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Quaternary Ammonium Salts as Alkylating Reagents in C−H Activation Chemistry

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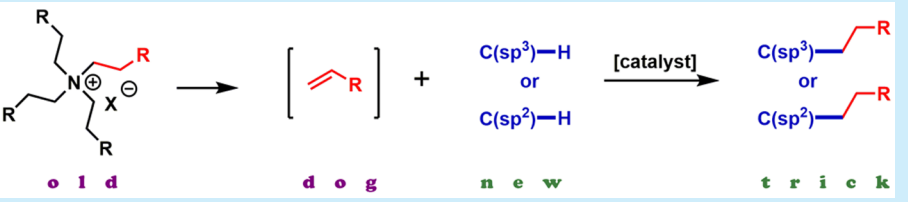
Supporting Information



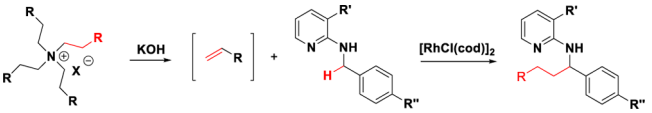
ABSTRACT: A rhodium(I)-catalyzed alkylation reaction of benzylic amines via C(sp^3)−H activation using quaternary ammonium salts as alkyl source is described. The reaction proceeds via *in situ* formation of an olefin via Hofmann elimination, which is the actual alkylating reagent. This represents an operationally simple method for substituting gaseous and liquid olefins with solid quaternary ammonium salts as alkylating reagents, which is transferable to other C−H activation protocols as well.

Selective C−C bond-forming reactions are very fundamental and often-used reactions in organic chemistry, since they are key to building the skeletons of any organic compound. Among the plethora of reported C−C bond forming reactions, metal-catalyzed transformations have gained significant prominence, initially, due to the Nobel prize-winning chemistry of cross-coupling reactions,[1] and, more recently, due to transition-metal-catalyzed C−H activation reactions,[2] which can be considered as the logical advancement of cross-coupling reactions. These reactions generally eliminate the need for at least one prefunctionalized substrate by replacing it with a C−H bond, giving rise to more step- and atom-efficient transformations. Additionally, C−H activation methods often show remarkable functional group tolerance. Thus, in recent years, C−H activation processes for assembly and functionalization of organic molecules were able to greatly simplify the synthesis of pharmaceuticals, natural products, and general feedstock chemicals.[3]

Among C−H transformation methods, alkylation reactions are tremendously important and frequently used in the organic laboratory. Conventional approaches use either primary alkyl halides[4] or olefins[5] as alkylation agents, whereas both alkyl sources have their advantages and disadvantages. Alkyl halides are applied in general when an electrophilic carbon atom is needed. Using alkyl halides faces the drawback of producing stoichiometric amounts of byproducts, which lowers the overall atom efficiency of the reaction. Olefins as alkylating reagents are highly atom efficient in C−C bond-forming reactions, and they have been also used successfully in transition-metal-catalyzed C−H activation reactions in numerous examples in the past two decades.[5] However, one drawback is faced when short-chained alkyl chains should be introduced, since the required olefins are gaseous and therefore high-pressure equipment is typically required. The goal of the present work was to find an alternative alkyl source, which acts as an olefin surrogate and allows introduction of short-chained alkyl chains using solid starting materials.

Our approach was based on a very fundamental organic reaction, taught in every basic Organic Chemistry course: the Hofmann elimination.[6] In this transformation a quaternary ammonium salt eliminates to the least substituted olefin and a tertiary amine (Scheme 1). Since quaternary ammonium salts are solid materials, they would represent an easy-to-handle olefin replacement, eliminating the need for high-pressure equipment if the elimination can take place under the same reaction conditions required for the subsequent C−H activation step.

Scheme 1. A Hofmann Elimination Step Generates the Olefin *in Situ*.



In our case, we had previously reported on a Rh(I)-catalyzed alkylation reaction of **1** with olefins, which served as a model reaction to test our hypothesis (Scheme 2).[7]

In a first experiment, the reaction conditions of this original protocol were used on substrate **1** but the olefin was replaced with

Scheme 2. Reaction Scheme for Using the Olefin Directly

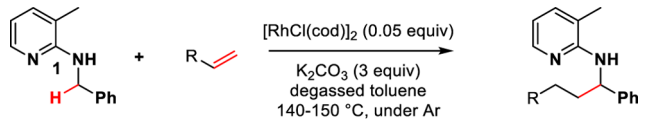


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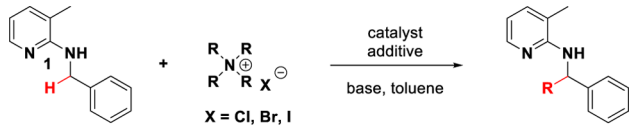
Table 1. Selected Base Screening Results for Alkylation of 1 Using Quaternary Ammonium Salts[a]



entry	no.	R	base	time [h]	yield [%][b]
1	2	ethyl	K_2CO_3	28	80
2[c]	4	butyl	K_2CO_3	28	4
3	4	butyl	C_4H_9OK	28	24
4	4	butyl	NaH	28	traces
5	4	butyl	NaOH	28	56
6	4	butyl	KOH	28	72
7[d]	4	butyl	KOH	3	72
8[e]	4	butyl	KOH	3	71
9[f]	4	butyl	KOH	3	72

[a]General reaction conditions: Substrate **1** (50 mmol, 1 equiv), tetraalkylammonium salt (1 equiv), additive Ag_2CO_3 (5 mol %), catalyst $[RhCl(cod)]_2$ (5 mol %), toluene (2 mL), 140 °C, argon atmosphere. [b]Yields determined by calibrated GC-Analysis relative to dodecane as internal standard. [c]Temperature 160 °C. [d]No additive. [e]No additive, 2 equiv tetraalkylammonium salt. [f]No additive, 10 mol % $[RhCl(cod)]_2$.

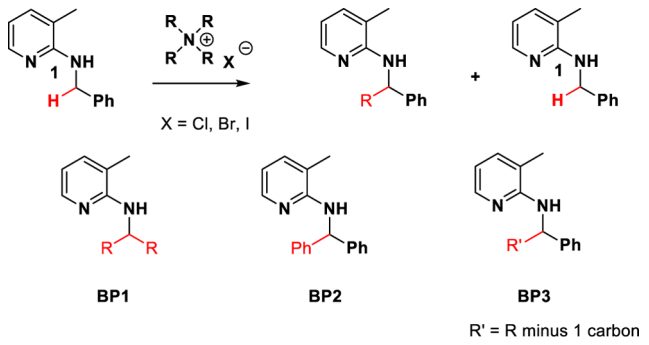


Figure 1. Reaction always leads to the same byproducts to some extent.

tetraethylammonium bromide. It was found that using K_2CO_3 as a base in the ethylation, although not very fast, yields the desired product showing good conversion within 28 h (Table 1, entry 1). Before further optimization efforts were undertaken, it was tested whether the counterion has an impact on the conversion. It was found that switching to tetraethylammonium chloride or iodide gave essentially the same yield (see Supporting Information), which means that quaternary ammonium salts can be selected according to their availability and price without worrying about the nature of the halide ion. Notably, 1 equiv of the tetraalkylammonium salt is sufficient to obtain good conversion. It has to be mentioned that it was not possible to achieve full conversion of the product and about 5−10% of starting material remained, which could be recovered. Additionally, the same byproducts were detected in every reaction (Figure 1). We had shown previously that the substrate **1** and byproducts of type **BP1** and **BP2** are in equilibrium,[7a] which explains the incomplete conversion of the starting material. All three byproducts require that the catalyst is able to break C−C bonds as well, besides forming the desired new C−C bond. This behavior of rhodium was reported previously.[8]

The long reaction time of 28 h suggested that the turnover-limiting step is the Hofmann elimination under these conditions, since the corresponding reaction with olefins (e.g., hex-1-ene)

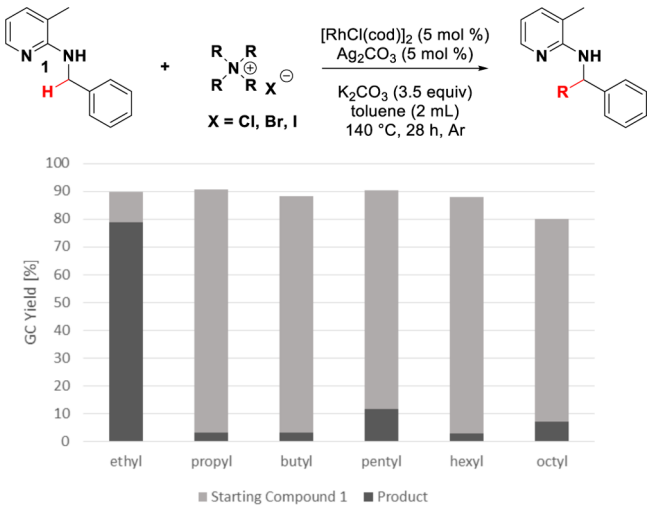


Figure 2. Using quaternary ammonium salts with longer alkyl chains resulted in low conversion when employing the initial reaction conditions.

had already completed after 3 h. Encouraged by these good initial results, we tried to use other quaternary ammonium salts with longer alkyl chains (Figure 2, entries 2−6). Surprisingly, all of these examples showed very low conversion, and only 3−11% of the corresponding product was detected by GC-MS analysis (Figure 2).

Scanning the literature to find an explanation for this observation brought forward a study by Pivovar and co-workers.[9] In a computational study of reactions of hydroxide with quaternary ammonium salts they calculated the Gibbs free energies of activation for the Hofmann elimination of tetraalkylammonium salts and found that, when moving from tetraethylammonium to tetrapropylammonium salts, the Gibbs free energy of activation increases significantly. However, it does not get much higher when going to even longer alkyl chains.

Thus, further optimization focused on accelerating the Hofmann elimination step in order to produce olefin in the reaction mixture more rapidly and to increase the overall rate of the reaction. These reactions were carried out using tetrabutylammonium chloride as a but-1-ene source. Since a higher temperature (Table 1, entry 2) did not improve conversion, it was tested whether bases other than K_2CO_3 would have a beneficial impact. Potassium *tert*-butoxide already showed an improved conversion of 24% (Table 1, entry 3), but sodium hydride gave only traces of the desired product (Table 1, entry 4).

A major leap forward was the use of NaOH, which already gave 56% conversion (Table 1, entry 5), which was further surpassed by using KOH (Table 1, entry 6). This goes in line with the lower stability, and hence more rapid Hofmann elimination, of quaternary ammonium hydroxides in comparison to the corresponding halides.[10] The better conversion of KOH could be attributed to the lower water content of this base as compared to NaOH, which is very hygroscopic. In previous experiments, we have already shown that a too high water content is detrimental for the alkylation reaction with olefins.[7] Moreover, when using KOH, no more additives were needed and the base loading could be reduced slightly as well. In addition, the reaction accelerated significantly and completed within 3 h. Additionally, the yield is similar to that of the transformation using olefins as the alkyl source (Table 1, entry 7). Since the reaction always stopped around 68−73% conversion to the desired alkylated product,

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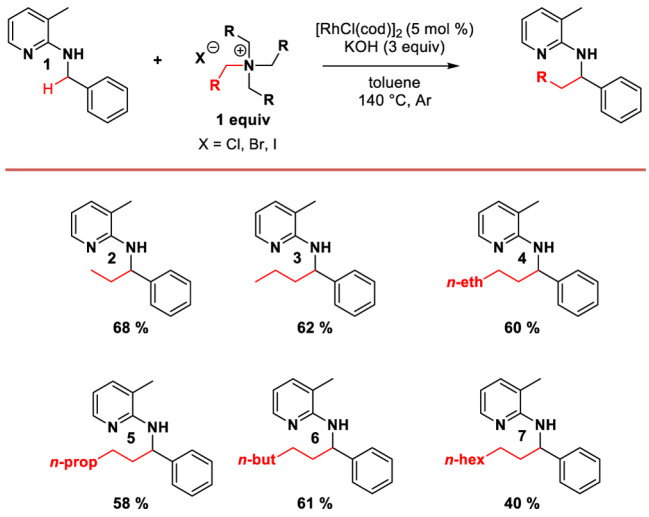


Figure 3. Scope of the reaction using different lengths of alkyl chains at the tetraalkylammonium salt. General reaction conditions: Substrate **1** (50 mmol, 1 equiv), tetraalkylammonium bromide (1 equiv), catalyst $[RhCl(cod)]_2$ (5 mol %), KOH (3 equiv), dry and degassed toluene (2 mL), 140 °C, overnight, argon atmosphere.

modifying the amount of reagent or catalyst was tested, but did not show beneficial impact (Table 1: entries 8–9).

With the optimized protocol in hand, we performed alkylation reactions with different quaternary ammonium salts using various substrates similar to **1** to demonstrate the scope of the present transformation. First, we used different tetraalkylammonium salts with a carbon chain length up to C8 (Figure 3, products **2**–**7**). Prolonging the chains up to C6 gave the same isolated yield, within experimental error (compounds **2**–**6**, 58–68%). Only with tetraoctylammonium bromide, the reaction slowed down, always stopping at 40% yield (Figure 3, **7**).

To increase atom efficiency, it was also tested whether trimethylhexylammonium bromide could be used for hexylation of **1**. Interestingly, in this case only 8% of hexylated product **7** was detected, accompanied by 12% of the methylated product. Since the methylation cannot proceed via an olefin intermediate, it is hypothesized that a Rh-carbene species is involved in this reaction, but further investigations are required to confirm this.

Furthermore, we changed the substitution pattern at the 3-pyridyl-position, as well as at the benzylic *para*-position of our starting material. These substrates were tested solely in the ethylation reaction, since this is the most attractive application of our protocol. As can be seen in Figure 4 (compounds **8**–**16**) again the same range of yield was obtained (50–71%). The substituent in position 3 of the pyridine has basically no influence on the yield of the transformation (Figure 4, **8**–**11**). The substituents on the benzyl group did have an influence, although not a significantly dramatic one. It was observed that electron-donating moieties at the benzylic *para*-position increase the conversion and yield in comparison to the unsubstituted starting compound **1** (Figure 4, **13** and **15**). A 4-methoxy- or 4-isopropoxy group gave good yields of 71% and 69%, respectively. On the other hand, electron-withdrawing substituents seem to have an unfavorable impact on the conversion since both a 4-CF_3- and 4-F-group decreased the yield to 53% and 50%, respectively (Figure 4, **14** and **16**).

Next, it was tested whether the developed alkylation protocol is only limited to our type of substrate and catalyst, since the utility and acceptance of the protocol depend largely on the possibility of general applicability. It was hypothesized that other alkylation

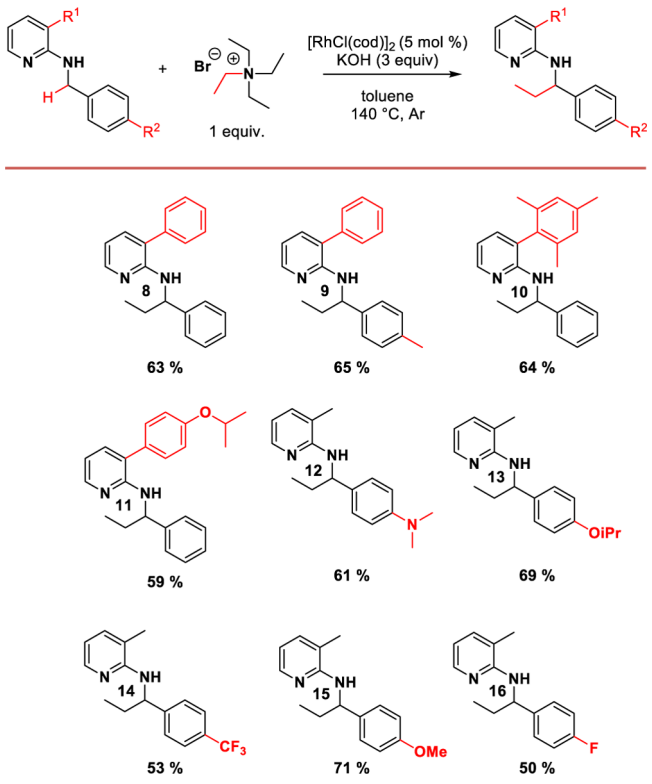
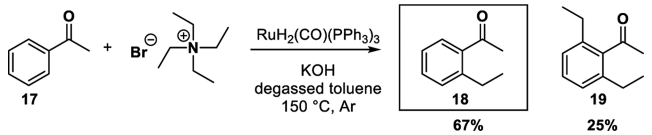


Figure 4. Scope of isolated compounds using our alkylation conditions exploiting different substrates similar to **1**. General reaction conditions: Benzylic amine (50 mmol, 1 equiv), tetraethylammonium bromide (1 equiv), catalyst $[RhCl(cod)]_2$ (5 mol %), KOH (3 equiv), dry and degassed toluene (2 mL), 140 °C, overnight, argon atmosphere.

reactions using olefins should be accessible to our protocol as long as the catalyst and substrates tolerate the presence of KOH.

About three decades ago, the Murai group set a landmark in directing group-assisted C–H activation.[11] They used a ketone as directing group to guide the alkylation in a specific position. More specifically, the group used acetophenone and alkylated the aromatic *ortho*-position, exploiting a Ru(II)-catalyst and using olefins as alkylating agents. We choose this very fundamental reaction for the field of C–H activation to test our new protocol further, using the 1993-published reaction conditions, but substituting olefins for tetraalkylammonium salts and adding KOH to the reaction (Scheme 3).

Scheme 3. Reaction Scheme for Applying Our Ethylation Protocol to the C–H Alkylation Reaction Conditions Published by Shinji Murai in 1993[5]



The reaction worked well with a 67% yield of **18** (Murai reported 75% using triethoxyvinylsilane as an alkylating reagent[11]), showing that a different directing group can be applied for use in conjunction with our method and that it is not limited to rhodium catalysts. As typically found in direct functionalization of acetophenone, considerable amounts of diethylated byproduct **19** were formed.

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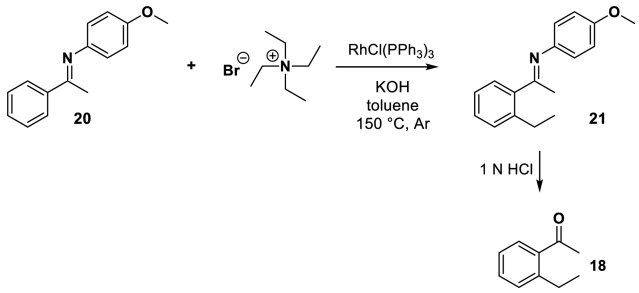
Scheme 4. Reaction Scheme for Imine-Directed C−H Alkylation Reaction with Tetraethylammonium Bromide as an Alkyl Source[8]



As a second example, imine **20** was chosen as a substrate and the alkylation was carried out according to the reaction conditions published by Jun,[12] again substituting the olefin with tetraethylammonium bromide and KOH (Scheme 4).

The reaction worked according to protocol, but always stopped at about 40% conversion to the product. Since product **21** was unstable upon aqueous workup, we decided to hydrolyze the reaction mixture before. This led to 39% of product **18** and 61% of acetophenone **17**, which corresponds to unreacted starting material **20** after hydrolysis. No bis-alkylated product was detected in this case.

Obviously, this yield is not satisfying and more reaction optimization is needed. However, since this was only an experiment to demonstrate the applicability of this protocol and to show that quaternary ammonium salts should be considered as ethene (or generally olefin) alternatives when developing new alkylation reactions, additional reaction optimization was not carried out. Further investigations toward expansion of our protocol to other systems are underway in our laboratory.

To summarize, benzylic amines were alkylated using quaternary ammonium salts as an alkyl source. Hofmann elimination was found to be the crucial step in order to obtain effective conversion to the product. Optimization of the reaction conditions led to a universal and practical protocol for alkylation reactions via C−H activation where gaseous olefins can be substituted for solid quaternary ammonium salts. It was shown that different directing groups (pyridine, ketone, imine) can be used, as well as different catalysts based on both rhodium and ruthenium. Next, use of palladium will be tested, as well as, most importantly, nonprecious metals for this type of alkylation reactions.

The newly developed method also works for literature-known reactions and, hence, will be broadly applicable. Further investigations for the development of new transformations and application studies on reported systems are currently underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b01946.

Detailed experimental procedures and analytical data of all synthesized compounds (PDF)

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Notes

The authors declare no competing financial interest.

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