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Direct C−H Allylation of *N*-Acyl/Sulfonyl Tetrahydroisoquinolines and Analogues

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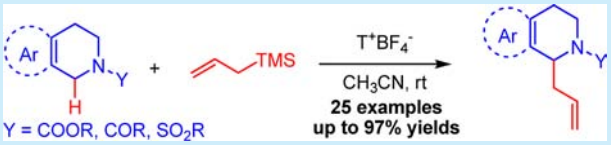
Supporting Information

ABSTRACT: A highly efficient direct C−H allylation reaction at the α position of *N*-acyl/sulfonyl tetrahydroisoquinolines under mild conditions was developed. The reaction was also suitable for allylation of other protected nitrogen-containing heterocycles. Several interesting transformations of the products into valuable synthetic intermediates are featured with the successful total synthesis of (±)-crispine A.

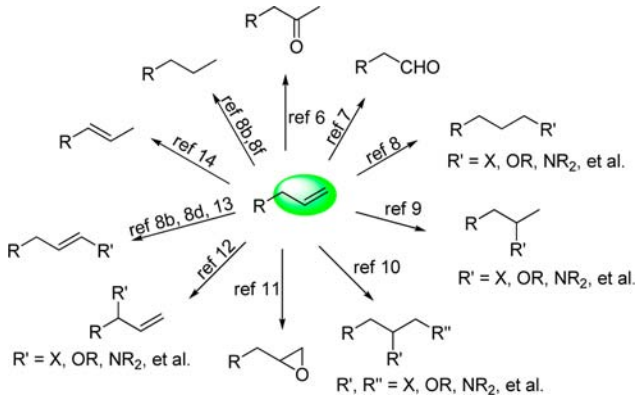


The direct transformation of C−H bonds into useful functional groups, called C−H functionalization, is a fascinating synthetic strategy for the construction of new chemical bonds (especially C−C bonds) from an atom- and step-economic point of view.[1] Oxidative C_{sp^3}−H functionalization of nitrogen-containing heterocycles such as tetrahydroisoquinolines (THIQs), which are common structural motifs in alkaloids,[2] has achieved impressive progress in the past decade;[3] however, the scope is limited to highly reactive *N*-aryl substituted substrates, which limits the synthetic utility because of the difficulty in removing the *N*-aryl group.[4] Thus, functionalization of the adjacent C_{sp^3}−H bond to readily removable acyl moieties has attracted the attention of organic chemists, and several examples have been disclosed.[5] However, the nucleophile scope is limited, likely owing to the decomposition of unstable *N*-acyliminium ions in the reaction conditions.[5h] The addition of a stabilizer such as alcohol can lead to a troublesome operation.[5h,i] Using a nucleophile that can be easily manipulated to access various functional groups after the C−C bond formation instead would increase the possibility of solving the problem.

The allyl moiety is an exceptionally versatile functional group, offering a wealth of opportunities for further functionalizations (Scheme 1).[6−14] Traditionally, the S_N2 reaction was used to realize the α-allylation of *N*-acyl THIQs, which required strong bases and a limited substrate scope.[15] In 2001, an electrochemical method was developed by the Yoshida group, in which a specific device was needed, thereby limiting its academic and industrial applications.[16] Despite this progress, the development of a mild and efficient method for direct α-C−H allylation of *N*-acyl THIQs is still in high demand. Herein, we report our recent effort on the direct C−H allylation of *N*-acyl tetrahydroisoquinolines with allyltrimethylsilane and further derivatization of the product to representative natural compounds.

Based on our and others' previous work, we believed that the *N*-acyliminium species could be generated after α-oxidation, which would undergo nucleophilic addition by allyltrimethylsilane (Scheme 2).[5] We used *N*-Cbz THIQ (**1a**) and allyltrimethylsilane as the substrates to optimize the reaction conditions (Table 1). Initially, 2,2,6,6-tetramethylpiperidine-1-oxoammonium tetrafluoroborate ($T^+BF_4^-$) was used which had been reported to be an excellent oxidant to oxidize **1a** to *N*-acyliminium.[5h,i] Fortunately, when CH_3CN was used as the solvent, the reaction was complete within 2 h and gave the expected **2a** in a yield of 97% (entry 1). Triphenylcarbenium tetrafluoroborate resulted in a lower yield of 77% (entry 2). The commonly used oxidant 1,2-dichloro-4,5-dicyanobenzo-

Scheme 1. Various Transformations of the Allyl Group



Scheme 2. Mechanism of the Allylation Reaction

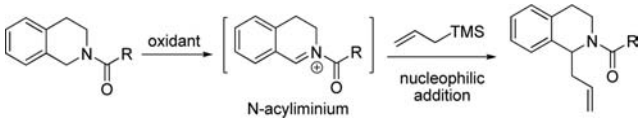


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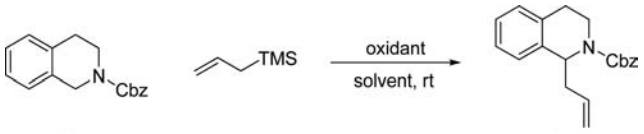
Table 1. Optimization of Reaction Conditions[a]



1a **2a**

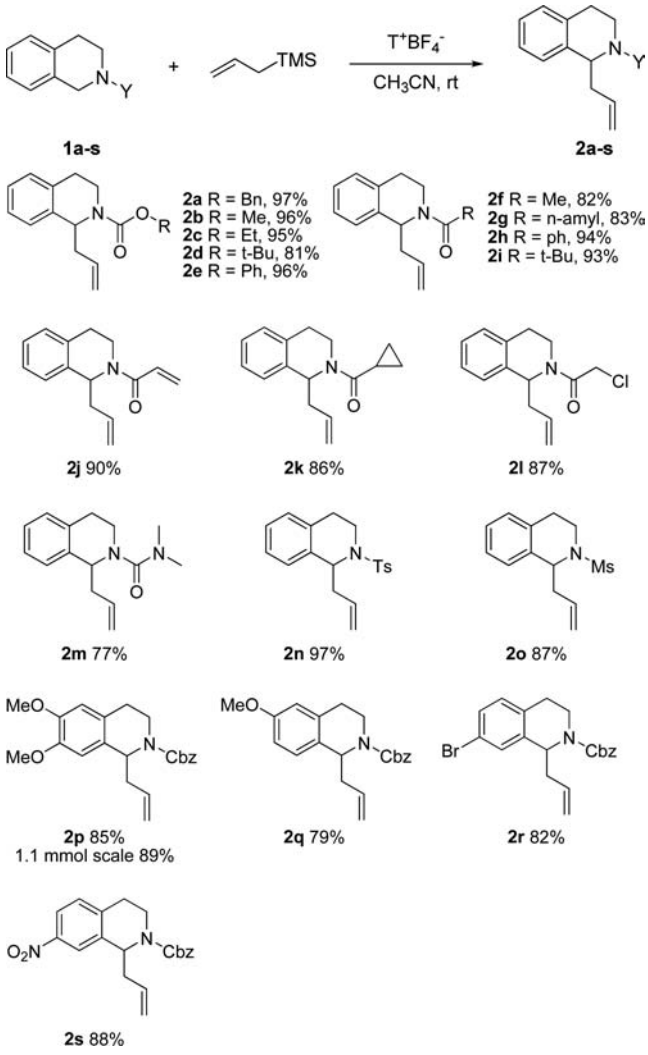
entry	solvent	oxidant	time (h)	yield (%)[b]
1	CH_3CN	$T^+BF_4^-$	2	97
2	CH_3CN	Ph_3CBF_4	2	77
3	CH_3CN	DDQ	24	92
4	CH_3CN	CAN	24	<5
5	CH_3CN	$Na_2S_2O_8$	24	<5
6	$CHCl_3$	$T^+BF_4^-$	12	96
7	CH_2Cl_2	$T^+BF_4^-$	2	94
8	$ClCH_2CH_2Cl$	$T^+BF_4^-$	2	93
9	DMF	$T^+BF_4^-$	2	62
10	DMSO	$T^+BF_4^-$	24	<5
11[c]	THF	$T^+BF_4^-$	24	63
12	CH_3OH	$T^+BF_4^-$	24	<5
13[d]	**CH_3CN**	**$T^+BF_4^-$**	**2**	**96**
14[d,e]	CH_3CN	$T^+BF_4^-$	2	87

[a]Reaction conditions: **1a** (0.4 mmol, 1 equiv), oxidant (1.5 equiv), allyltrimethylsilane (1.5 equiv) in solvent (4 mL) at rt under Ar unless otherwise noted. [b]Isolated yield; NR, no reaction. [c]16% of **1a** was recovered. [d]$T^+BF_4^-$ (1 equiv), allyltrimethylsilane (1.2 equiv). [e]Under air atmosphere.

quinone (DDQ) could also give a high yield of 92%, but with a longer reaction time of 24 h (entry 3). However, only a trace amount of product was obtained when ceric ammonium nitrate (CAN) and $Na_2S_2O_8$ were used (entries 4 and 5). Therefore, we used $T^+BF_4^-$ as the appropriate oxidant for further solvent screening. Chloralkanes such as $CHCl_3$, CH_2Cl_2, and $ClCH_2CH_2Cl$ as solvents also gave good yields (entries 6–8). However, due to the poor solubility of $T^+BF_4^-$, a longer reaction time was needed when $CHCl_3$ was used (entry 6). Other commonly used solvents such as DMF, DMSO, THF, and CH_3OH resulted in lower yields or no reaction (entries 9–12). Because $T^+BF_4^-$ can dissolve in CH_3CN excellently, we think that the quantity of the oxidant can be lowered. An experiment indicated that the yield was not significantly affected when 1.0 equiv of $T^+BF_4^-$ and 1.2 equiv of allyltrimethylsilane were used (entry 13). The reaction can also proceed smoothly under an air atmosphere but with a slightly lower yield (entry 14). By this time, we obtained the optimization conditions without using any transition metal.

With the optimized conditions in hand, we then investigated the scope of *N*-acyl/sulfonyl THIQs of the reaction (Scheme 3). A variety of carbamates of THIQ were examined. The reactions of benzyl carbamate (**1a**), methyl carbamate (**1b**), and ethyl carbamate (**1c**) all gave corresponding products (**2a–c**) in high yields. The allylic *tert*-butyl carbamate (**2d**) was obtained with a lower yield of 81%, maybe because of the high steric hindrance. The reaction of phenyl carbamate (**1e**) also gave a very high yield. A different result was obtained from the reaction of amide substrates when compared to the reaction of carbamate substrates. Acetamide (**1f**) and *n*-hexanamide (**1g**) (which has a long alkyl chain) underwent direct C–H allylation to afford the expected products in lower yields than sterically bulky benzamide (**1h**) and pivaloylamide (**1i**). This phenomenon can be explained by the stability of the *N*-acyliminium intermediates. The *N*-acyliminium intermediates of the latter

Scheme 3. Reaction Scope with Different *N*-Acyl THIQs[a,b]



[a]Reaction conditions: **1a** (0.4 mmol, 1 equiv), $T^+BF_4^-$ (1 equiv), allyltrimethylsilane (1.2 equiv) in solvent (4 mL) at rt under Ar unless otherwise noted. [b]Isolated yield.

substrates were more stable than the *N*-acyliminium intermediates of the former ones. Many functional groups such as a double bond, cyclopropyl, and halogen at the acyl moiety were well tolerated, and corresponding products (**2j–l**) were obtained in good yields. To explore the regioselectivity of the reaction, we used *N*,*N*-dimethyl carboxamide (**1m**) as the substrate and found that the reaction gave **2m** as the only product in 77% yield; no *N*-methyl allylation product was detected. This result indicated that the C–H allylation proceeded selectively at the benzyl of the *N*-acyl THIQs. Both the allylic *N*-sulfonyl THIQs **2n** and **2o** were obtained in good yields. We also investigated various substituents on the benzene ring of the THIQs. THIQs with electron-donating methoxy groups (**1p** and **1q**), an electron-withdrawing nitro group (**1r**), and a halogen (**1s**) all underwent the reaction with good yields. Notably, enlarging the scale of the reaction resulted in a similar yield (see **2p**).

The direct C–H allylation of other carbobenzoxy (Cbz) protected nitrogen-containing heterocycles were studied next (Figure 1). For Cbz protected tetrahydro-*β*-carboline, a moderate yield of 43% was obtained (see **3**). Cbz-protected

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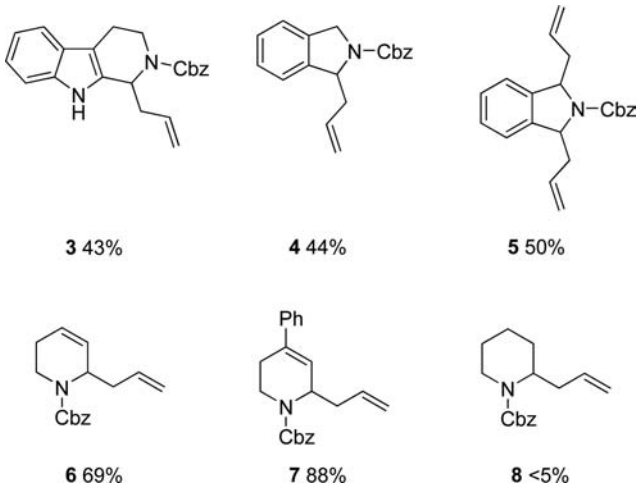


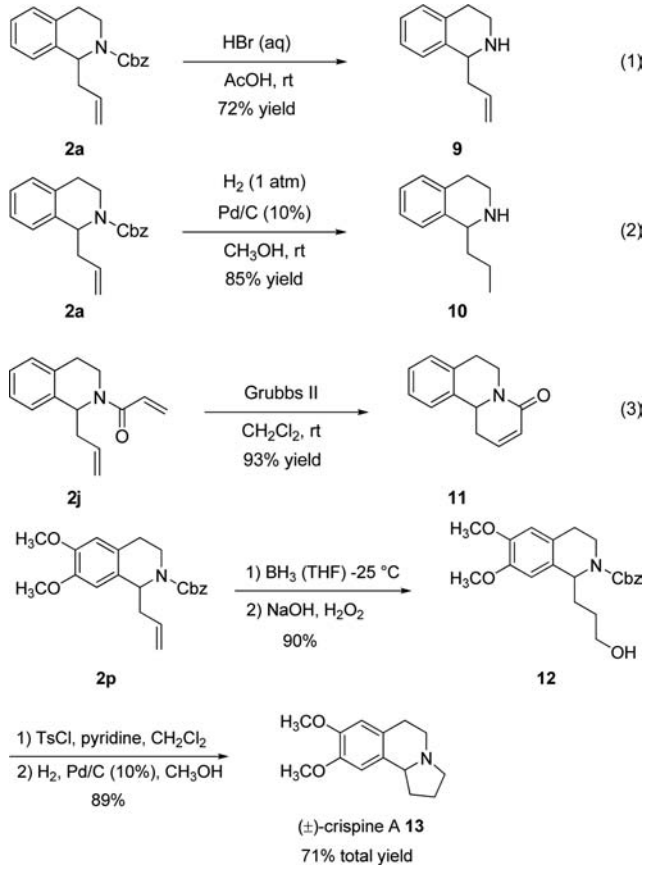
Figure 1. Reaction scope with other nitrogen-containing heterocycles. Reaction conditions: **1a** (0.4 mmol, 1 equiv), $T^+BF_4^-$ (1 equiv), allyltrimethylsilane (1.2 equiv) in solvent (4 mL) at rt under Ar unless otherwise noted. Isolated yields provided. In the case of **5**, $T^+BF_4^-$ (2.5 equiv) and allyltrimethylsilane (2.5 equiv) were used.

isoindoline was also tolerated and gave a 44% yield under standard conditions with a trace amount of diallylic product **5**. When 2.5 equiv of oxidant and allyltrimethylsilane were used, **5** was formed as the only product. We also investigated 1,2,5,6-tetrahydropyridine which is an important synthon in natural product synthesis. The reaction proceeded smoothly to give a good yield. 4-Phenyl-substituted tetrahydropyridine could also be converted with a higher yield of 88%. Unfortunately, with piperidine as the substrate, the desired product **8** was not detected, probably because *N*-acyliminium could not be generated due to the higher energy of the C–H bond. Similarly, linear amine derivatives such as Cbz-protected benzylic amine and Cbz-protected *N*-methyl benzylic amine were proven to be not tolerated.

The utility of our reaction was further demonstrated. The Cbz group of **2a** could be easily removed under acidic conditions (Scheme 4, reaction 1). Deprotection and double-bond reduction could be realized in good yield by one step involving catalytic hydrogenation (Scheme 4, reaction 2). *N*-Acyl products are also very important organic synthetic intermediates. For example, **2j** could be converted to a tricyclic product **11** which is a core scaffold of a number of alkaloids[17] via a ring closure metathesis reaction (Scheme 4, reaction 3). Eventually, we applied our method to the synthesis of (±)-crispine A[8a] (**13**) adopting a three-step sequence viz. hydroboration–oxidation, tosylation, and *N*-deprotection–cyclization in an overall 71% yield. In addition, compound **12** could serve as an advanced intermediate for the synthesis of crispine C and crispine E after simple synthetic elaboration.[8f]

In conclusion, we report a highly efficient direct C–H allylation reaction at the α position of *N*-acyl/sulfonyl THIQs and analogues that proceeded under mild conditions. The products of the reaction are suitable for various further modifications, and the methodology has been successfully exploited in the synthesis of (±)-crispine A. Further synthetic exploration toward the enantioselective variant of this strategy is currently under active investigation and will be reported in due course.

Scheme 4. Transformation of the Products and Total Synthesis of (±)-Crispine A



■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b03042.

Detailed experimental procedures and characterization data of relevant compounds (PDF)

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Notes

The authors declare no competing financial interest.

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