N-Heterocyclic Carbene-Catalyzed α-Alkylation of Ketones with Primary Alcohols

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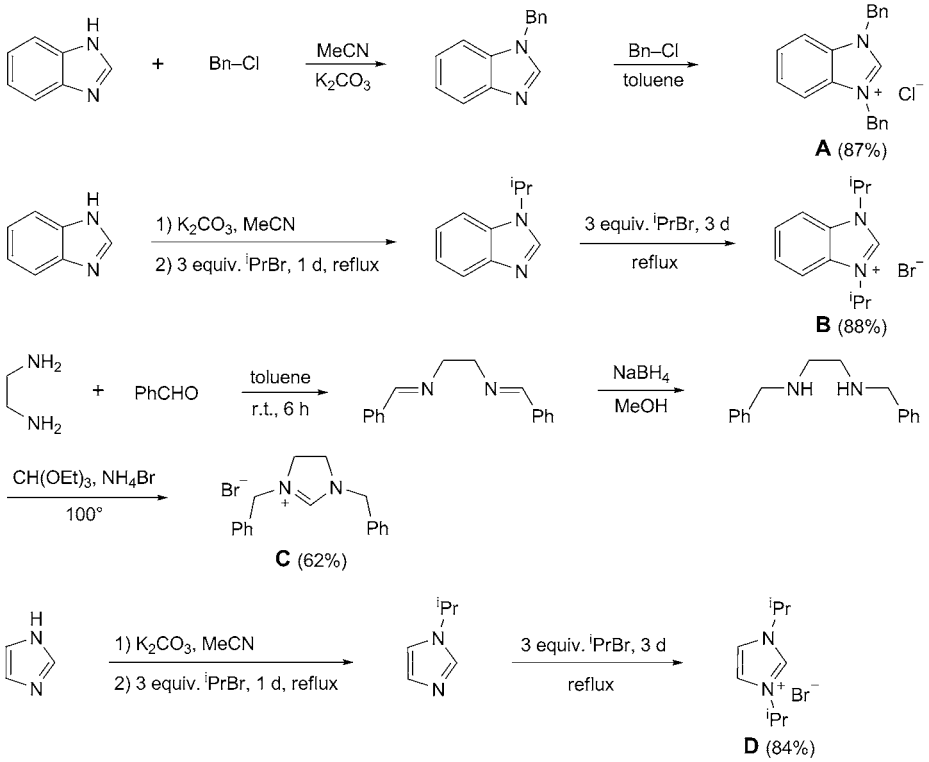
Several N-heterocyclic carbene precursors are synthesized and used in the α-alkylations of ketones with primary alcohols. With the assistance of a base, these N-heterocyclic carbenes can catalyze the reaction smoothly to furnish dialkylated ketones in good-to-excellent yields.

Introduction. – The alkylation of ketones is a pivotal method to increase the molecular complexity of simple organic substrates [1][2], and α-alkylation of ketones with electrophiles such as alcohols has become a novel and efficient tool to form C–C bonds. Since the pioneering work of *Cho et al.* [3], many catalytic systems for the α-alkylation of ketones have been screened. For example, $[Ru(DMSO)_4]Cl_2$ [4], $[Ir(cod)Cl]_2/PPh_3$ [5][6], $[Cp^*IrCl_2]_2$ [7][8], Pd/AlO(OH) [9], Pd-NPs(nanoparticles)/$Ba(OH)_2 \cdot H_2O$ [10][11], Ni-NPs [12],TiO_2 [13], Ag/Mo [14], [Os(η^6-*p*-cymene)(OH)(Ipr)]Otf [15] and $RuHCl(CO)/(PPh_3)_3$ [16] were reported as catalytic systems to achieve this kind of alkylation. Metal-based catalytic systems play a dominant role in this field since the yields are high, and the only by-product is H_2O. However, ligands are always used in these catalytic systems, and the catalysts are hard to be reused. Very recently, *Liang et al.* Reported the α-alkylation of ketones with alcohols by a catalyst-free reaction [17]. However, this reaction needs excess ^{t}BuOLi, long reaction time, and an Ar atmosphere. This prompted us to achieve a more efficient approach using metal-free catalysts for the α-alkylation of ketones.

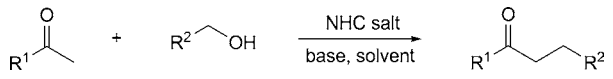
Recently, organocatalysis has attracted considerable attention because of its facile reaction course, selectivity, and environmental friendliness. The application of organocatalysts made many new synthetic pathways possible. N-Heterocyclic carbenes (NHC) as organocatalysts have been applied in numerous organic reactions [18–23]. In many cases, NHCs were used for the 'umpolung' of the C=O group, serving as a kind of *Lewis* base organocatalysts [18]. Since they are strong bases [24], we concluded NHCs catalyst could be used for the α-alkylation of ketones.

With these considerations in mind, we synthesized several known N-heterocyclic carbene precursors (*Scheme 1*) and applied them in α-alkylation reactions of ketones with alcohols (*Scheme 2*). To our delight, these reactions proceeded very smoothly to afforded the corresponding products in good-to-excellent yields with satisfactory selectivity.

Scheme 1. *Synthesis of N-Heterocyclic Carbene Precursors*

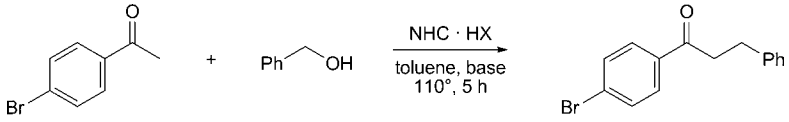


Scheme 2. *NHC-Mediated α-Alkylations of Ketones with Primary Alcohols*



Results and Discussion. – At the outset of our study, using precatalyst **A**, and 4-bromoacetophenone (**1a**) and benzyl alcohol (BnOH; **2a**) as model substrates, we examined the α-alkylation under several conditions (*Table 1*). When **1a** was reacted with **2a** in the presence of 0.2 mol-% of **A** and 1.0 equiv. of KOH at 110° (bath temp.) for 5 h, the desired α-alkylated ketone **3a** was formed in 98% yield (*Table 1*, *Entry 1*). As evident from *Table 1*, the NHC precursors **A** – **D** all facilitated the reaction to afford the expected product **3a** (*Table 1*, *Entries 1 – 4*), while precatalysts **A** and **C** provide almost the same excellent yields of **3a** (*Table 1*, *Entries 1* and *3*). After survey of several bases, we found that KOH gave a good yield of **3a** (*Table 1*, *Entry 1*). The influence of the amount of the catalyst was also examined. When the amount of **A** was decreased to 0.1 mol-%, or no precatalyst was used in the reaction, the results were unsatisfactory (*Table 1*, *Entries 9* and *10*). However, an increase in the amount of catalyst (*Table 1*, *Entries 11* and *13 – 15*) had a negative effect. In addition, decreased base amount was

Table 1. *Optimization of Reaction Conditions*[a])



1a **2a** **3a**

Entry	NHC·HX ([mol-%])	Base ([mol-%])	Yield [%][b])
1	**A** (0.2)	KOH (100)	98
2	**B** (0.2)	KOH (100)	74
3	**C** (0.2)	KOH (100)	96
4	**D** (0.2)	KOH (100)	84
5	**A** (0.2)	NaOH (100)	93
6	**A** (0.2)	Cs_2CO_3 (100)	4
7	**B** (0.2)	NaOH (100)	92
8	**B** (0.2)	Et_3N (100)	trace
9	**A** (0.1)	KOH (100)	74
10	–	KOH (100)	58
11	**A** (1)	KOH (100)	54
12	**A** (0.2)	KOH (50)	63
13	**A** (1)	KOH (50)	70
14	**A** (2)	KOH (50)	62
15	**A** (5)	KOH (50)	58

[a]) Reaction conditions: **1a** (1.0 mmol), **2a** (1.2 mmol), and precatalyst (0.002 mmol) were mixed together in 3 ml of toluene in air, and finally base (1 equiv.) was added; 110°; 5 h. [b]) Yield of isolated product; product identified by ^{1}H-NMR.

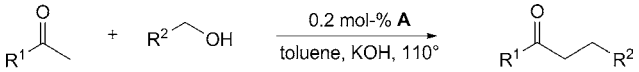
found to have a significantly negative effect (*Table 1*, *Entry 12*). It should be noted that the modified α-alkylation of ketones using the NHC catalyst could proceed readily at a shorter time, a lower base equivalent, and under an atmosphere of air, as compared to that using ^{t}BuOLi reported in the literature.

Having established the optimum reaction conditions for the NHC-mediated α-alkylation of acetophenone with BnOH, we then examined the further scope and general applicability of this process (*Table 2*). Thus, a range of acetophenones with different substituents were employed which provided the desired products **3** in excellent yields (*i.e.*, **3a**–**3e**). At the same time, using benzyl alcohols with various substituents gave the corresponding products **3f**–**3k** also in moderate-to-good yields. Tetralone **1f** and 2-acetylpyridine (**1g**) were alkylated by **2a** to give **3l** and **3m** in good and moderate yields, respectively. A hydroxymethyl heteroaryl such as pyridine-3-methanol (**2e**) also reacted with acetophenone (**1a**) to give **3n** in moderate yield.

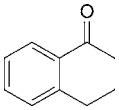
Unfortunately, only when ketones contained an aromatic substituent in α-position and alcohols also contained aromatics substituents, the reaction occurred smoothly. The reaction of aliphatic ketones with BnOH was achieved in only 16% yield (**3o**) and the reaction using EtOH (**2f**) gave an unsatisfactory result ($\rightarrow$ **3b**) as well. These results might be ascribed to the participation of the aromatic ring in conjugation.

In conclusion, we have synthesized several N-heterocyclic carbene precursors and disclosed a simple and efficient NHCs-catalyzed reaction of α-aryl ketones with various

Table 2. *α-Alkylation of Ketones with Alcohols Catalyzed by NHCs*[a])



1 2 3

Entry	Ketone (**1**)	R^1	Alcohol (**2**)	R^2	Product (**3**)	Time [h]	Yield [%][b])
1	**1a**	Ph	**2a**	Ph	**3a**	5	83
2	**1b**	2-Br–C_6H_4	**2a**	Ph	**3b**	5	98
3	**1c**	2-Cl–C_6H_4	**2a**	Ph	**3c**	5	85
4	**1d**	2-MeO–C_6H_4	**2a**	Ph	**3d**	5	86
5	**1e**	2-Me–C_6H_4	**2a**	Ph	**3e**	5	87
6	**1b**	2-Br–C_6H_4	**2b**	2-MeO–C_6H_4	**3f**	5	95
7	**1b**	2-Br–C_6H_4	**2c**	4-Br–C_6H_4	**3g**	1	88
8	**1b**	2-Br–C_6H_4	**2d**	4-Cl–C_6H_4	**3h**	5	94
9	**1e**	2-Me–C_6H_4	**2c**	4-Br–C_6H_4	**3i**	5	76
10	**1e**	2-Me–C_6H_4	**2d**	4-Cl–C_6H_4	**3j**	1	85
11	**1e**	2-Me–C_6H_4	**2b**	2-MeO–C_6H_4	**3k**	5	86
12	 **1f**		**2a**	Ph	**3l**	3	81
13	**1g**	Pyridin-2-yl	**2a**	Ph	**3m**	5	60
14	**1a**	Ph	**2e**	Pyridin-3-yl	**3n**	1	69
15	**1h**	Me	**2a**	Ph	**3o**	5	16
16	**1b**	2-Br–C_6H_4	**2f**	Me	**3p**	5	3

[a]) The reaction was carried out with ketone (1 mmol), alcohol (1.2 mmol), precatalyst **A** (0.2 mol-%), and KOH (1 equiv.) in toluene (3 ml) at 110°. [b]) Yield of isolated product.

benzyl alcohols in high yields. This procedure constitutes an excellent example of very high atom efficiency reaction. The advantages of these catalyst precursors such as being air-stable and easy to handle and to prepare render the NHCs-catalyzed alkylation as a significant development compared to the established alkylation protocols. A detailed mechanistic study involving the precise role of N-heterocyclic carbenes in the promotion of α-aryl ketones with primary alcohols, as well as synthetic applications of the present reactions, is currently underway in our laboratory.

Experimental Part

General. All chemicals were commercially available and used without further purification. GC: *Agilent 7890A* instrument. ^{1}H- and ^{13}C-NMR spectra: *Bruker DRX 500*; δ in ppm rel. to Me_4Si as internal standard, *J* in Hz. The ^{1}H-NMR data of the precatalysts are in agreement with those reported in the literature [25–28].

*Synthesis of 1,3-Dibenzyl-1*H*-benzimidazol-3-ium Chloride* (**A**). To a 100-ml three-necked round-bottomed flask charged with 1*H*-benzimidazole (5.90 g, 50 mmol) was added K_2CO_3 (75 mmol), followed by MeCN (40 ml) at reflux (80°) for 30 min. Then BnCl (50 mmol) was added slowly over 30 min, and the mixture was refluxed at 80° for 24 h. After cooling to r.t., the mixture was concentrated *in*

vacuo, and the residue was dissolved in CH_2Cl_2 (20 ml) and washed with H_2O (20 ml). The aq. layer was extracted with CH_2Cl_2 (3 × 30 ml), and the combined org. phase was dried (anh. Na_2SO_4), filtered, and concentrated *in vacuo* to afford 1-benzyl-1*H*-benzimidazole (95%).

In a 50-ml three-necked round-bottomed flask, 1-benzyl-1*H*-benzimidazole (10 mmol) was dissolved in toluene (20 ml), and BnCl (10 mmol) was added dropwise, and the mixture was refluxed for 24 h. Upon completion of the reaction, the solvent was evaporated *in vacuo*. The residue was washed with AcOEt and dried *in vacuo* to afford the product (92%). M.p. 210–212°. ^{1}H-NMR ((D_6)DMSO, 25°): 10.21 (*s*, 1 H); 7.98–8.01 (*m*, 2 H); 7.63–7.65 (*m*, 2 H); 7.56 (*d*, *J* = 7.2, 4 H); 7.35–7.45 (*m*, 6 H); 5.81 (*s*, 4 H).

*Synthesis of 1,3-Di(propan-2-yl)-1*H*-benzimidazol-3-ium Bromide* (**B**). A mixture of 1*H*-benzimidazole (591 mg, 5 mmol) and K_2CO_3 (760 mg, 5.5 mmol) was suspended in MeCN (3 ml) and stirred at r.t. for 1 h. To the suspension was added ^{i}PrBr (1.40 ml, 15 mmol). The mixture was stirred under reflux conditions for 24 h, followed by a second addition of ^{i}PrBr (1.40 ml, 15 mmol). Stirring under reflux was continued for an additional 72 h. After removing the volatiles *in vacuo*, CH_2Cl_2 (50 ml) was added to the residue, and the resulting suspension was filtered over *Celite*. The filter cake was washed with CH_2Cl_2 (5 × 20 ml), and the solvent was removed *in vacuo* to give a spongy solid, then this solid was washed with AcOEt to afford **B** (88%). White powder. M.p. 136–138°. ^{1}H-NMR (500 MHz, $CDCl_3$): 11.26 (*s*, 1 H); 7.83 (*m*, 2 H); 7.63 (*m*, 2 H); 5.20 (*m*, 2 H); 1.84 (*d*, *J* = 6.5, 12 H).

*Synthesis of 1,3-Dibenzyl-4,5-dihydro-1*H*-imidazol-3-ium Bromide* (**C**). A mixture of $NH_2CH_2CH_2NH_2$ (1.0 ml, 14.8 mmol) and PhCHO (3.32 ml, 32.5 mmol) was stirred in toluene (10 ml) at r.t. for 6 h. The solvent was then removed *in vacuo* to give the diimine as a yellow liquid. $NaBH_4$ (3.4 g, 77.3 mmol), dissolved in MeOH (10 ml), was slowly added to the diimine in MeOH (10 ml) at 0°. The mixture was allowed to stir overnight at r.t. MeOH was then removed *in vacuo*, and the residue was dissolved in Et_2O (30 ml) and washed with H_2O (2 × 20 ml) and brine (20 ml). Drying of the Et_2O layer gave the diamine as a yellow liquid. To the diamine, $CH(OEt)_3$ (7.4 ml, 44.4 mmol) and NH_4Br (1.45 g, 14.8 mmol) were added, and the mixture was stirred for 4 h at 100°. The mixture was cooled to r.t., and excess $CH(OEt)_3$ was removed *in vacuo* at 60°. The residue was dissolved in a minimal amount of CH_2Cl_2, and the soln. was added dropwise to the mixed soln. of Et_2O and THF. Filtration gave **C** (3.04 g, 62%). White solid. M.p. 163–165°. ^{1}H-NMR (500 MHz, $CDCl_3$): 10.36 (*s*, 1 H); 7.37–7.43 (*m*, 10 H); 4.90 (*s*, 4 H); 3.77 (*s*, 4 H).

*Synthesis of 1,3-Di(propan-2-yl)-1*H*-imidazol-3-ium Bromide* (**D**). Compound **D** was prepared as described for **B**. The product was collected as a white solid after washing with AcOEt (84%). M.p. 132.0°. ^{1}H-NMR (500 MHz, $CDCl_3$): 10.84 (*s*, 1 H); 7.43(*d*, 2 H); 5.00 (*m*, 2 H), 1.64 (*d*, *J* = 6.5, 12 H).

General Procedure for the Reaction of Ketones with Alcohols. To a soln. of catalyst precursor (0.6 mg, 0.002 mmol) and KOH (0.056 g, 1 mmol) in toluene (3 ml) was added the corresponding ketone (1 mmol), followed by the corresponding alcohol (1.2 mmol). The mixture was stirred and heated at 110° for an appropriate time. Then, the reaction was quenched by the addition of a sat. NH_4Cl soln. (20 ml), and the mixture was extracted with AcOEt (3 × 15 ml). The combined org. layers were dried (Na_2SO_4), filtered, and the solvents were removed under reduced pressure. The resulting residue was purified by flash chromatography to afford the corresponding products. All the products were known compounds and were characterized by comparison of their physical and spectroscopic data with those described in the literature.

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