

Enhanced Hydride Donation Achieved Molybdenum Catalyzed Direct *N*-Alkylation of Anilines or Nitroarenes with Alcohols: From Computational Design to Experiment

Weikang Li, Ming Huang, Jiahao Liu, Yong-Liang Huang, Xiao-Bing Lan, Zongren Ye, Cunyuan Zhao, Yan Liu, and Zhuofeng Ke*



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The N-alkylation of amines is an important application in pharmaceutical chemistry and fine chemicals.¹ The borrowing hydrogen or hydrogen autotransfer (BH/HA) methodology (Scheme 1a)² using alcohols as alkylation reagents is a green and sustainable method to replace the traditional synthetic way, in which the hazardous alkyl halides are used as reactants while undesirable side products or wastes are unavoidable. Various catalytic systems for *N*-alkylation have been developed using this BH/HA methodology, including widely investigated noble-metal-based homogeneous catalysts, like Ir,³ Ru,⁴ Pd,⁵ etc.,⁶ and recently emerging nonprecious metal homogeneous systems such as Fe,⁷ Co,⁸ Mn,^{7g,9} Ni,¹⁰ Cr,¹¹ and W.¹²

In contrast, directly using nitroarenes to replace anilines as starting material for the N-alkylation reaction with alcohols is more attractive due to improved step economy and functional group compatibility.¹³ However, the nitroarenes should be able to be catalytically hydrogenated into anilines to guarantee a successful N-alkylation.¹⁴ Thus, the direct N-alkylation of nitroarenes with alcohols is still a big challenge, and the reported homogeneous catalysts for it are rare yet. Among them, the noble metal complexes (Ru, ^{13a,15} Pd, ¹⁶ and Ir¹⁷) were generally required. In 2019, Morrill reported the nonprecious metal Mn catalyzed one-pot conversion of nitroarenes into Nmethylarylamines with synthesis grade methanol (Scheme 1b).¹⁸ The key point in realizing this transformation should rely on the reduction of nitroarenes by a highly active catalyst via metal-hydride species with an enhanced hydride-donating ability. We recently found that bis-NHC-Mn(I) could catalyze *N*-alkylation of amines with alcohols at room temperature,¹⁹ due

to the higher M–H orbital energy of *bis*-NHC-Mn(I)-hydride than those of traditional PNP-Mn(I) catalysts. Inspired by this, we envision that a low-valent d^6 metal center with a strong electron-donating ligand could be a proper catalyst with enhanced hydride-donating ability.

To further prove our hypothesis, a density functional theory (DFT) study was conducted to predict the M-H bonding orbital energy for various d⁶ transition metals with easily accessible bis-pyridine, NHC-pyridine, and bis-NHC ligands. These NHC-M complexes bearing strong field ligands, though with metal centers in different oxidation states, would operate similar hydrogenation/dehydrogenation mechanisms.^{20a} Inspiringly, the *bis*-NHC-Mo(0)-hydride **Mo**-C1 is predicted to have the highest M-H orbital energy, implying the strongest hydridedonating ability (Figure 1a). The relationship between M–H orbital energy and hydricity was built with an R^2 up to 0.99 (section 8.2 in the SI). Encouragingly, Beller and Madsen have successfully applied molybdenum to the hydrogenation of amides as well as the dehydrogenative synthesis of imines from alcohols and anilines.²¹ Also, some heterogeneous molybdenum catalytic systems for the BH/HA process have been reported previously.²² The homogeneous Mo-catalyzed BH/HA Nalkylation of amines or nitroarenes with alcohols is yet to be

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Scheme 1. Molybdenum Catalyzed N-Alkylation of Anilines or Nitroarenes with Alcohols

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



b) N-Alkylation of Nitroarenes with Alcohols



⊖ Usually noble metal needed: Ru, Pd, Ir

⊖ Only one non-noble metal example: Mn

c) This work: strong hydride-donating bis-NHC-Mo(0) catalyst



realized. As part of our ongoing interest in BA/HA,^{12,19,23} herein, we reported the first example of a non-noble Mo catalytic system for this transformation (Scheme 1c).

Based on the computational design results, using the commercially available $Mo(CO)_6$ and easily accessible bis-NHCs or NHC-pyridines as sources, five Mo(0) complexes Mo-1-5 were synthesized with satisfying yields of 46-65% (Figure 1b, synthesis and characterization details in the SI). Their structures were further characterized by X-ray diffraction (XRD) analysis of single crystals except for Mo-3. The molecular structure of Mo-1 shows similar Mo- C_{NHC} bond distances to the reported *bis*-BenzNHC-Mo(0).²⁴ After that, these complexes were investigated for the N-alkylation of aniline with benzyl alcohol as the model reaction in 130 °C. The designed bis-NHC-Mo(0) complex Mo-1 was found more active than pyridyl-NHC-Mo(0) (Mo-4) or picolyl-NHC-Mo(0) (Mo-5), which emphasizes the important donation effect of the NHC ligand, after considering both the σ donation and the π backdonation^{20b} via Charge Decomposition Analysis (section 8.3 in the SI). Note that, the larger substituent -iPr(Mo-2) or -nBu(Mo-3) on the NHC ligand did not improve the yield.¹⁹ Therefore, Mo-1 was chosen as the precatalyst for the Nalkylation of anilines with alcohols, and the optimal reaction conditions were established when 2 mol % Mo-1, 1.3 equiv of alcohols, 1.1 equiv of KO^tBu, and 0.5 mL of *n*-hexane solvent were used. For details of the conditions' screenings, see Tables S1-S9.

The scopes of alcohols were first explored (Figure 2). The electron-donating groups -Me (3b-d), -OMe (3k), and -SMe (3l) led to good yields of 76–92%, and the substrates with conjugated aromatic or bulky substituted groups like naphthalene (3m and 3n), diphenyl (3q), and benzyloxy (3r) reacted smoothly with yields of 85–89%. Heteroaromatic alcohols like pyridine derivative 3o and thiophene derivative 3p slightly decreased in yields (61–63%). Besides, several aliphatic alcohols like cyclohexanol methanol (3s), *n*-butanol



Figure 1. (a) The M–H bonding orbital energies (eV) for the predicted metal-hydride species (n = -1, M = Cr(0), Mo(0), W(0); n = 0, Mn(I), Re(I); n = 1, M = Fe(II), Ru(II); n = 2, M = Co(III)). (b) N-alkylation of aniline with benzyl alcohol with different Mo(0) complexes.^{a,b} aReaction conditions: **1a** (0.5 mmol), **2a** (0.5 mmol), **[Mo]** (1 mol %), KO'Bu (1 equiv), *n*-hexane (1 mL), seal tube, 130 °C oil bath, 24 h. ^bGC yields. °**2a** (0.5 mmol), **1a** (0.65 mmol), **Mo-1** (2 mol %), KO'Bu (1.1 equiv), *n*-hexane (0.5 mL), 130 °C oil bath, 24 h, reaction tube capped with a rubber septum. Molecular structure of **Mo-1**, selected bond lengths [Å] and angles [deg]: Mo1–C1 2.028(3), Mo1–C2 1.994(3), Mo1–C3 1.984(3), Mo1–C4 2.034(3), Mo1–C5 2.260(3), Mo1–C6 2.246(3); C1–Mo1–C4 170.25(13), C2–Mo1–C6 175.15(11), C3–Mo1–C5 170.71(11). (Thermal ellipsoids are shown at 50% probability, and C–H atoms are omitted for clarity.)

(3t), *n*-hexanol (3u), and *n*-octanol (3v) were verified to be reactive, with moderate yields (45-55%). However, when alcohols with shortened carbon chains (methanol, ethanol) were tested, no obvious products were detected. Note that, when halide-substituted benzyl alcohols were investigated, various amounts of side-product 3a were detected. This dehalogenation probably happened because of the strongly basic environment and high temperature, similar to previously observed phenomena.²⁵ The fluoro benzyl alcohol was almost all transferred to **3a**. Chloro benzyl alcohols 1e furnished 37% chloro-product (3e) and 44% 3a. para- and meta-Chlorobenzyl alcohols resulted in 74% and 75% chloro-product (3f-g), as well as 10% 3a. metaand para-Bromobenzyl alcohols produced 51-64% bromoproduct (3h-i), along with 11-24% 3a. Surprisingly, 70% metatrifluoromethyl product (3j) was exclusively obtained with the -CF₃ electron-withdrawing group.

Compared with primary alcohols, the *N*-alkylations of anilines with secondary alcohols were reported much less, mainly due to the steric hindrance.²⁶ Gratifyingly, **Mo-1** was found capable of realizing the *N*-alkylation of anilines with secondary alcohols. Diphenylmethanol and its methyl and methoxy derivatives were



Figure 2. Scopes of alcohols and anilines.^{a,b a}General reaction conditions: 2 (0.5 mmol), 1 (0.65 mmol), Mo-1 (2 mol %), KO'Bu (1.1 equiv), *n*-hexane (0.5 mL), 130 °C oil bath, 24 h, reaction tube capped with a rubber septum. ^bIsolated yield. n.d = not detected. ^cGC yields. ^d1b (1.3 mmol), Mo-1 (5 mol %), KO'Bu (2.2 equiv), *n*-hexane (1 mL), 150 °C oil bath, seal tube.

successfully reacted with anilines, achieving good yields of 82–90% (3w-z).

Next, scopes of anilines were investigated by reacting with 4methylbenzyl alcohol **1b** as a model reactant (Figure 2). Pleasingly, chloro- and bromoanilines smoothly yielded halidesubstituted secondary aniline products (4b-e: 55-80%), although the fluoroaniline was found to conduct dehalogenation totally. Substrates bearing electron-donating groups like methyl (4f-h), methoxy (4i), thiomethyl (4j), and *tert*-butyl (4k) afforded the mono-*N*-alkylated anilines in good yields (60-90%). The *ortho*-phenylaniline (41) however led to a lower yield of 50% due to adjacent steric hindrance. The conjugated aromatic naphthylanilines (4m-n) resulted in satisfying yields of 68-75%. Besides, pyridine derivatives could have a good yield of product (4r: 68%). Interestingly, when vinylaniline was used, 81% double-bond-reduced product 4p instead of a vinyl product was detected under slightly harsher conditions.

Encouraged by the total reduction of vinylaniline, the more challenging nitroarene substrates were investigated and proved effective for the *N*-alkylation reaction catalyzed by **Mo-1** (Figure 3). In this transformation, three more hydrogen molecules



Figure 3. *N*-Alkylation of nitroarenes with alcohols.^{a,b} ^aGeneral reaction conditions: **5** (0.5 mmol), **1** (3 mmol), **Mo-1** (5 mol %), KO'Bu (5 equiv), and *n*-hexane (1 mL), 150 °C oil bath, 24 h, seal tube. ^bIsolated yield. ^cGC yields.

would be consumed (Scheme 1b), and excessive alcohols are needed. When more alcohols, KO^tBu, and Mo-1 were utilized, nitrobenzene 5a and benzyl alcohol 1a successfully yielded the N-alkylation product **6a** in 89% yield at 150 °C (Table S10). Benzyl alcohol and its derivatives like -Me, -OMe, and -'Pr reacted with nitrobenzene 5a affording good yields of 79-90% (6a-d). Also, 5a could couple with 1-naphthalene methanol to 81% N-alkylation product 6e. However, substrates with bulkier substituents like -Bn and $-^{t}Bu$ did not perform so well with 42-48% yields (6f-g). Comfortingly, challenging secondary alcohol diphenylmethanol and its methoxy derivative could afford products 6h-i at 70-73% yields. On the other hand, -Cl, -Me, and -OMe substituted nitroarenes could smoothly react with 4-methybenzyl alcohol 1b affording N-alkylation products 6j-n at 45-90% yields. These results indicated the potential of this *bis*-NHC-Mo(0) catalyst as a highly active catalytic system for BH/HA processes.

Experimental and theoretical studies were further performed to gain mechanistic insight into this catalytic system. The Hg poisoning experiment suggested that the catalysis probably proceeds homogeneously (Figure 4a). The control experiment of N-benzylideneaniline 3a' with benzyl alcohol could yield 88% of product 3a, which supported the BH/HA mechanism (Figure 4b). Deuterium-labeling experiments could produce 22% of 3ad2 (Figure 4c), indicating an H/D exchange in the mechanism.^{10c} More importantly, a kinetic isotope effect (KIE = 2.2) was measured by the parallel reactions, indicating the alcohol dehydrogenation is most likely involved in the ratedetermining step (RDS) (Figures 4d and S19). According to the outcomes of the substrates, the electron-donating substituted substrates (like 3d) have a better performance than the electronwithdrawing substituted substrates (like 3g). Consequently, the electron-donating substituted substrates would be more favorable for the alcohol dehydrogenation step, which can be further supported by our mechanism studies (see discussion below).



Figure 4. Experimental and theoretical mechanism study.

A possible outer-sphere mechanism for this catalyst system was proposed,^{12,19,23a} which includes precatalyst activation, alcohol dehydrogenation, imine in situ formation, and imine hydrogenation. First, one CO ligand would disassociate to form the active species **Mo-1a** with a vacant site. DFT studies (Figures 4e and S24–S26) suggest that this activation process requires overcoming an energy barrier of 39.7 kcal/mol, which might be the reason the catalysis operated at a relatively high temperature. Second, deprotonated alcohol would be dehydrogenated to aldehyde generating Mo(0)-hydride intermediate **A3** through transition state **TS1** (17.7 kcal/mol). As anticipated, intermediate **A3** is highly active and high in free energy (11.8 kcal/ mol). Exhaustive tries to trap the Mo(0)-hydride species were unsuccessful probably due to its thermodynamical instability kinetically high reactivity, though the Mo(0)–H species has been reported previously.²⁷ Luckily, indirect evidence for the involvement of crucial intermediate Mo(0)–H A3 species was provided by the hydrogen detection experiment (Figure 4e and Table S11). A reaction tube capped with a rubber septum would thus enhance the borrowing hydrogen due to the Mo(0)–H and Mo(0)…H₂ equilibrium. At last, the in situ generated imine would be hydrogenated by A3 through transition state TS2 (15.9 kcal/mol). The RDS of the catalytic cycle was calculated to be the dehydrogenation step ($\Delta G^{\ddagger} = 17.8$ kcal/mol), which is in good agreement with the KIE study. Further computational method comparisons suggest that optimization in the solvent led to similar results due to the insignificant effect of the nonpolar solvent, as shown in section 8.1 in the SI.

To better understand the enhanced hydride-donating ability of this *bis*-NHC-Mo(0) system, DFT calculations were further performed to study the hydrogenation of nitrobenzene in comparison with Mn(I) and Fe(II) systems (Figure 4f). As anticipated, the activation free energy of **Mo**–**C1** (14.7 kcal/ mol) is much lower than those of **Mn**–**C1** (20.8 kcal/mol) and **Fe**–**C1** (22.7 kcal/mol), which is well reflected by the highest M–H orbital energy (-0.75 eV) for *bis*-NHC-Mo(0).

In summary, a new type of *bis*-NHC-Mo(0) complex with an enhanced hydride-donating ability was rationally designed by both computational and experimental studies. The easily accessible *bis*-NHC-Mo(0) complex was successfully applied in the *N*-alkylation of anilines and challenging nitroarenes with alcohols through BH/HA transformation. This *N*-alkylation system has good substrate tolerance, including heteroatom-containing substrates and challenging secondary alcohols. In total, 44 secondary anilines were synthesized and isolated in yields up to 92%. More importantly, the direct *N*-alkylation of nitroarenes with alcohols was achieved by this molybdenum-mediated system. The total reduction of the vinyl substrate and nitroarenes could be ascribed to the enhanced hydride-donating ability of the Mo–H species. This Mo system presents a new example of a highly active catalyst for BH/HA transformations.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acscatal.1c02956.

Experimental and computational details (PDF)

CIF file 1 (CIF)	
CIF file 2 (CIF)	
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AUTHOR INFORMATION

Corresponding Author

Zhuofeng Ke – School of Materials Science & Engineering, School of Chemistry, PCFM Lab, Sun Yat-sen University, Guangzhou 510275, P. R. China; © orcid.org/0000-0001-9064-8051; Email: kezhf3@mail.sysu.edu.cn

Authors

- Weikang Li School of Materials Science & Engineering, School of Chemistry, PCFM Lab, Sun Yat-sen University, Guangzhou 510275, P. R. China
- Ming Huang Department School of Clinical Pharmacy, Guangdong Pharmaceutical University, Guangzhou 510006, P. R. China; o orcid.org/0000-0001-8597-8259
- Jiahao Liu School of Materials Science & Engineering, School of Chemistry, PCFM Lab, Sun Yat-sen University, Guangzhou 510275, P. R. China

- Yong-Liang Huang Department of Chemistry, Shantou University Medical College, Shantou, Guangdong 515041, P. R. China; ◎ orcid.org/0000-0003-1569-014X
- Xiao-Bing Lan School of Materials Science & Engineering, School of Chemistry, PCFM Lab, Sun Yat-sen University, Guangzhou 510275, P. R. China; Orcid.org/0000-0001-5301-069X
- Zongren Ye School of Materials Science & Engineering, School of Chemistry, PCFM Lab, Sun Yat-sen University, Guangzhou 510275, P. R. China
- Cunyuan Zhao School of Materials Science & Engineering, School of Chemistry, PCFM Lab, Sun Yat-sen University, Guangzhou 510275, P. R. China; orcid.org/0000-0002-3600-7226
- Yan Liu School of Chemical Engineering and Light Industry, Guangdong University of Technology, Guangzhou 510006, P. R. China; ⊙ orcid.org/0000-0002-3864-1992

Complete contact information is available at: https://pubs.acs.org/10.1021/acscatal.1c02956

Notes

The authors declare no competing financial interest.

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