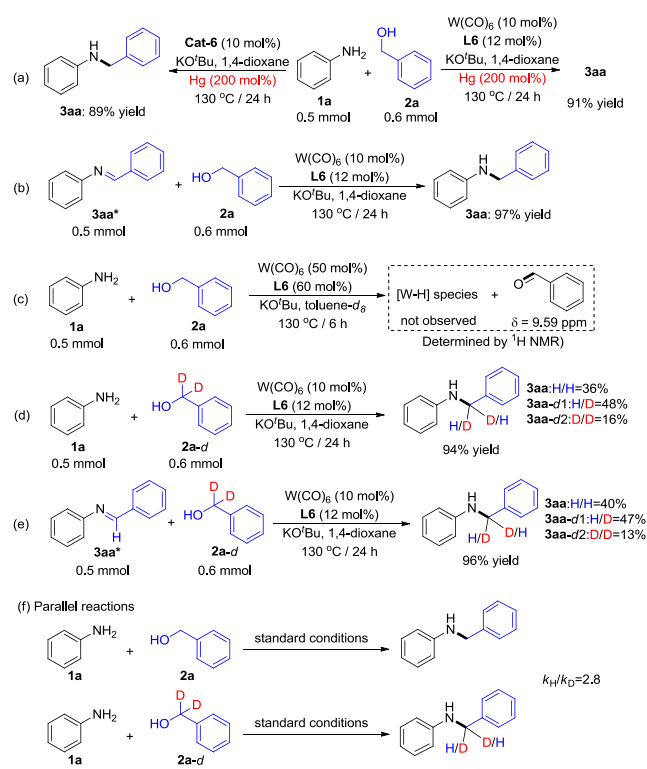


^a Reaction conditions: 1 (0.5 mmol), 2 (0.6 mmol), $W(CO)_6$ (0.05 mmol), L6 (0.06 mmol), KO^tBu (0.5 mmol) and 1,4-dioxane (1 mL), at 130 °C for 24 h, isolated yield. ^b New compounds.

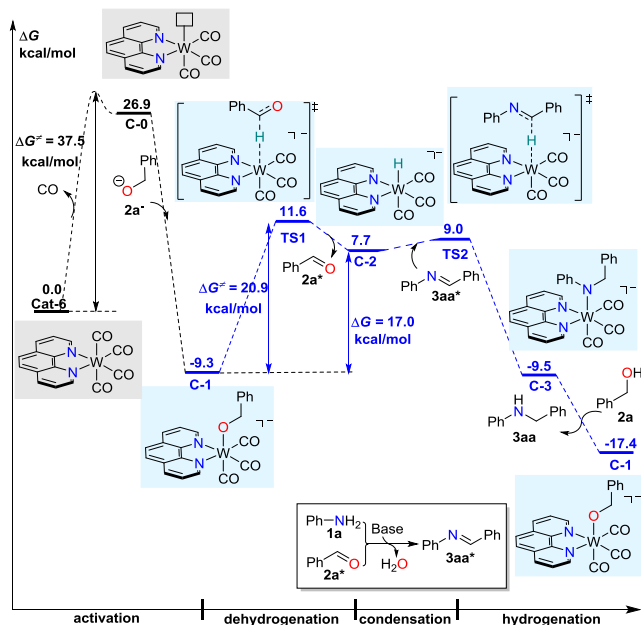
To understand the mechanism of this *W*-catalyzed direct *N*-alkylation of amine by alcohol, various control experiments were conducted as shown in Scheme 4. Firstly, elemental mercury was added to the reactions by *in-situ* conditions or by molecular pre-catalyst Cat-6, and there was no retardation observed in comparison to the reaction without mercury, which indicated that the catalytic reaction is homogeneous in nature (Scheme 4a). Secondly, the reaction 3aa* with benzyl alcohol under standard conditions afforded 3aa in 97% yield (Scheme 4b), suggesting the *N*-alkylation process follows the BH/HA pathway with imine as

the key intermediate. Furthermore, ¹H NMR characterization was performed (Scheme 4c, details see SI) to detect the *in-situ* generated [W-H] species, with 50 mol% pre-catalyst loading.^{1c, 8q} Unfortunately, the trap of [W-H] species was not successfully probably due to the thermodynamical instability and the high reactivity of the [W-H] species (See DFT results below). No paramagnetic phenomena were observed during characterization, which implies the function of diamagnetic W(0) species for the catalysis. The detection of benzaldehyde formation by ¹H NMR further strengthened a BH/HA process. Subsequently, we conducted deuterium-labeling experiments. The reaction of 1a with 2a-d (97% D) under the standard reaction conditions gave a mixture of *N*-alkylated products 3aa (36%), 3aa-d1 (48%) and 3aa-d2 (16%) in 95% yield (Scheme 4d). Similarly, the imine (3aa*) was allowed to react with 2a-d (97% D) under the standard reaction conditions and gave a mixture of *N*-alkylated products 3aa (40%), 3aa-d1 (47%) and 3aa-d2 (13%) in 96% yield (Scheme 4e). These results imply that a mechanism involving H/D exchange in this reaction. All the deuterated experimental evidence is in agreement with the previous literature observation.^{8s} Formation of 3aa/3aa-d1 (Scheme 4d) and 3aa-d2 (Scheme 4e) indicates the reversibility in the imine formation and the H/D exchange related to the active [W-D] species. Furthermore, a parallel experiment revealed a $k_H/k_D = 2.8$ (Scheme 4f), which indicates that the alcohol oxidation should be involved in the rate-determining step (RDS) of the catalytic cycle. All of these findings strongly imply a BH/HA mechanism, involving the dehydrogenation of alcohol to aldehyde, which reversibly couples with the amine to imine. And the imine is hydrogenated by the [W-H] species to furnish the alkylated amine.

Scheme 4. Control experiments. Yields are for the isolated.



Based on the experimental findings, DFT calculations were performed to further elucidate the mechanism of this W-catalyzed N-alkylation of amines with alcohols. After the activation of precatalyst Cat-6 by CO dissociation ($\Delta G^\ddagger = 37.5$ kcal/mol), under base conditions, the alkoxide will coordinate to the metal center after deprotonation (C-1, -9.3 kcal/mol⁻¹, Scheme 5). The catalytic cycle consists of three major steps: (1) the hydride elimination of the alkoxide to aldehyde, (2) the condensation of aldehyde and amine to imine, (3) the hydrogenation of imine. The hydride elimination occurs via transition state TS1 ($\Delta G^\ddagger = 20.9$ kcal/mol⁻¹) to form [W-H] species C-2 and the aldehyde. Then the aldehyde reacts with the amine to form imine reversibly. The hydrogenation of imine by [W-H] species C-2 to amido complex C-3 goes through transition state TS2 ($\Delta G^\ddagger = 1.3$ kcal/mol⁻¹ relative to C-2). Finally, the protonation of amido in C-3 leads to secondary amine as the final product and regenerates active species C-1. DFT results indicate the hydride elimination through transition state TS1 to be the RDS in the catalytic cycle, which is in good accordance with the KIE studies (Scheme 4f). On the other hand, DFT studies suggest that the dissociation of CO from Cat-6 needs to overcome a free energy barrier of 37.5 kcal/mol⁻¹, which could be responsible for the relatively high reaction temperature for this system. Notably, DFT studies revealed a highly active [W-H] species ($\Delta G = 17.0$ kcal/mol⁻¹), which well explains the difficulties in characterizing the [W-H] species in our ¹H NMR studies (Scheme 4c). This is in sharp difference from other non-noble transition metal catalysts.⁸ The highly active [W-H] species may serve as a distinguishing feature for tungsten systems as alternative BH/HA catalysts, for example, to achieve unique functional group tolerance or asymmetric transformations in the future.

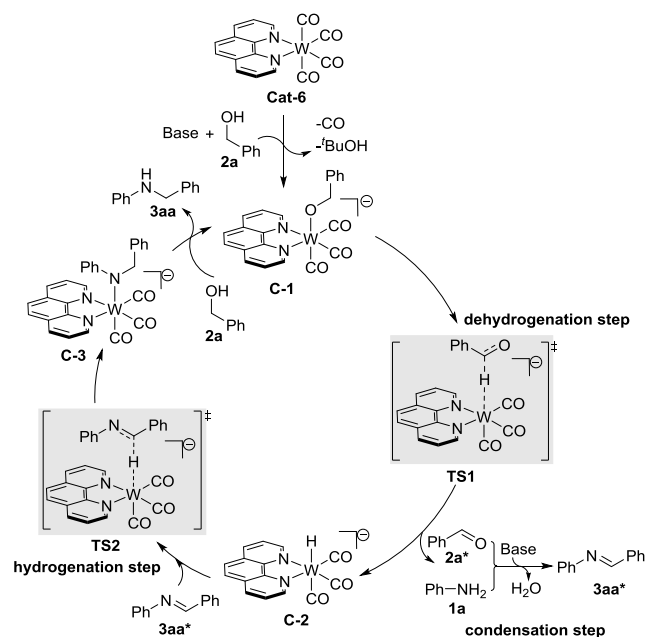


Scheme 5. Potential energy surface of the catalytic cycle for Cat-6 catalyzed alkylation of 1a by 2a at the B3LYP-D3/(ECP&6-311++G**)/SMD(1,4-dioxane)//B3LYP-D3/(ECP&6-31+G**) level of theory (details see SI). Free energies are given in kcal/mol.

On the basis of the above mechanistic results and literature precedents,^{15, 7k, 8o} a plausible direct outer-sphere mechanism for this W-catalyzed transformation is presented in Scheme 5.

Precatalyst Cat-6 reacts with alcohol in the presence of a base to form the alkoxy complex C-1, after the dissociation of the CO ligand. This active species C-1 subsequently underwent an outer sphere hydride elimination to release aldehyde. Then, a base mediated coupled reaction between the aldehyde and amine produces the imine (3aa*). The highly active W-hydride (C-2) then reduce the imine to form amido complex C-3, which is further protonated by alcohol to release the N-alkylated product, regenerating alkoxy complex C-1 for next catalytic cycle.

Scheme 6. Plausible reaction mechanism.



In summary, the first example of tungsten-catalyzed direct N-alkylation of amines by alcohols through BH/HA is reported. This phosphine-free W(phen)(CO)₄ system is simple, easily accessible, and *in-situ* operated. It has extensive functional group tolerance, including challenging substrates with sterically hindered substituents or heteroatoms (49 amines, 16 of which have not been reported so far). Experimental and computational studies indicated a plausible BH/HA mechanism and the involvement of the benzylic C-H bond in the rate-determining step. Our results imply that tungsten complexes can serve as a new type of non-noble catalysts for BH/HA reactions, alternative to the reported Fe, Co, Ni, Mn, and Cr, which could be potential to extend the tool-box and the scope of the (de)hydrogenative transformations.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at <http://pubs.acs.org>.

Detailed experimental procedures, characterization data, computational details and structures, copies of ¹H NMR and ¹³C NMR spectra for all isolated compounds.

AUTHOR INFORMATION

Corresponding Author

*E-mail for Y. Liu: yanliu@gdut.edu.cn

*E-mail for Z. F. Ke: kezhf3@mail.sysu.edu.cn

ORCID

Xiao-Bing Lan: 0000-0001-5301-069X

Zongren Ye: 0000-0002-1877-7999

Jiahao Liu: 0000-0002-7820-042X

Ming Huang: 0000-0001-8597-8259

Yan Liu: 0000-0002-3864-1992

Zhuofeng Ke: 0000-0001-9064-8051

Author Contributions

§ X.-B. Lan (exp.) and Z.R. Ye (comput.). These two authors contributed equally to this work.

Notes

The authors declare no competing financial interests.

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