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Direct Hydroxylation and Amination of Arenes via Deprotonative Cupration

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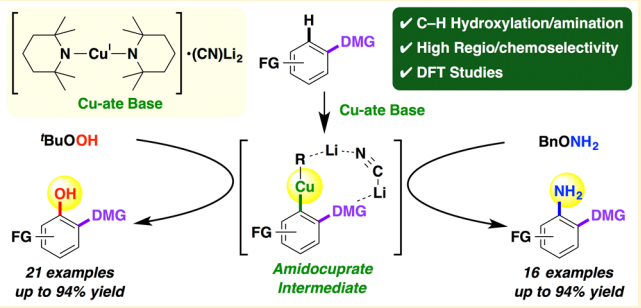
Supporting Information

ABSTRACT: Deprotonative directed ortho cupration of aromatic/heteroaromatic C−H bond and subsequent oxidation with *t*-BuOOH furnished functionalized phenols in high yields with high regio- and chemoselectivity. DFT calculations revealed that this hydroxylation reaction proceeds via a copper (I → III → I) redox mechanism. Application of this reaction to aromatic C−H amination using $BnONH_2$ efficiently afforded the corresponding primary anilines. These reactions show broad scope and good functional group compatibility. Catalytic versions of these transformations are also demonstrated.



INTRODUCTION

Directed ortho metalation (DoM) reaction was discovered over 75 years ago by Gilman[1] and Wittig[2] and is now a fundamental synthetic reaction for the regioselective preparation of aryl metal compounds.[3] Since the development of improved chemoselective bases,[4] DoM has become a general tool for access to a wide range of aromatic and heteroaromatic substrates and for regiocontrolled synthesis of multifunctionalized aromatics by utilizing intermediary aryl metal species as aryl anion equivalents and as cross-coupling partners. However, only limited attention has been paid to application of DoM for phenol[5]/aniline[6] synthesis, probably due to the lack of efficient and reliable transformation routes from the aryl metal intermediates.[7,8] This situation is in contrast to recent extensive developments in Pd-catalyzed aromatic C−H hydroxylation chemistry pioneered by Fujiwara,[9] Yu,[10] and others,[11] as well as Ru-[12] and Cu-based[13] methodologies (though most of those are only for use in phenol synthesis). Densely functionalized phenol and aniline derivatives are found in natural products and biologically active compounds (Figure 1); thus, functional-group-compatible, high-yielding, and reliable C−H hydroxylation/amination reactions should of significant value in synthesis and drug discovery. Therefore, a new, simple, chemoselective method suitable for late-stage installation of OH and NH_2 on arenes would still be highly desirable to complement currently available reactions.

We have recently shown that TMP-Cu-ate base (RCu(CN)-(TMP)Li_2, R = alkyl, phenyl, or TMP; TMP = 2,2,6,6-tetramethylpiperidido) promotes chemo- and regioselective deprotonative cupration of functionalized aromatics in the presence of various directed metalation groups (DMGs).[14]

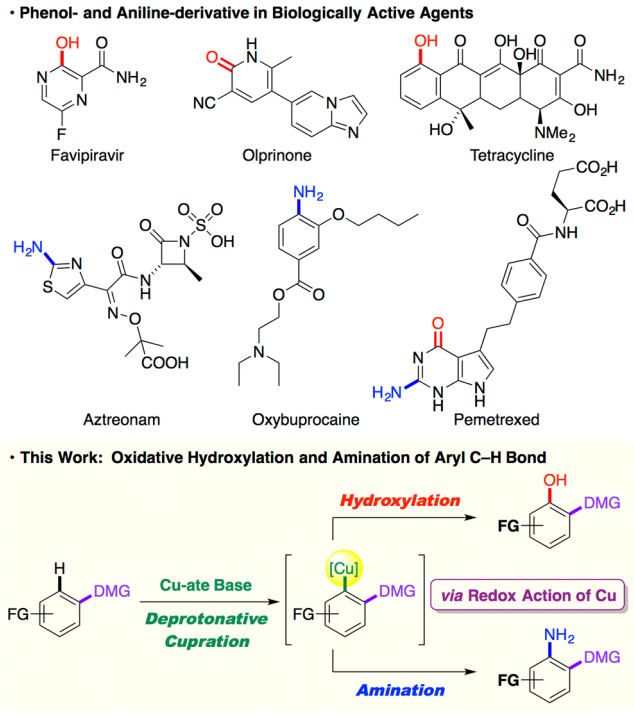


Figure 1. Aromatic hydroxylation and amination.

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Functionalized aryl cuprate intermediates act as versatile and potent aryl anions, reacting with various electrophiles in a polar fashion. The intermediates also undergo oxidative ligand coupling reaction in the presence of $PhNO_2$,[14a,15] and furthermore can be transformed into the corresponding phenols by reaction with molecular oxygen.[14a] However, this method suffers from significant limitations; for example, oxidation by molecular oxygen usually results in poor yields and incomplete conversion of aryl metal intermediates and is accompanied by formation of ligand-coupling side products. Additionally, the oxidation requires a stoichiometric amount of CuCN, and the operationally tedious procedure shows poor reproducibility and chemoselectivity.

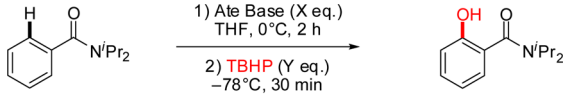
We present here a chemo- and regioselective direct aromatic C−H hydroxylation via deprotonative cupration followed by hydroxylation with *tert*-butyl hydroperoxide (TBHP). DFT calculations revealed the hydroxylation pathway and the key role of a copper redox process. We utilized this theoretical information to design a direct aromatic C−H amination as well as catalytic versions of these transformations, and confirmed their utility.

RESULTS AND DISCUSSION

Optimization of Hydroxylation Reaction. We focused on screening of suitable reagents/processes for smooth introduction of phenolic OH by using *N*,*N*-diisopropylbenzamide (**1a**) as a model substrate. All initial attempts to oxidize the intermediary aryl cuprates with various metal oxidants such as CAN, permanganate, or chromate salts, or organic oxidants including percarboxylic acid derivatives, DDQ, or oxone were unsuccessful. The employment of ROOLi[7d,16] occasionally gave the desired phenols, but the process suffered from low substrate generality and irreproducible yields. Surprisingly, the direct use of TBHP, where the deprotonation of TBHP was omitted, gave the corresponding phenols in good to excellent yields with good reproducibility (Table 1).[17] TMP-Cu-ates are effective for this transformation (one bulky amide is required, but the scope of the other ligands is rather wide). However, no product formation was observed using the HMDS complex, probably due to the low basicity (entries 1−5). Decreasing the amounts of both $(TMP)_2Cu(CN)Li_2$ and TBHP did not lead to a significant decrease of product yield (entry 6). Cumene hydroperoxide (CHP) gave results comparable to those of TBHP (entry 7). The use of excess TBHP (2 equiv) evaded protonation of the aryl anion and improved the yield of the desired oxidation reactions (entry 8). However, the TMP-Zn-ate base developed by our group[4h] also efficiently underwent DoM reaction, but installation of the OH group with TBHP did not occur at all. Only the starting benzamide **1a** was recovered (entry 9). This observation ruled out a nucleophilic oxidation mechanism, and the combination of Cu-ate intermediate and hydroperoxide proved to be crucial for smooth oxidation.

With the optimized reaction conditions in hand (Table 1, entry 8), we examined the scope of this hydroxylation reaction (Table 2). 4-Halogenated *N*,*N*-diisopropylbenzamides were efficiently converted to the corresponding phenols in high yields (**2b**, **2c**, and **2d**). It is worth emphasizing that 4-iodo-*N*,*N*-diisopropylbenzamide (**1d**), in which the C−I bond is generally susceptible to metal reagents, afforded corresponding phenol **2d** in excellent yield without any loss of iodine atom. A strongly electron-withdrawing CF_3 group was well-tolerated

Table 1. Optimization of Conditions

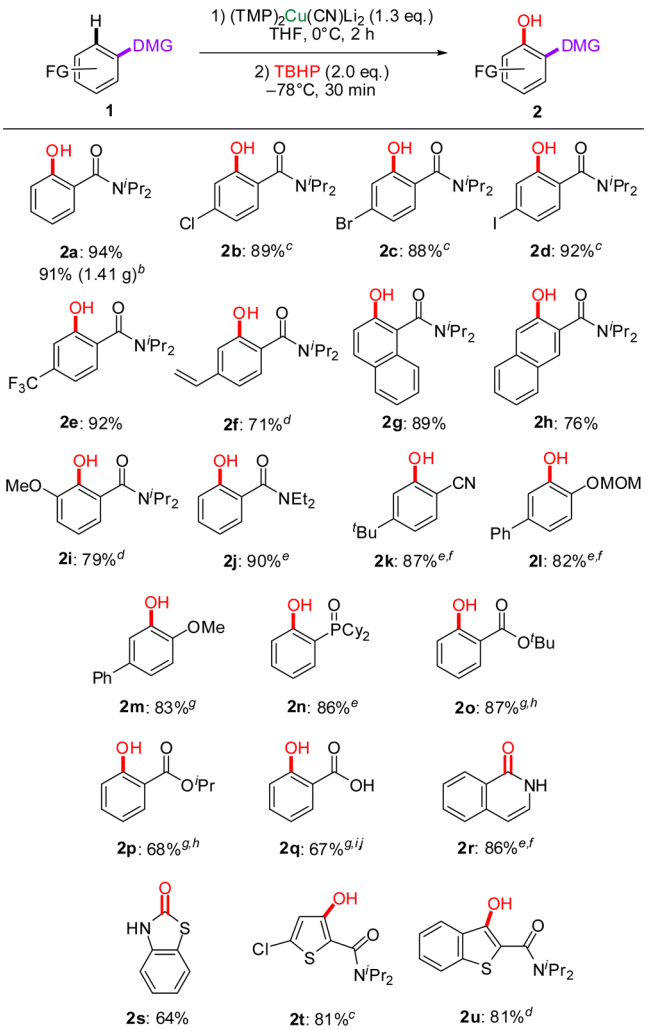


1a **2a**

entry	ate base	X	Y	yield (%)[a]
1	$(TMP)_2Cu(CN)Li_2$	2.2	2.0	98
2	$(i\text{-}Pr_2N)_2Cu(CN)Li_2$	2.2	2.0	79
3	*n*-BuCu(CN)(TMP)Li_2	2.2	2.0	93
4	*t*-BuCu(CN)(TMP)Li_2	2.2	2.0	79
5	$(HMDS)_2Cu(CN)Li_2$	2.2	2.0	0
6	$(TMP)_2Cu(CN)Li_2$	1.3	1.2	92[c]
7	$(TMP)_2Cu(CN)Li_2$	1.3	1.2[b]	89[c]
8	$(TMP)_2Cu(CN)Li_2$	1.3	2.0	94[c]
9	*t*-Bu_2Zn(TMP)Li	2.2	2.0	0

[a]NMR yields based on mesitylene as an internal standard. [b]Oxidized with CHP instead of TBHP. [c]Isolated yields. HMDS = 1,1,1,3,3,3-hexamethyldisilazido.

Table 2. Ortho Hydroxylation of Aromatics[a]



[a]Isolated yields. [b]7.0 mmol scale. [c]Cupration at −78 °C. [d]TBHP (1.2 equiv). [e]$(TMP)_2Cu(CN)Li_2$ (1.5 equiv). [f]TBHP (1.4 equiv). [g]$(TMP)_2Cu(CN)Li_2$ (2.2 equiv). [h]Oxidized by CHP. [i]Sodium benzoate as substrate. [j]NMR yield based on mesitylene as an internal standard.

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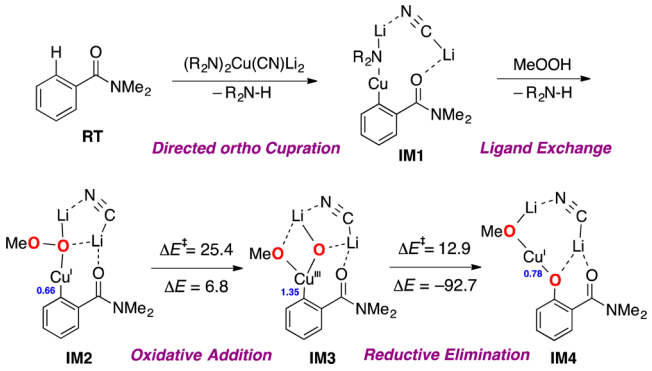
(**2e**: 92%). Styrene-type substrate **1f** could be chemo- and regioselectively oxidized at the aromatic C−H bond without any side polymerization reactions via this deprotonative cupration/oxidation sequence (**2f**: 71%) Naphthyl derivatives gave the corresponding products in moderate to high yields (**2g**: 89%, **2h**: 76%). The substrate derived from 3-anisic acid **1i** was selectively hydroxylated at the 2-position by virtue of the double-directing effect of the amide and methoxy groups (**2i**: 79%). The sterically less hindered *N*,*N*-diethylbenzamide (**1j**) was also tolerated, affording desired product **2j** in 90% yield. Next, several other DMGs were examined. CN, OMOM, simple OMe, and $PO(Cy)_2$ groups effectively assisted ortho metalation, and the subsequent oxidation reaction proceeded smoothly (**2k**, **2l**, **2m**, and **2n**). It should be emphasized that this reaction is easily scaled-up and **2a** was obtained in 91% yield (1.41 g). High-yielding formation of **2n** demonstrates the potential utility of this methodology in derivatization of phosphine ligand structure. An ester moiety is generally vulnerable to strong nucleophiles. Alkyl benzoates **1o** and **1p** were converted to salicylates **2o** and **2p** by using less nucleophilic CHP in 87 and 68% yields, respectively. Benzoic acid itself was also a good substrate in the form of the sodium salt (**2q**: 67%). The sp^2-hybridized nitrogen atom in aromatic rings served as an efficient DMG. Isoquinoline and benzothiazole gave isoquinolin-1(2*H*)-one (**2r**) and benzo[*d*]-thiazol-2(3*H*)-one (**2s**) regioselectively in good yields. Even thiophene **1t** could be converted to its corresponding hydroxylated product **2t** in 81% yield without degradation of the thiophene ring under the oxidative conditions. The oxygen atom was also introduced on the benzothiophene ring in 81% yield (**2u**).

DFT Calculations. To shed light on the reaction mechanism, DFT calculations (M06/631SVP)[18] were performed to examine the hydroxylation reaction. The putative reaction pathway is depicted in Scheme 1. We employed *N*,*N*-dimethylbenzamide (**RT**) and methyl hydroperoxide as chemical models for the substrate and oxidant, respectively. Directed ortho cupration reaction of **RT** using $(R_2N)_2Cu(CN)Li_2$ proceeds to form intermediary aryl-Cu-ate, $ArCu(NR_2)(CN)Li_2$ (**IM1**). Deprotonation of methyl hydroperoxide by the amido ligand NR_2 of **IM1** was shown to be kinetically advantageous over the thermodynamically favored deprotonation by aryl ligand and leads to ligand exchange forming a new aryl-Cu-ate, ArCu(CN)(OOMe)Li (**IM2**). Less efficient product formation with ROOLi (*vide supra*) and no product formation with *t*-BuOO*t*-Bu indicate that deprotonative ligand exchange[17] on the copper center is the key step for the following oxidation reaction. The results of several examinations indicated that the reaction pathway of OH installation shown in Scheme 1 is the most probable.[19] This transformation takes place as a two-step reaction involving two electron-oxidation/reduction of the copper center during the reaction. Oxidative addition of the peroxide ligand to the copper atom ($Cu^I \rightarrow Cu^{III}$) occurs with an activation barrier of +25.4 kcal/mol. The subsequent reductive elimination step from **IM3** would proceed smoothly ($\Delta E^{\ddagger}$ = +12.9 kcal/mol), and the system would gain large stabilization energy (−92.7 kcal/mol) because of the reformation of a typical Lipshutz-type cuprate with several stable O−Cu and O−Li bonds. Natural bond orbital (NBO) analysis of **IM2**, **IM3**, and **IM4** supported an increase and then decrease of the positive charge of the Cu atom as it goes from Cu(I) to Cu(III) and then back to Cu(I) along the reaction pathway. These results strongly suggest that this hydroxylation reaction is not a simple ionic reaction between carbanion and peroxide but occurs via redox reaction of the copper center in accordance with the experimental observations (Tables 1, entry 9).

Scheme 1. DFT Calculation of the Reaction Mechanism[a]



[a]M06/SVP for Cu and 6-31+G* for others; energy in kcal/mol. Natural charge of Cu in blue.

C−H Amination Reactions. Taking this mechanism in account, we applied this oxidation reaction of the Cu-ate complex to amination reaction of aromatics.[20,21] This reaction was shown to be triggered by deprotonative ligation of the oxidant to the Cu center,[21] and we speculated that $RONH_2$ should enable amination to occur via formation of ArCu(NHOR)(CN)Li, followed by redox reaction of Cu. Indeed, this deprotonative amination worked well, and an electron-donating substituent (R = Bn or Me) on the oxygen atom of $RONH_2$ gave better results than did an electron-withdrawing group (R = nitrobenzoyl or mesitylsulfonyl), as expected from the DFT findings.

Representative results of the amination of various functionalized arenes are summarized in Table 3. The aminations gave comparable results/chemoselectivities to those of the hydroxylations with ROOH. Standard substrate **1a** was smoothly aminated to give **3a** in 93% yield. In this amination reaction, the C−I bond survived, as was the case in the hydroxylation reaction (**3d**). The desired amination products were obtained using substrates with a CF_3 group and naphthalene ring in 70 and 76% yields, respectively (**3e** and **3g**). DMG groups other than *N*,*N*-diisopropylamides worked well, and the corresponding anilines were obtained in high yields (**3j**−**3o**). The ester moiety was well-tolerated even in the presence of highly nucleophilic alkoxyamine, giving 2-aminobenzoate **3o** in 79% yield. Various kinds of heteroaromatic substrates could be tolerated under these reaction conditions. Electron-poor isoquinoline **1r** and heteroaromatics with electron-rich π-systems **1t** and **1v**−**1x** were well-converted to the corresponding aminated products, which are otherwise almost inaccessible synthetically, in moderate to high yields (**3r**, **3t**, and **3v**−**3x**). Amination reaction also proceeded with a ferrocene-based substrate in 63% yield (**3y**). In contrast to research aimed at synthesizing primary anilines via transition-metal-catalyzed cross-coupling between aryl halides and ammonia,[22−24] this reaction is to our knowledge the first reliable and versatile method for direct installation of a free NH_2 group in an aromatic ring via C−H bond cleavage in a regio- and chemoselective manner.[25]

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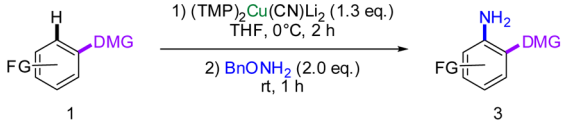
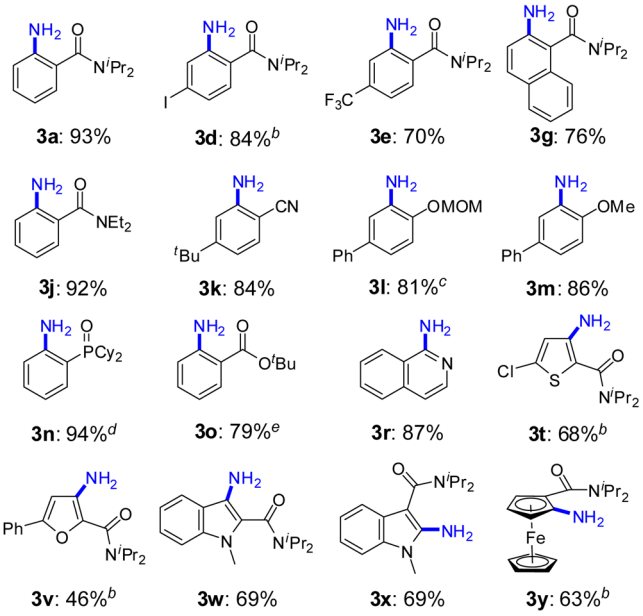
Table 3. Ortho Amination of Aromatics[a]





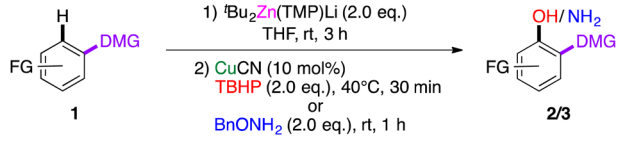
[a]Isolated yields. [b]Cupration at −78 °C. [c]Inseparable contamination of 4-phenylphenol. [d](TMP)$_2$Cu(CN)Li$_2$ (1.5 equiv). [e](TMP)$_2$Cu(CN)-Li$_2$ (2.2 equiv) and BnONH$_2$ (2.0 equiv).

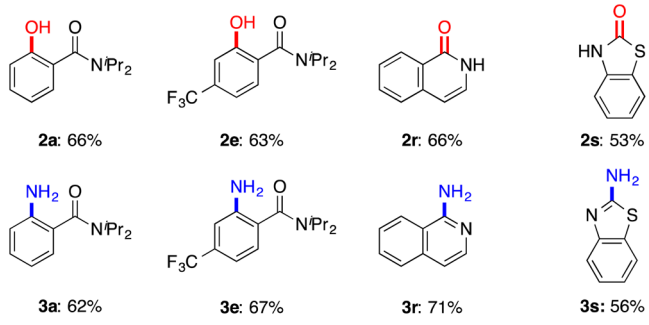
Catalytic Reactions in Copper. Finally, we examined the CuCN-catalyzed hydroxylation/amination of metalated aromatics. The redox action of Cu in the hydroxylation/amination process, according to DFT calculation (*vide supra*), implies that a catalytic system can potentially be achieved by appropriate reaction design. We employed the redox-inactive TMP-Zn-ate for deprotonation of the substrate and TBHP for subsequent oxidation in the presence of a catalytic amount of CuCN (Table 4). After extensive optimization, desired phenol **2a** was gratifyingly obtained in good yield (66%), whereas no product was formed in the absence of CuCN (Table 1, entry 9). Under these reaction conditions, functionalized benzamide **1e**, isoquinoline **1r**, and benzothiazole **1s** were successfully hydroxylated (**2e**, **2r**, and **2s**). Catalytic amination reactions with the same substrates proceeded smoothly as well (**3a**, **3e**, **3r**, and **3s**). This Cu-catalyzed approach is expected to be applicable to oxidation of organometallics other than zinc (lithium, magnesium, etc.) and should also broaden the synthetic scope for phenols and anilines.

CONCLUSIONS

We have developed efficient aromatic hydroxylation and amination reactions via directed ortho cupration. DFT calculation indicated that oxidative addition of peroxide to aryl copper species is the key step for introduction of the hydroxyl group, and this unique redox characteristic of copper also enables amination reaction using alkoxyamines. This hydroxylation/amination methodology shows high chemo- and regioselectivity and is applicable to a wide range of functionalized aromatic and heteroaromatic compounds. This reaction is the first example of an efficient one-pot synthesis of functionalized phenols and anilines from the same substrates via deprotonative cupration and successive oxidation by choosing appropriate oxidants. We also demonstrated Cu-catalyzed hydroxylation/amination of aryl zincates prepared by deprotonative zincation of (hetero)aromatic compounds. Work to expand the scope of the reactions (i.e., introduction of other heteroatoms and hydroxylation and amination at sp^3 carbon) and mechanistic studies on the catalytic reaction are in progress in our laboratory.

Table 4. CuCN-Catalyzed Ortho Hydroxylation and Amination of Aromatics[a]





[a]Isolated yields.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.6b03855.

Experimental details, and NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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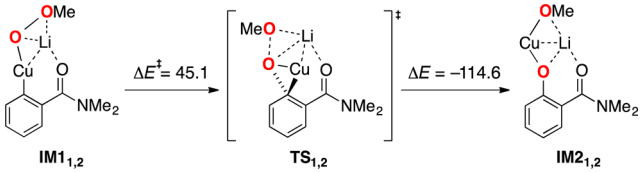

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