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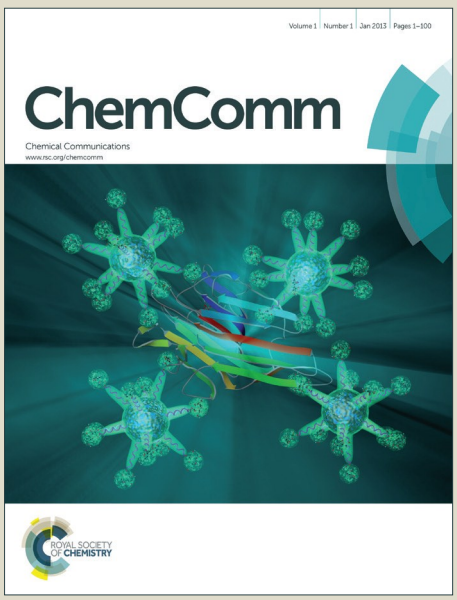





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# N-Heterocyclic Olefins as Efficient Phase-Transfer Catalysts for Base-Promoted Alkylation Reactions

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Marcus Blümel,[a,b] Reece D. Crocker,[a] Jason B. Harper,[a] Dieter Enders[b] and Thanh V. Nguyen*[,a]

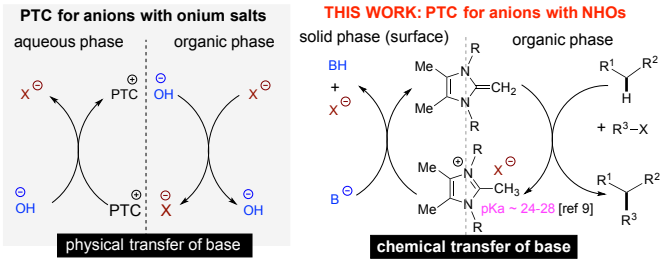
**N-Heterocyclic Olefins (NHOs) have very recently emerged as efficient promoters for several chemical reactions due to their strong Brønsted/Lewis basicities. Here we report the novel application of NHOs as efficient phase-transfer organocatalysts for synthetically important alkylation reactions on a wide range of substrates, further demonstrating the great potential of NHOs in organic chemistry.**

In the last two decades, the utility of N-Heterocyclic carbenes (NHCs) has evolved dramatically in many important areas, most notably organometallic and organocatalytic chemistry.[1] These intriguing chemical species have played critical roles in the development of a wide range of transition metal-NHC complexes with unusual stability and catalytic activity.[2] At the same time, NHCs have been used extensively as organocatalysts to promote fascinating chemical reactions.[1] While NHC organocatalysts are mostly well-known for their umpolung chemistry of carbonyl compounds via the formation of the acyl anion intermediates,[3] their role as Brønsted/Lewis base catalysts has been inadequately investigated due to limitations in basicity and scope of reaction types.

N-Heterocylic Olefins (NHOs), previously known in the literature as heterocyclic ketene aminal or ene-1,1-diamine substrates used in several types of cycloaddition reactions,[4] have lately emerged as an interesting class of ligands and reaction promoters. These alkylidene derivatives of NHCs possess an exocyclic carbon center with particularly high electron density due to the electron donating effect of the two conjugate heteroatoms and the partial aromatization of the heterocycle. This nucleophilic carbon center can act as a very strong Lewis basic site, resulting in several important applications of NHO ligands in transition metal complexation and catalysis.[5] Recent studies have also revealed interesting catalytic activities of NHOs for $CO_2$-sequestration[6] and ring-opening polymerization reactions.[7] We postulated that with suitable structural design, NHOs can overtake their parent NHC compounds to serve as an *evolved* class of organocatalysts with enhanced Brønsted/Lewis basicity for a wide range of chemical reactions.[8] We have recently established the use of NHOs as organocatalysts for transesterification reactions.[9] In this article, we report another investigation for the development of NHOs as promoters of organic chemical transformations. Thus, NHOs and their azolium salt precursors were employed as very efficient organocatalysts for solid-liquid phase-transfer alkylation reactions.

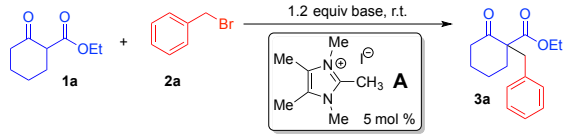
Phase-transfer catalysis (PTC) has been widely used in laboratory synthesis as well as the industrial production of fine chemicals.[10] Apart from the host-guest cation transfer by crown ethers,[11] phase-transfer catalysis has generally utilized ammonium and phosphonium salts for *physical* anion transfer catalysis (Scheme 1).[12] Recent developments have included phase-transfer chemistry promoted by imidazolium,[13] triazolium,[14] cyclopropenium[10,15] and tetraamino-phosphonium[16] salts. Although these salts can efficiently facilitate numerous chemical transformations, a versatile catalytic system with highly tunable structure, also with high stability and easy accessibility on large scale at the same time, has always been in high demand. Based upon our original concept of utilizing NHOs as Brønsted base catalysts,[8] we envisaged that NHOs or their azolium salt precursors could be used cooperatively with a strong base in a '*chemically active*' fashion for solid/organic phase-transfer catalysis (Scheme 1). This system is distinguished from the other catalysts in that it presumably proceeds through the deprotonation of the azolium salt in the organic solution by the solid base, which

**Scheme 1.** Phase-transfer catalysis with N-Heterocyclic Olefins.




[a] School of Chemistry, University of New South Wales, Sydney, NSW 2052, Australia. E-mail: t.v.nguyen@unsw.edu.au
[b] Institute of Organic Chemistry, RWTH Aachen University, Landoltweg 1, 52074 Aachen, Germany.

**Table 1.** Optimization of the NHO catalyzed phase-transfer alkylation reaction[a]




| Entry | Solvent | Base | Time [min][b] | Yield [%][c] |
|---|---|---|---|---|
| 1 | toluene | KO$^t$Bu | 30 | 94 |
| 1a[d] | toluene | KO$^t$Bu | 4320 | 77 |
| 2 | hexane | KO$^t$Bu | 60 | 93 |
| 2a[d] | hexane | KO$^t$Bu | 1440 | 80 |
| 3 | $Et_2O$ | KO$^t$Bu | 60 | 93 |
| 4 | THF | KO$^t$Bu | 10 | 92 |
| 5 | $CH_2Cl_2$ | KO$^t$Bu | 5 | 94 |
| 5a[d] | $CH_2Cl_2$ | KO$^t$Bu | 210 | 86 |
| 6 | $CH_2Cl_2$ | $K_2CO_3$ | >1440[e] | 16 |
| 7 | $CH_2Cl_2$ | $K_3PO_4$ | >1440[e] | 28 |
| 8 | $CH_2Cl_2$ | KOH | 180 | 89 |
| 9 | $CH_2Cl_2$ | KH | 5 | 80 |
| 10 | $CH_2Cl_2$ | KHMDS | >1440[e] | 66 |

[a] The reactions were carried out with 1.0 mmol of **1a**, 1.2 mmol of base, and 1.25 mmol of BnBr (**2a**) in the presence 0.05 mmol NHO precursor **A** in 4 mL of solvent at ambient temperature. [b] Reactions were monitored using TLC until complete consumption of starting material, unless otherwise noted. [c] Yield of the isolated products. [d] Reaction without catalyst. [e] The reaction was not completed after one day.

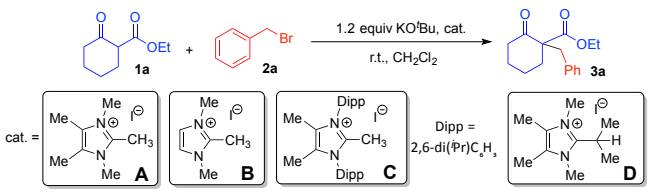
results in the free NHO as the active catalyst. This NHO catalyst then promotes the reaction in the organic phase, in this context being the alkylation reaction, to regenerate the azolium salt for another catalytic cycle. Within seconds of mixing suitable solid inorganic bases, such as KO$^t$Bu, and organic solutions of imidazolium precursors, we observed the immediate formation of NHOs,[17,18] which confirmed the feasibility of our proposed phase-transfer catalytic system.

We chose a family of the readily available imidazolylidene-derived NHO precursors[7,18] for an initial investigation of the typical PTC benzylation reaction of a β-ketoester substrate (Table 1). To our delight the reaction between β-ketoester **1a** and alkyl bromide **2a** in the presence of base and the pentamethyl NHO precursor **A** in toluene proceeded smoothly to produce the desired product **3a** in 94% yield within a short reaction time of 30 minutes. Encouraged by this preliminary result, we started the optimization of the reaction conditions by firstly focusing on the solvent and base used (Table 1). Excellent yields were obtained for all tested solvents, irrespective of their polarity (Table 1, entries 1-4). However, $CH_2Cl_2$ (Table 1 entry 4) was found to be superior to the other solvents, including $Et_2O$ and THF (Table 1, entries 2, 3) due to the significantly shorter reaction time. Therefore $CH_2Cl_2$ was chosen for the subsequent screening of various bases.[19] In accordance with our envisioned mechanism, $K_2CO_3$ and $K_3PO_4$ as weak inorganic bases gave poor conversions even after one day (Table 1, entries 6,7). Better yields of 89%, 80%, and 66% were observed for KOH, KH, and KHMDS, respectively (Table 1, entries 7-9). With the exception of KHMDS, an increased basicity correlates well to increased reactivity. However, the use of KH and KHMDS resulted in lower yields than KO$^t$Bu. Control reactions without catalyst (Table 1, entries 1a, 2a and 5a) gave lower yields with much longer reaction times.[20]

We subsequently turned our attention to different imidazolium-based NHO precursors (Table 2). The NHO precursor **B** without methyl groups at C4-C5 catalyzed the reaction with comparable results to its analogous catalyst **A** (Table 2, entry 2). Therefore we assume that a deprotonation at C4 or C5 of the imidazolium ring[8] was not taking place or interfering with the phase-transfer catalysis. Sterically demanding aryl groups in close proximity to the reactive center had no impact on the efficiency of the reaction (catalyst **C**, Table 2, entry 3). Presumably, due to the electronic stabilization by the π-systems, the acidity of the C2-methyl group is increased, which allows for an easier deprotonation to the NHO. Indeed the acidity of these NHO precursor catalysts was determined to be in agreement with this observation,[9] which aligned well with the acidity trend for their corresponding NHC precursors.[1b] C2-$^i$Pr substituted catalyst **D** also afforded the alkylation product in excellent yield, albeit a slightly prolonged reaction time was necessary (Table 2, entry 4). A similar observation on the effect of steric hindrance to the reaction outcomes was also observed by other groups.[7] Comparable yields could be achieved with decreased catalyst loadings to 2, 1 and 0.5 mol % when using the most readily available catalyst **A** (Table 2 entries 5-7); the reaction times, however, predictably increased from 5 to 40 minutes. Thus, we found the best balance between catalyst loading and reaction time at 1 mol % catalyst (Table 2, entry 6).

With the optimized reaction conditions in hand we went further to extend the scope of the NHO-catalyzed alkylation reaction (Scheme 2). Activated electrophiles like allyl bromide, dimethylallyl bromide, and propargyl bromide gave the alkylation products in high to excellent yields (Scheme 2, **3b-d**). The use of inactivated alkyl halides usually resulted in no conversion (Scheme 2, **3f**). However, methyl iodide, with the smallest alkyl group, gave the desired product **3e** in 77% yield within an hour. When the 1,3-dicarbonyl compound 2-acetyl cyclopentanone was subjected to the PTC reactions, the

**Table 2.** Screening of different catalysts and loadings[a]




| Entry | Catalyst | Cat. [mol %] | Time [min] | Yield [%][b] |
|---|---|---|---|---|
| 1 | **A** | 5 | 5 | 94 |
| 2 | **B** | 5 | 10 | 95 |
| 3 | **C** | 5 | 5 | 93 |
| 4 | **D** | 5 | 15 | 94 |
| 5 | **A** | 2 | 10 | 95 |
| 6 | **A** | 1 | 20 | 94 |
| 7 | **A** | 0.5 | 40 | 93 |

[a] The reactions were carried out with 1.0 mmol of **1a**, 1.2 mmol of KO$^t$Bu, and 1.25 mmol of BnBr (**2a**) in 4 mL of $CH_2Cl_2$. [b] Yield of the isolated products.

alkylation products could be isolated in high yields (Scheme 2, **3g-i**). In the same fashion, the cyclic β-ketoester 2-acetyl γ-butyrolactone smoothly underwent the transformations (Scheme 2, **3j-l**). At this stage, we were interested in monitoring the selectivity of the reaction when a 2-unsubstituted β-ketoester was used (Scheme 2, **3m,n**). Unfortunately, no selectivity to *mono*- or *bis*-alkylation could be observed and the process gave a mixture of products. Furthermore, the reaction with 2.5 equivalents of base and benzyl bromide yielded only 56% of the *bis*-alkylated product (Scheme 2, **3m**). The synthetically interesting cyclization reaction with a dibromo substrate successfully gave the 1,1-disubstituted cyclopentane product **3n**, albeit in a yield of only 37%. The substrate scope was further extended to the glycine imine derivative (Scheme 2, 3**o-r**) with excellent outcomes. The bis-alkylation reactions of the weakly acidic α-tetralone (Scheme 2, 3**s-u**) also proceed smoothly to give the products in high yields. The use of catalyst **E** for these transformations, in addition to catalyst **D** in Table 2, proved that bulky substituents on the exocyclic carbon of the NHO precursor catalyst do not have a significant negative effect on the catalytic activity. This is of importance for the strategic design of improved NHO catalysts in the future.

In order to compare the efficiency of NHO-precursors with other known PTC systems and provide evidence for our proposed mechanism (Scheme 1), we conducted a series of further control experiments. Firstly, we compared the results of the NHO precursor **A** catalyzed process to those of other typical PTCs such as $(^{n}Bu)_4NI$ and $Ph_4PBr$, as well as the reaction without any catalyst (Figure 1). A comparative reaction with the parent imidazolium[13] NHC-precursor **A'** as phase-transfer catalyst was also carried out. For all tested solvents the uncatalyzed reactions were found to be much

**Scheme 2.** Substrate scope of the NHO-catalyzed alkylation reaction.[17]

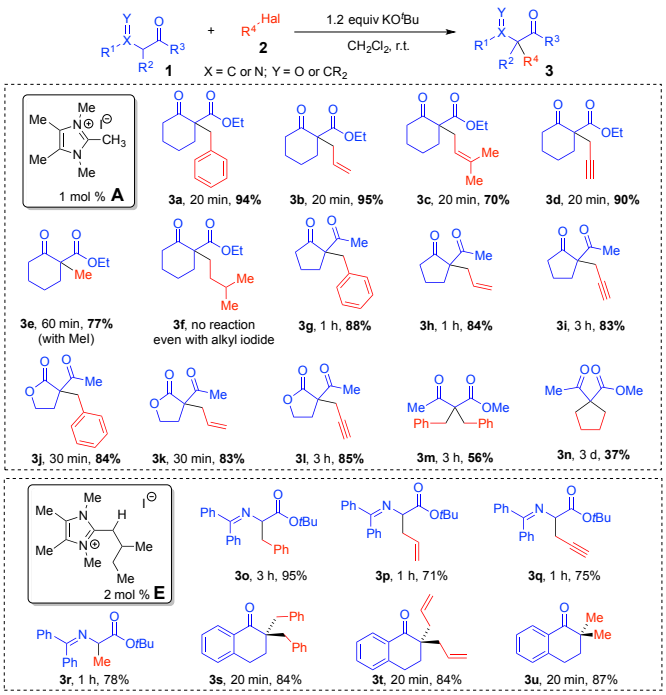
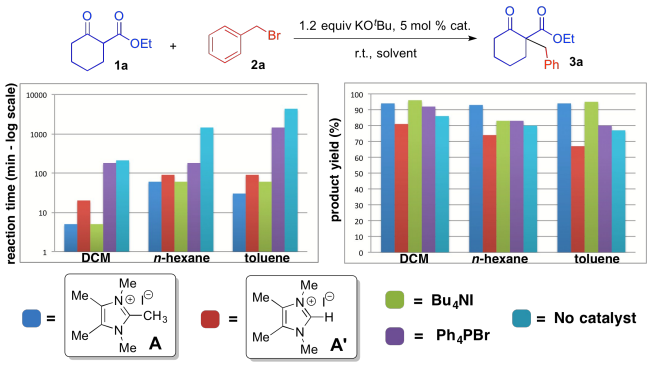


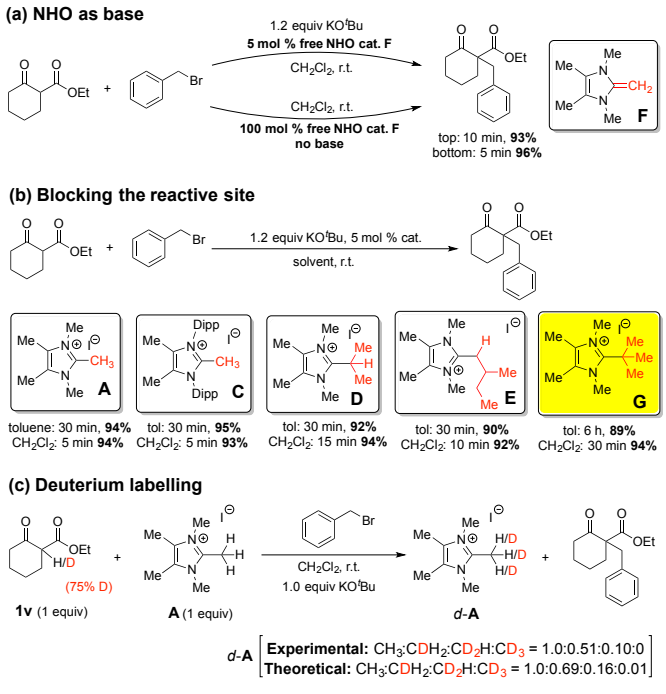

**Figure 1.** Comparative studies with other phase-transfer catalysts




more sluggish than the ones with phase-transfer catalysts (Figure 1). Catalyst **A** was more efficient with shorter reaction times than the standard PTCs $(^{n}Bu)_4NI$ and $Ph_4PBr$, particularly in non-polar solvents. Interestingly, the structurally analogous NHC precursor **A'** was the least effective catalyst for this type of chemical transformation.

We originally proposed that the deprotonation of the imidazolium salt to the free NHO is the key step in the catalytic cycle (Scheme 1). The alkylation reaction failed in the absence of base, proving that the base is crucial. $^1$H NMR studies of the PTC reactions confirmed the deprotonation of catalysts **A** and **C** during the course of the reactions.[9,17] We then designed three new experiments (Scheme 3) in order to provide more evidence for this deprotonation step. In the first case, the free NHO **F**, as a derivative of **A**, was used as catalyst with base as well as a stoichiometric reagent without base. Both reactions provided the same excellent results (Scheme 3a). In the second reaction, we tested the imidazolium catalyst **G** with a blocked reactive site, so that a deprotonation reaction to form the NHO cannot occur (Scheme 3b). The dramatic increase in reaction time in comparison to catalysts **A**, **C**, **D** and **E** shows that at least one hydrogen atom at the C2-exocyclic carbon is required for an efficient PTC. That the steric hindrance of the $^t$Bu group was not the cause for this decrease in catalytic activity was evidenced by the effectiveness of **C**, **D** and **E**, all bearing bulky substituents in close proximity to the reactive sites. At this point, however, we cannot completely rule out the possibility of "normal" phase-transfer catalysis occurring in parallel with the deprotonation-to-NHO pathway. To further underline the role of the hydrogen at the C2 exocyclic carbon, we conducted the alkylation reaction with the deuterium-labelled β-ketoester **1v** and pre-catalyst **A**. We observed a substantial amount of deuterium transfer to the *C2-methyl* group of the pre-catalyst (*d*-**A,** Scheme 3c).[17] Similar results were obtained with deuterated catalyst and protiated substrate.[17] This indicates repeated protonation/deprotonation events, which is consistent with our proposed phase-transfer mechanism (Scheme 1). The distribution ratios of deuterated products *d*-**A** were very close to the theoretical values, suggesting that even if there was any "normal" phase-transfer catalysis occurring, the chemically active NHO catalytic pathway is still predominant. This type of catalytic activity is conceptually significant to the advancement of PTC in a similar

**Scheme 3.** Mechanistic studies




way to the elegant H-bonding tetraalkylammonium salt systems reported by Shirakawa, Maruoka and co-workers recently.[21]

In conclusion, the novel application of NHOs as phase-transfer organocatalysts for synthetically important alkylation reactions was successfully developed. NHOs and their azoliumsalt precursors were employed as very efficient organocatalysts for solid-liquid phase-transfer alkylation reactions. The work illustrates the great potential of NHO organocatalysts in organic synthesis and will certainly stimulate further interest in N-heterocyclic olefin chemistry. We are currently working on other types of NHO-organocatalyzed chemical transformations and will report these studies in due course.

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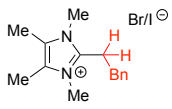


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