Synthetic Methods

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Mild Metal-Free Tandem α-Alkylation/Cyclization of *N*-Benzyl Carbamates with Simple Olefins**

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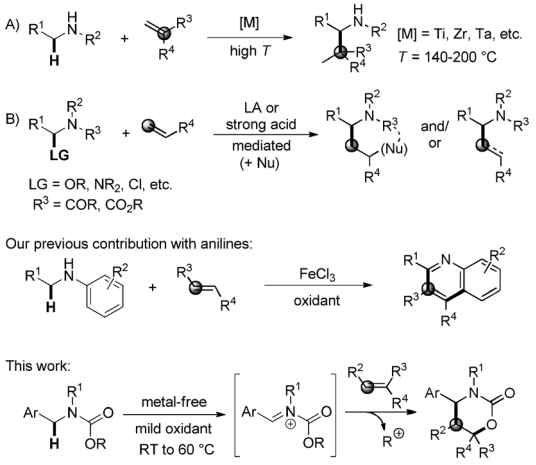
The aminoalkyl moiety is one of the most frequently occurring functionalities in natural products and synthetic biologically active compounds.[1] Thus, the direct functionalization of C–H bonds in the α-position to a nitrogen group is of special interest for both academia and industry.[2,3] Among the various synthetic strategies for the introduction of these aminoalkyl residues, the hydroamination of olefins and alkynes[4] and the hydroaminoalkylation of olefins[5,6] have attracted great interest in the past few years. Several methods for the metal-catalyzed activation of α-C(sp^3)–H bonds in amines and the subsequent addition to olefins, to form mostly α,β-branched amines, have been developed recently (Scheme 1 A).[5–7] However, these procedures, usually catalyzed by Group 4 and 5 metals, suffer from regioselectivity issues and still require high temperatures (typically around 140–200 °C) and long reaction times. On the other hand, the related α-amidoalkylations of simple olefins typically require a Lewis acid or a strong acid and preactivation in the α-position to the nitrogen atom, such that OR, OCOR, NHCOR, NR_2, NR_3^+, SiR_3, or halogen act as a leaving group (Scheme 1 B).[8,9] Therefore, the development of more general and milder methods for the direct α-alkylation of nitrogen compounds with olefins remains a challenge. Herein, we describe the first mild metal-free method for the highly selective direct oxidative α-alkylation/cyclization tandem reaction of *N*-benzyl carbamates with simple olefins. Moreover, this oxidative approach makes it possible to avoid the use of both metal catalysts and α-activated nitrogen reagents.



Scheme 1. α-Alkylation of nitrogen compounds with olefins. LG = leaving group, LA = Lewis acid, Nu = nucleophile.

Since numerous olefins are readily available and cheap, they are preferred reagents for conducting alkylation reactions. It would be highly desirable to develop a new mild and general method for the reaction of nonactivated olefins to form C–C bonds in the α-position to a nitrogen atom. Encouraged by our initial studies on the $FeCl_3$-catalyzed oxidative synthesis of quinolines from *N*-alkylanilines (Scheme 1, middle),[10] we therefore decided to explore the direct oxidative C(sp^3)-H α-alkylation of simple carbamates with nonactivated olefins, in which a subsequent nucleophilic attack of the carbamate oxygen could lead to interesting heterocyles such as oxazinones[11,12] (Scheme 1, bottom).

The reaction of N-protected tetrahydroisoquinolines (THIQs) with styrene in the presence of $Cu(OTf)_2$ as the catalyst (10 mol%) and a 2,2,6,6-tetramethylpiperidine *N*-oxide (TEMPO) salt[13,14] (R′ = H/$T^+BF_4^-$, 1.1 equiv) as the oxidant at room temperature was chosen as the starting point for the optimization. Different simple alkyl-substituted carbamates such as methyl (**1a**), isopropyl (**1b**), and benzyl derivatives (**1c**) were explored. In these cases no reaction was observed or a complex reaction mixture formed in which we identified a small amount of the corresponding Heck-type product (Table 1, entries 1–3). These initial results at room temperature were quite promising, although the necessity of a good leaving group R at the carbamate was apparent. Thus, when the Boc-protected THIQ **1d** was reacted with styrene, the desired cyclic product **3a** was formed in 57% yield (Table 1, entry 4). We were surprised to observe the concomitant formation of product **3b** (35% yield), derived from a formal C–H bond functionalization of the *t*Bu group. This compound is, however, more likely to be formed by the reaction of **1d** with isobutene generated in situ upon the partial decomposition of the substrate.[12] As expected, **3b** was also obtained in the absence of an external olefin in 48% yield (Table 1, entry 5).[15] The reaction in the absence of a transition-metal catalyst, using 4 equivalents of styrene, was next carried out. Surprisingly, the efficiency of the reaction was retained (Table 1, entry 6). When we switched from $T^+BF_4^-$ to the 4-acetamido derivative of TEMPO (4-

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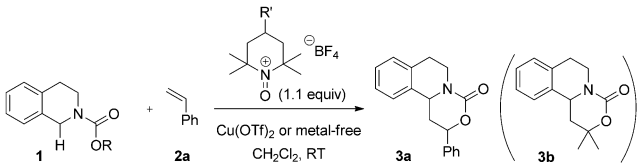
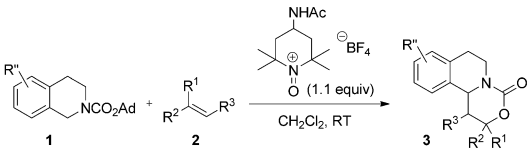
Table 1: Optimization of the reaction conditions.[a]



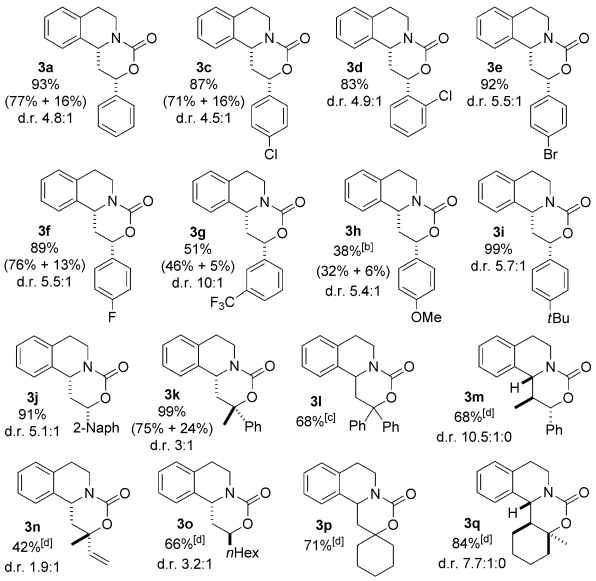
Entry	**1** (R)	**2a** [equiv]	$Cu(OTf)_2$ [mol%]	Oxidant	Yield [%][b] **3a**	**3b**
1	**1a** (Me)	2.0	10	$R'T^+BF_4^-$ (R′=H)	–[c]	
2	**1b** (*i*Pr)	2.0	10	$R'T^+BF_4^-$ (R′=H)	–	
3	**1c** (Bn)	2.0	10	$R'T^+BF_4^-$ (R′=H)	–	
4	**1d** (*t*Bu)	2.0	10	$R'T^+BF_4^-$ (R′=H)	57	35
5	**1d**	–	10	$R'T^+BF_4^-$ (R′=H)	–	48
6	**1d**	4.0	–	$R'T^+BF_4^-$ (R′=H)	58	22
7	**1d**	4.0	–	$R'T^+BF_4^-$ (R′=NHAc)	63	15
8	**1e** (Ad)	2.0	–	$R'T^+BF_4^-$ (R′=NHAc)	93	
9	**1e**	1.2	–	$R'T^+BF_4^-$ (R′=NHAc)	93[d]	
10	**1e**	1.2	–	–	–	
11	**1e**	1.2	–	DDQ	6	
12	**1e**	1.2	–	*t*BuOOH	–	
13	**1e**	1.2	–	O_2[e]	–	

[a] **1** (0.1 mmol), **2a** (1.2–4.0 equiv), and oxidant (1.1 equiv) in CH_2Cl_2 (0.2 M) at RT for 24 h. [b] Yield of isolated product. [c] A complex mixture was formed. [d] Same yield was obtained in a 0.5 mmol scale reaction. [e] 1 atm of O_2 was used.

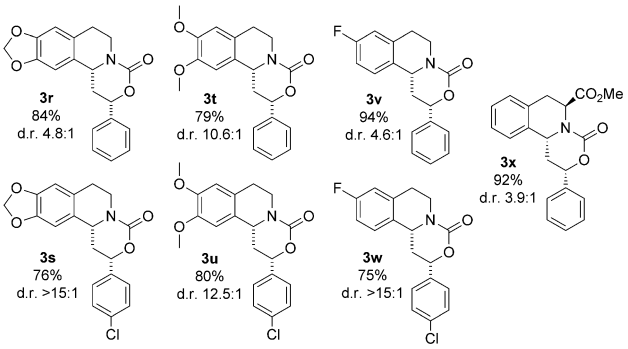
Table 2: Substrate scope.[a]



Variation of the olefin



Variation of the tetrahydroisoquinoline



[a] **1** (0.1 mmol), **2** (1.2 equiv), and 4-$NHAcT^+BF_4^-$ (1.1 equiv) in CH_2Cl_2 (0.2 M) at RT for 24 h. (The relative configuration of the major isomer is represented.[21]) [b] A solution of the styrene in CH_2Cl_2 was slowly added (over 5 h). [c] **3l′** was also isolated in 12% yield. [d] 5 equiv of olefin used.

$NHAcT^+BF_4^-$),[16] **3a** was obtained in a slightly improved yield of 63% (Table 1, entry 7).[17] However, certain amounts of **3b** were still formed. To avoid this and achieve high chemical selectivity, we ultimately envisioned the use of an adamantyl (Ad) group as a substituent on the carbamate moiety. Owing to the high stability of the adamantyl cation[18] it should be a good leaving group and, according to Bredt's rule, it would not undergo elimination to introduce another olefin to the reaction mixture. Consequently, when the reaction was carried out using **1e**, with 2 equivalents of styrene, **3a** was obtained in an excellent yield of 93% (Table 1, entry 8). The same efficiency was obtained by reducing the amount of styrene to 1.2 equivalents and by scaling up the reaction by a factor of 5 (Table 1, entry 9). Moreover, it is worth mentioning that other common oxidants like DDQ, *t*BuOOH, and O_2, which are used for the formation of iminium-type intermediates in dehydrogenative couplings, were not efficient in promoting the reaction (Table 1, entries 11–13).[3,19] This fact underlines the unique action of the TEMPO-derived salts as oxidants in this alkylation coupling reaction.

With the optimized conditions in hand, we investigated the scope of the reaction (Table 2). Initially, styrene derivatives bearing either electron-withdrawing (EGW) (**3c**–**g**) or electron-donating groups (EDG) (**3h**–**j**) were explored. The desired oxazinones **3** were generally furnished in good to excellent yield (83–99%), with the exception of substrates with strong EWGs (e.g. R = *m*-CF_3: **3g**, 51%; or *p*-NO_2: traces). On the other hand, highly electron-rich substrates such as the *p*-MeO-substituted derivative (**3h**, 38%) suffer from the favored competitive oxidative polymerization of the styrene.[20] Most of the generated diastereomeric mixtures obtained with styrenes could be separated by chromatography (e.g. **3a**, **3f**, **3g**, and **3h**).[21]

Next, α-branched styrenes were tested. α-Methylstyrene gave **3k** in almost quantitative yield, while the reaction with the more hindered 1,1-diphenylethylene produced **3l** in a lower yield of 68% (along with 12% yield of the olefinated compound **3l′**, see Scheme 3). The reaction of **1e** with *trans*-β-methylstyrene proceeded smoothly and **3m** was isolated in 68% yield and 10.5:1 d.r. On the other hand, the reaction with isoprene gave exclusively **3n**, indicating the chemoselective coupling of the more substituted double bond.

To further establish the scope of this transformation, aliphatic olefins were next investigated. Interestingly, a simple olefin like 1-octene was also a suitable substrate and compound **3o** was formed in 66% yield. Moreover, the use of methylenecyclohexane as the coupling partner provided selectively the spiro compound **3p** in a good yield of 71%. Next, we addressed the synthesis of trisubstituted oxazinones. Although it is reported in the literature that oxoammonium salts undergo ene-like addition to trisubstituted alkenes,[22] under our conditions the reaction of **1e** with 1-methyl-1-cyclohexene gave exclusively the tetracyclic compound **3q** in a remarkable 84% yield. After demonstrating the generality of the nucleophile, we explored several THIQ derivatives. Substrates containing either electron-donating or electron-withdrawing groups were efficiently employed (Table 2, bottom). To show the variation at the saturated N-heterocyclic unit, an enantiomerically pure compound having an ester in the C3 position of the THIQ was prepared starting from L-phenylalanine. The ester group was well tolerated and **3x** was obtained in 89% yield with the complete preservation of chirality. Our method is thus compatible with optically active compounds and suitable for the synthesis of complex molecules.

The more challenging acyclic benzyl carbamates were also suitable substrates for this transformation. Thus, when the reaction was performed at 60°C in the presence of 4-$NHAcT^{+}BF_4^{-}$ (1.5 equiv), the corresponding oxazinones **4a–f** were obtained in moderate to excellent yield (66–99%, Figure 1).[23] Moreover, more hindered 1,1-disubstituted olefins could also be employed, leading to the products **4e** and **4f**, which possess a quaternary center, in 40–42% yield.

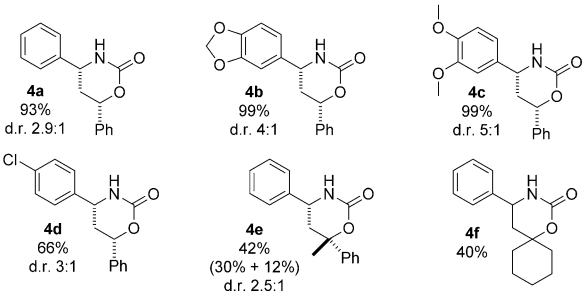
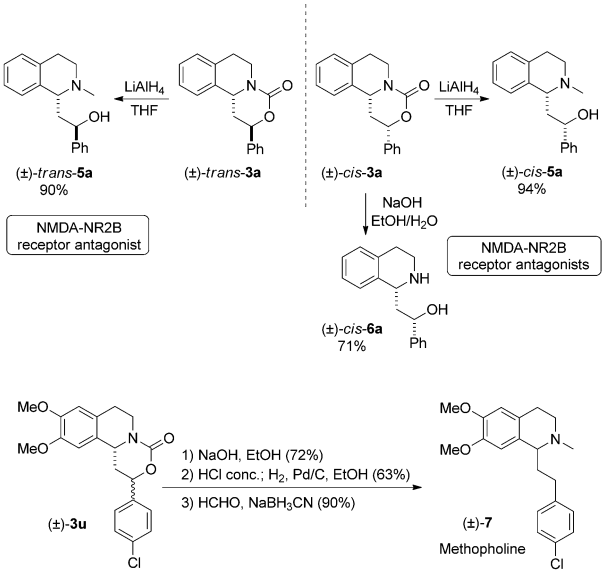


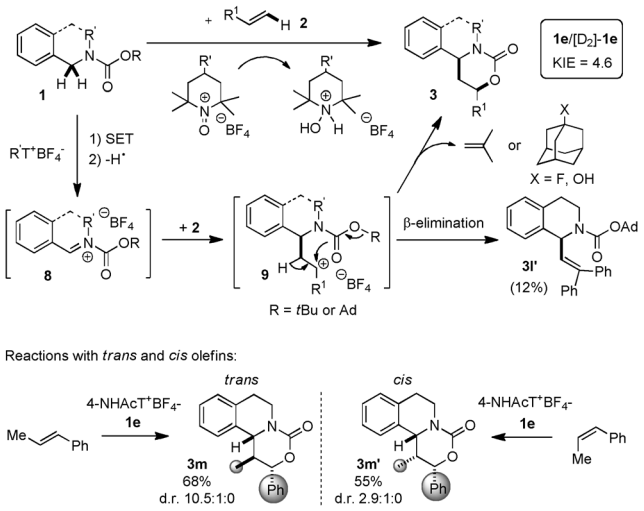
Figure 1. Products obtained from the reaction with acyclic benzyl carbamates.

Oxazinones **3** derived from THIQ were next easily transformed into other valuable biologically active derivatives such as the corresponding substituted aminoalcohols **5** and **6**.[24,25] Thus, the two separated diastereomers of **3a** were reduced with $LiAlH_4$ to give the corresponding *N*-methyl-1-alkyl-THIQ compounds *trans*-**5a** and *cis*-**5a** in excellent yield (90% and 94%, respectively). These β-hydroxy-THIQ structures are interesting since they are present in several natural and synthetic bioactive compounds such as NMDA-NR2B receptor antagonists.[25] Additionally, treatment of *cis*-**3a** with NaOH in an ethanol/water mixture gave the free amino-alcohol *cis*-**6a** in good yield (71%). Finally we applied our method to the synthesis of the racemic form of the analgesic drug Methopholine (**7**)[26] in three steps from oxazinone **3u**. The direct reduction of **3u** with $LiAlH_4$ to generate the *N*-methyl derivative of type **5** was not selective, and we observed the concomitant significant reduction of the aromatic C–Cl bond. However, when initial carbamate deprotection with base (NaOH) was followed by a one-pot treatment with HCl (conc.), reduction with the H_2 on Pd/C, and a final *N*-methylation, **7** was obtained in good overall yield (Scheme 2).



Scheme 2. Modification of oxazinones and synthetic applications.

Finally, based on experimental observations,[27] we propose a mechanism for the alkylation/cyclization reaction in which an initial α-oxidation with the TEMPO salt generates the *N*-acyliminium ion **8**,[8] which undergoes nucleophilic addition of the olefin (Scheme 3). Subsequently, the cleavage of the O–adamantyl bond and the concomitant attack of the carbamate oxygen atom at the carbocation center in **9** release oxazinone **3** and an adamantyl cation.[28,29] The participation of the cationic intermediate **9** in the course of the reaction was confirmed by the formation of the **3l′** (Scheme 3).[28] Thus, in the reaction with sterically hindered 1,1-diphenylethylene, the β-proton elimination from the proposed intermediate **9** can compete with the intramolecular cyclization (**3l**/**3l′**). However, because of the selectivities observed and the complete retention of the stereochemistry in the reactions with both *trans*- and *cis*-β-methylstyrene (Scheme 3, bottom), a fast cyclization of the highly reactive cationic intermediates of type **9**, or even a concerted cycloaddition pathway, can be assumed. Moreover, if one considers that the reaction with the different styrenes proceeded in similar reaction times (14–18 h) and that the acyclic substrates required higher reaction temperatures,[30] the generation of the active iminium species **8** might be involved in the rate-determining step. Thus, to differentiate between a proton- or hydrogen-abstraction mechanism in the formation of **8** after an initial single-electron transfer (SET) to form an N-centered radical cation



Scheme 3. Mechanistic observations and proposal. SET = single-electron transfer.

intermediate, we carried out kinetic isotope studies with **1e** and α,α-dideuterated [D_2]-**1e** (see the Supporting Information). A high kinetic isotope effect (KIE) of 4.6 was observed, suggesting that hydrogen abstraction (C–H cleavage) is more likely to be the rate-determining step.

In summary, we have developed a novel and general tandem α-alkylation/cyclization of *N*-benzyl carbamates with nonactivated olefins in the absence of metal catalysts. Moreover, a C–H bond in the α-position to a nitrogen group can be directly functionalized, and thus no preactivation of the substrate is required. The reaction takes place under mild conditions in the presence of 4-NHAcT$^+$BF$_4^-$ as a unique nontoxic mild oxidant. This method constitutes the first example of metal-free direct α-alkylation of *N*-benzyl carbamates using simple mono-, di-, and trisubstituted olefins. We also demonstrated the generality of this reaction and its applicability to the synthesis of a variety of oxazinones and other different bioactive derivatives.

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[30] Only traces of products **4** were detected at room temperture after 18–24 h.

Communications

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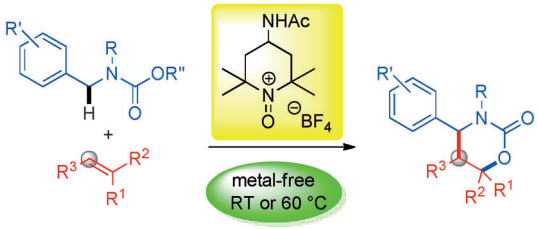
Mild Metal-Free Tandem α-Alkylation/Cyclization of *N*-Benzyl Carbamates with Simple Olefins



Easy does it! The chemoselective oxidative α-C(sp^3)–H alkylation/cyclization reaction of *N*-benzyl carbamates using simple mono-, di-, and trisubstituted olefins provides functionalized N-heterocycles such as oxazinones (see picture). A TEMPO oxoammonium salt serves as the oxidant, making it possible to carry out the reaction at low temperatures. Neither a metal catalyst nor preactivation in the α-position to the nitrogen group are needed.