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N-Heterocyclic Carbene-Mediated Redox Condensation of Alcohols

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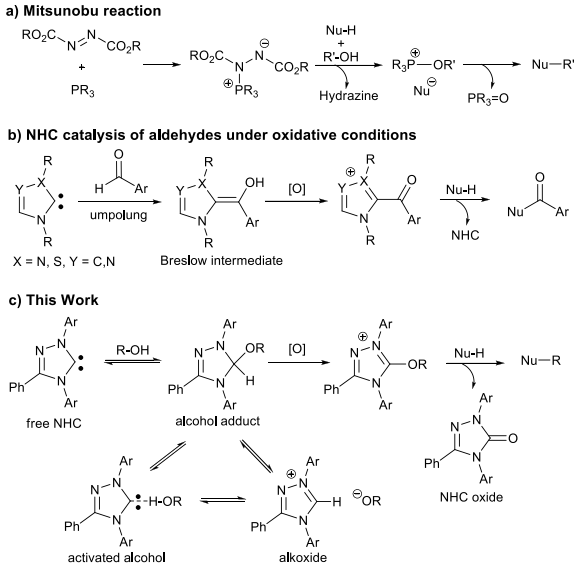
N-Heterocyclic carbenes (NHCs) with a variety of oxidants promote the Mitsunobu-type coupling reactions of alcohols with phenols, carboxylic acids, and phthalimide. Experiments using a chiral alcohol indicate that these reactions proceed via S_N1 or S_N2 pathways depending on the polarity of the used solvents. The NHCs are consumed as reducing reagents to form their oxides as readily separable byproducts.

The Mitsunobu reaction[1] is a synthetically useful redox condensation[2] of alcohols with pronucleophiles such as phenols, carboxylic acids, thiols, and phthalimide (Scheme 1a). Azodicarboxylates and phosphines have been generally used as oxidants and reducing agents, respectively, but the stoichiometric byproducts, hydrazine carboxylates and phosphine oxides, are not easily removed from reaction mixtures. To overcome such drawbacks and to expand the reaction scope, a variety of the Mitsunobu protocols using modified reagents[3] and catalytic systems[4] have been studied. Alternative methods such as the Mukaiyama redox reaction,[2,5] the sulfonyl transfer reaction,[6] and the PhenoFluor-mediated condensation[7] have been also developed.

N-Heterocyclic carbenes (NHCs) have been widely used as ligands for transition metal complexes and organocatalysts.[8] NHCs have nucleophilic properties similar to phosphines, but show a large number of the advantages in both ligand and organocatalyst chemistries.[8a] In particular, the NHC-catalyzed umpolung reactions of aldehydes[9] and Michael acceptors[10] via nucleophilic (deoxy)-Breslow intermediates has been extensively investigated. Among them, NHC catalysis under oxidative conditions allows the formation of esters, amides, and cyclic products from aldehydes, where a variety of oxidants convert the key Breslow intermediates to acyl cation equivalents[11] (Scheme 1b). Since NHC is unstable under air, the



Scheme 1. Overview of redox reactions promoted by phosphines or NHCs

alcohol adduct is often used as a stable precursor. Wanzlick et al. tried to prepare a NHC from the alcohol adduct of 1,3-diphenylimidazolin-2-ylidene,[12] and Enders et al. successfully synthesized 1,2,4-triazol-5-ylidene NHC (**A**, in Table 1) by the thermolysis of its air-stable alcohol adduct.[13] In general, there are equilibria between a free NHC with an alcohol, an NHC-alcohol adduct, an azolium alkoxide, and an NHC-activated alcohol (Scheme 1c).[14] The alkoxide and the activated alcohol serve as the intermediates for transesterifications[14c, 15] and the oxa-Michael addition.[16] The adducts are interesting species because of their relatively low thermodynamic stability. However, the structure-stability relationship has not been systematically studied, and there are no examples other than the above-mentioned reactivities. Previously, we found the transfer hydrogenation of activated unsaturated compounds mediated by NHC and water.[17] Given the many reactions promoted by the oxidation of phosphines (*e.g.* Wittig reaction, Staudinger reaction, and Appel reaction), this hydrogenation is the first reaction of NHC as a reducing reagent to form the NHC oxide. It should be noted that use of NHC as alternatives

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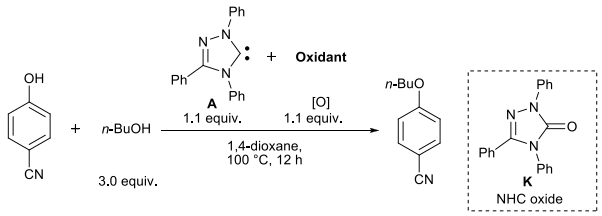
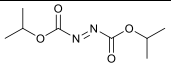
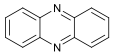
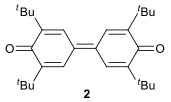
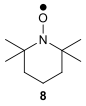
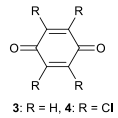
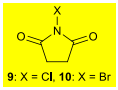
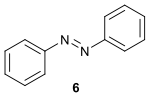
Electronic Supplementary Information (ESI) available: [Experimental procedure, characterization data, HPLC charts, and NMR spectra of all new compounds]. See DOI: 10.1039/x0xx00000x

Table 1. Screening of oxidants using NHC **A**[a]



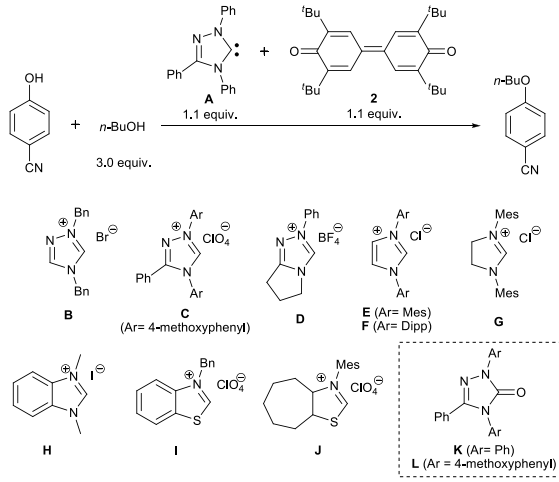
entry	oxidant	yield (%)[b]	entry	oxidant	yield (%)[b]
1	 **1**	61	6	 **7**	40
2	 **2**	77	7[c]	 **8**	54
3	 **3**: R = H, **4**: R = Cl	0	8	 **9**: X = Cl, **10**: X = Br	0
4	 **5**	14	9[d]	MnO_2 **11**	11
5	 **6**	< 5	10	No oxidant	0

[a]Reaction conditions, 4-cyanophenol; 0.22 mmol, *n*-butanol; 0.65 mmol, **A**; 0.24 mmol, oxidant; 0.24 mmol, 1,4-dioxane; 0.6 mL. [b]Isolated yield. [c]2.0 equiv of **8**. [d]5.0 equiv. of **11**.

to phosphines is expected to lead to reaction discovery. Herein, we report that the redox couple of NHC and an oxidant promotes the Mitsunobu-type condensation of alcohol with pronucleophiles such as phenols, carboxylic acids, and phthalimide (Scheme 1c)**.**

We initially focused on the synthesis of alkyl aryl ethers. They are generally synthesized by the Williamson reaction or transition metal-catalyzed reactions[18,19] of environmentally unfriendly halogenated reagents under highly basic conditions. In this respect, the direct coupling reactions of alcohols with phenols under neutral conditions by a Mitsunobu protocol are quite attractive. We first investigated the redox condensation of *n*-butanol with 4-cyanophenol by 1.1 equiv. of isolated NHC **A** and 1.1 equiv. of various oxidants **1**-**11** in 1,4-dioxane at 100 °C for 12 h (Table 1). The use of diisopropyl azodicarboxylate (DIAD) (**1**), a common oxidant for the Mitsunobu reaction, provided 4-butoxybenzonitrile in 61% yield (entry 1) and the NHC oxide (**K**) as a byproduct. This indicates that, similar to phosphines, the NHC can act as a reducing reagent for the Mitsuinobu reaction. It is noteworthy that a variety of oxidants can be employed, which is similar to the oxidation of the Breslow intermediates.[11] A tetrasubstituted diphenoquinone, 3,3',5,5'-tetra-*t*-butyl-4,4'-diphenoquinone (**2**) was found to be the most effective oxidant to give the product in 77% yield (entry 2). However,

Table 2. Reaction optimization using oxidant **2**[a]

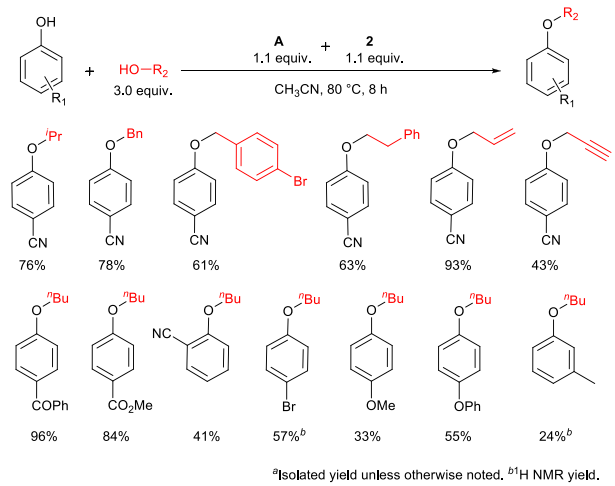


entry	NHC	base	solvent	temp (°C)	time (h)	yield[b] (%)
1	**A**	-	1,4-dioxane	80	8	79
2	**A**	-	THF	65	8	51
3	**A**	-	toluene	80	8	60
4	**A**	-	1,2-dichloroethane	80	8	44
5	**A**	-	CH_3CN	80	8	89
6	**A**	-	CH_3CN	80	4	68
7	**A**	-	CH_3CN	60	24	64
8	**A**	-	CH_3CN	0	48	0
9[c]	**A**	-	CH_3CN	80	8	80
10	**B**	K_2CO_3	CH_3CN	80	12	16
11	**C**	K_2CO_3	CH_3CN	80	12	62
12	**D-J**	K_2CO_3	CH_3CN	80	12	0
13	**B-J**	DIEA[d]	CH_3CN	80	12	0

[a]Reaction conditions, 4-cyanophenol; 0.22 mmol, *n*-butanol; 0.65 mmol, NHC ; 0.24 mmol, **2**; 0.24 mmol, base; 0.24 mmol, solvent; 0.6 mL. [b]Isolated yield. [c]1.0 equiv. of *n*-butanol. [d]DIEA; *N*,*N*-diisopropylethylamine.

sterically less hindered benzoquinones **3** and **4** proved to be ineffective probably because of their side reactions with the NHC (entry 3). A wide range of oxidants, such as nitrobenzene (**5**), azobenzene (**6**), phenazine (**7**), 2,2,6,6-tetramethylpiperidine 1-oxyl free radical (TEMPO) (**8**), and the heterogeneous oxidant of MnO_2 (**11**), afforded the product in low to moderate yields (entries 4-7, and 9). The oxidants other than **1** are inapplicable to the classical Mitsunobu reaction, because it is initiated by the nucleophilic attack of phosphines to azodicarboxylates (Scheme 1a). Thus, this protocol using NHC shows the advantage for the scope of oxidants, and this condensation has a different mechanism from phosphine-promoted counterpart (*vide infra*).

We then screened the solvents, reaction temperatures, and NHCs, constantly using **2** as an oxidant (Table 2 and Table S1 in Supporting Information). When a series of solvents such as tetrahydrofuran, toluene, 1,2-dichloroethane, and acetonitrile were tested using NHC **A** (entries 1-5), the reaction in acetonitrile at 80 °C for 8 h afforded the product in the highest isolated yield (89%, entry 5). Decreasing either the



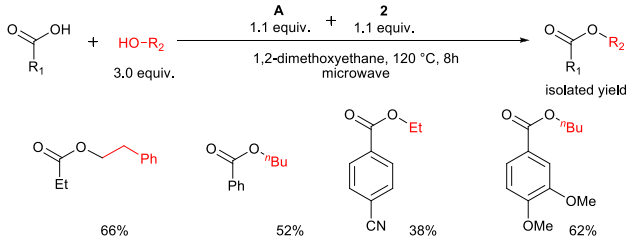
[a]Isolated yield unless otherwise noted. [b]^{1}H NMR yield.

Scheme 2. Substrate scope using NHC **A** and oxidant **2**[a].

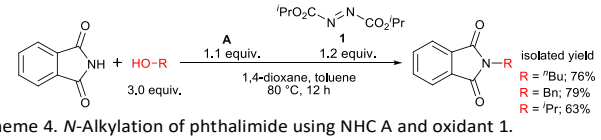
reaction temperature or time led to the lower yields (entries 6-8). However, decreasing the amount of *n*-butanol from 3 eq. to 1 eq. gave an almost comparable yield (entry 9). The precursors of 1,2,4-triazol-5-ylidene NHCs, **B** or **C**, with K_2CO_3 also gave the product in 16% and 62% yields, respectively (entries 10 and 11), while the other NHC precursors (**D**-**J**), such as imidazolium and thiazolium salts, were ineffective. In entries 5 and 11, the corresponding NHC oxides, **K** and **L**, were isolated in 80% and 62% yields, respectively, which were comparable to those of the produced ether. It is noteworthy that **K** and **L** were precipitated in the reaction mixture and readily separated by filtration.

With better reaction conditions in hand, the substrate scope was examined (Scheme 2). The corresponding ethers were produced in moderate-to-high isolated yields from various alcohols, such as isopropyl, benzyl, 4-bromobenzyl, 2-phenylethyl, allyl, propargyl alcohols, while no product was obtained from *tert*-butyl alcohol. Some phenols bearing electron-withdrawing groups, such as ketones and esters, at the *para* position are suitable substrates, giving the products in 96% and 89% yields, respectively. Other phenols such as 2-cyanophenol, 4-bromophenol, 4-methoxyphenol, 4-phenoxyphenol and 3-cresol resulted in low-to-moderate yields.

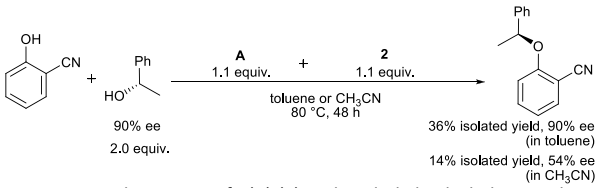
We then expanded the scope of this redox reaction. Esterifications of carboxylic acids as pronucleophiles were promoted by NHC **A** with oxidant **2**. (Scheme 3, Table S2 in Supporting Information). In a sealed vial under microwave irradiation at 120 °C for 8 h, the corresponding esters were obtained in moderate yields from propionic, benzoic, 4-cyanobenzoic, and 3,5-dimethoxy benzoic acids. This redox protocol also allows the *N*-alkylations of phthalimide (Scheme 4), the products of which are important precursors for the Gabriel amine synthesis. The combination of NHC **A** and **2** was not effective in this case, but use of oxidant **1** instead of **2** enabled the reactions of phthalimide with *n*-butyl, benzyl, and isopropyl alcohols to give the corresponding *N*-alkylated products in good yields through the deprotonation of



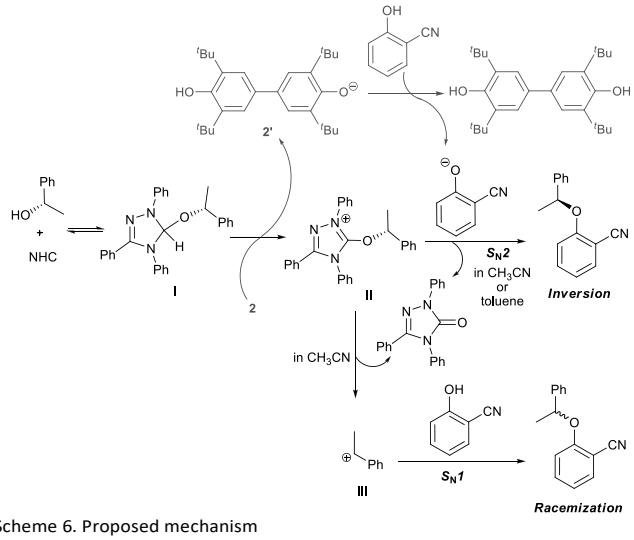
Scheme 3. Esterifications using NHC **A** and oxidant **2**.



Scheme 4. *N*-Alkylation of phthalimide using NHC A and oxidant 1.



Scheme 5. Condensation of (*R*)-(+)-1-phenylethyl alcohol in toluene or acetonitrile.



Scheme 6. Proposed mechanism

phthalimide by the zwitterionic intermediate derived from **A** and **1**.

To clarify the reaction mechanism, reactions using chiral alcohol were performed (Scheme 5). The reaction of 2-cyanophenol with (*R*)-(+)-1-phenylethyl alcohol (90% ee) in toluene at 80 °C for 48 h afforded the condensation product with complete inversion of configuration (90% ee). Although the yields and conversions are less than moderate because of the bulkiness of the two substrates, the optical purity of the produced ether derived from 2-cyanophenol can be readily analysed by HPLC. Use of a polar solvent, acetonitrile, induced

the partial racemization of the product with 81% inversion (54% ee). These results suggest the reaction mechanism in Scheme 6. The NHC reacts with the alcohol to generate alcohol adduct **I**, which is subsequently oxidized into triazolium cation **II** by **2** through the hydride transfer. The generated bulky mono anion of **2** (**2'**) can deprotonate 2-cyanophenol. The resulting phenoxide reacts with **II** in the S_N2 fashion in toluene to give the stereo-inverted condensation product together with the stable NHC oxide. This S_N2 process is quite similar to the final step of a typical Mitsunobu reaction, where the phosphonium undergoes the nucleophilic attack (Scheme 1a). The polar solvent acetonitrile causes the cleavage of the O-C bond of intermediate **II** to some extent to generate benzyl cation **III** and the NHC oxide. The S_N1 reaction of 2-cyanophenol with **III** affords the racemized product.

In conclusion, we have developed a Mitsunobu-type redox condensation of primary and secondly alcohols with various phenols, carboxylic acids and phthalimide by the redox couple of 1,2,4-triazol-5-ylidene NHCs and oxidants. The reaction mechanism uniquely involves the oxidation and nucleophilic substitution[20] processes. In contrast to the classical Mitsunobu reaction, 1) the reducing reagents, NHCs, act as a Brønsted base, 2) a wider range of oxidants, such as an azodicarboxylate, a diphenoquinone, and TEMPO, can be used, and 3) the byproducts, NHC oxides, are more readily removed. Following our previous report,[17] this is the second example in which the NHCs work as the reduction agent. We believe that NHC has further potential as a useful alternative in various redox reactions.

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