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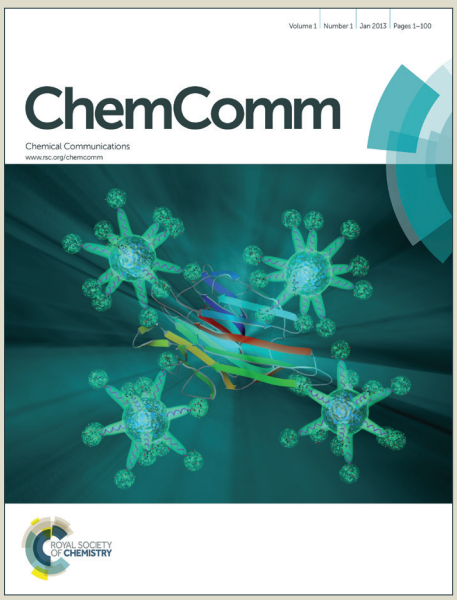

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Mn(III)/TEMPO-Co-Mediated Tandem Azidation/1,2-Carbon Migration Reaction of Allylic Silyl Ethers

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Zhi-Min Chen, Zhen Zhang, Yong-Qiang Tu,* Ming-Hui Xu, Fu-Min Zhang, Chen-Chen Li, and Shao-Hua Wang*

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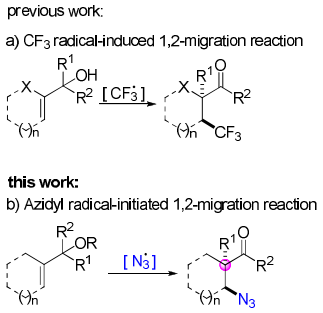
A novel Mn(III)/TEMPO-co-mediated tandem azidation/1,2-carbon migration reaction of allylic silyl ethers with unactivated C=C bond has been explored, generating α-aryl/alkyl β-azido ketones with an α-quaternary stereocenter.

Organic azides are an important class of organic compounds because of their remarkable properties for functional materials and broad synthetic utilities for bioactive molecules.[1] Accordingly, other than the S_N2 type azido-substitution, more and more progresses have been made on the direct azidation of carbon framework due to its high efficiency in introducing the azido group.[2] Among them, strategies via difunctionalization of alkenes, which could be trapped or initiated with an azide radical, have attracted broad attention of chemistry community in recent years. For example, the carboazidation and hydroazidation of olefins by trapping with azidyl radicals have been intensively reported.[3,4] In contrast, for procedures initiated with an azidyl radical, although transition metal-catalyzed or metal-free radical azidations of olefins leading to carbon-heteroatom bond formation have been documented,[5] there is still a lack of straightforward and efficient approaches to C-N_3 and C-C bonds within one step. To the best of our knowledge, only a few examples of azidoarylation of activated alkenes have been developed,[6] and there is no such an example of difunctionalization of unactivated alkenes, which is triggered by azidyl radical and terminated by a 1,2-migration step. Thus, further investigation toward this type of tandem reaction is still highly desirable.

1,2-Migration reactions have been considered as one of the most significant methods for constructing α-quaternary carbonyls and have found their wide applications in organic synthesis through the proper use of electrophilic reagents.[7,8] In our previous studies, a wide range of electrophiles such as halonium ions and even relatively low reactivity carbon-electrophiles have been used to initiate this type of reaction.[9] In 2013, the electrophile scope was further expanded to CF_3 radical by Wu, Sodeoka and our group (Scheme 1a).[10] Inspired by this result and recent progress in azidyl radical related reactions, we envisioned that under certain conditions, such a 1,2-migration reaction of allylic alcohols might be triggered by azidyl radical to deliver β-azidyl carbonyl derivatives (Scheme 1b). Herein, we describe the first Mn(III)/TEMPO-co-mediated tandem azidation/1,2-carbon migration reaction of allylic silyl ethers with unactivated C=C bond.

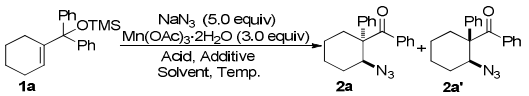


Scheme 1 Design of tandem azidation/1,2-migration reaction.

Since manganese(III) acetate has shown broad applications in various oxidative free-radical procedures,[11] we firstly chose 3.0 equiv of $Mn(OAc)_3·2H_2O$ as oxidant and allylic silyl ether **1a** as a model substrate to test the feasibility of designed azidation/1,2-migration reaction in the presence of 5.0 equiv of NaN_3 as an azide source in CH_3CN at ambient temperature. Disappointingly, no reaction occurred after 24 h (Table 1, entry 1). Based on previous studies,[11a] we speculated that the result might be caused by the low solubility of azide anion or low Lewis acidity of $Mn(OAc)_3·2H_2O$. Therefore, chloroacetic acid and trifluoroacetic acid (0.2 mL) were examined as acidic additives to generate the HN_3 *in situ*. As expected, the reactions proceeded smoothly to give the corresponding product **2a**, and the use of TFA could lead to a better yield of 44% and high diastereoselectivity at 0 °C (Table 1, entry 3). Next, changing the azide source to $TMSN_3$ led to poor result (entry 4). Inspired by the work of Magnus,[12] we envisioned that such a radical initiated process might also be facilitated by using of additives like TEMPO. Accordingly, different additives such as $Cu(OAc)_2$, $Co(OAc)_2$, TEMPO and 4-OH-TEMPO were investigated (entries 5–8). The results indicated that the additive played a key role in the yield and diastereoselectivity of this reaction. Especially, when TEMPO was used as an additive, the desired product was obtained in 86% yield with 6.3:1 d.r. value. Subsequently, variation of the ratio between TEMPO and NaN_3 as well as the reaction

temperature showed that these changes would slightly lower either the yield or the diastereoselectivity (entries 9–12). Thus, entry 7 was chosen as the optimal conditions.

Table 1. Optimization of azidation/1,2-migration reaction[a]

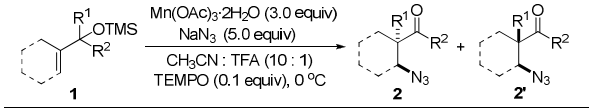


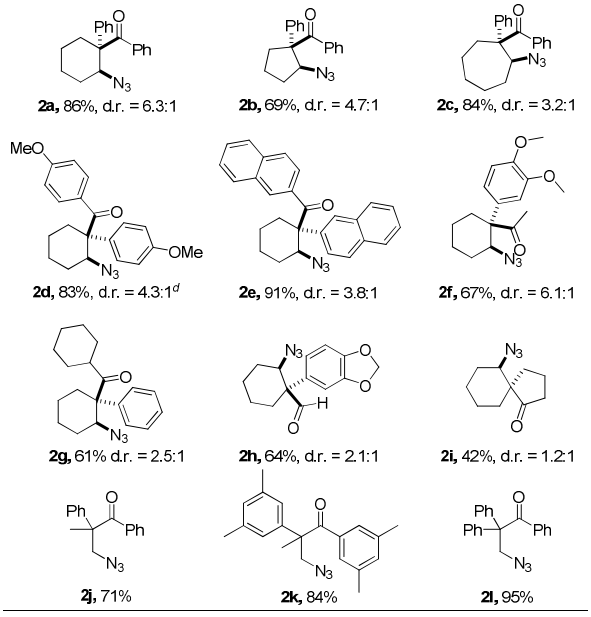
Entry	Temp.	Acid	Additive	Solvent	Yield (%)/d.r.[b, c]
1	RT	-	-	CH_3CN	-
2[d]	RT	**4**	-	CH_3CN	36/(>10:1)
3	0	TFA	-	CH_3CN	44/(>10:1)
4[e]	0	TFA	-	CH_3CN	trace
5	0	TFA	10% $Cu(OAc)_2$	CH_3CN	40/(>10:1)
6	0	TFA	10% $Co(OAc)_2$	CH_3CN	47/(>10:1)
7	**0**	**TFA**	**10% TEMPO**	**CH_3CN**	**86/(6.3:1)**
8[f]	0	TFA	10% **5**	CH_3CN	87/(5.0:1)
9	0	TFA	5% TEMPO	CH_3CN	79/(6.1:1)
10	0	TFA	20% TEMPO	CH_3CN	80/(6.5:1)
11	-10	TFA	10% TEMPO	CH_3CN	68/(6.5:1)
12[g]	0	TFA	10% TEMPO	CH_3CN	64/(6.0:1)

Reaction conditions: [a]$Mn(OAc)_3·2H_2O$ (0.6 mmol) was dissolved in 1.5 mL of solvent followed by addition of NaN_3 (0.10 mmol). After 10–20 min, **1a** (0.2 mmol) in 0.5 mL of solvent was added. [b]Isolated yield. [c]Diastereoisomeric ratio was determined by ^1H NMR. [d]**4** = CH_2ClCO_2H (9.0 equiv). [e]$TMSN_3$ was added instead of NaN_3. [f]**5** = 4-OH-TEMPO. [g]3.0 equiv of NaN_3 was added.

To test the generality of this transformation, we next subjected allylic silyl ethers **1b–l** to the optimized conditions. As shown in Table 2, all the substrates performed well and the desired β-azidyl carbonyl derivatives were obtained in moderate to excellent yields. Firstly, for the cyclic substrates with five- and seven-membered rings, this reaction was

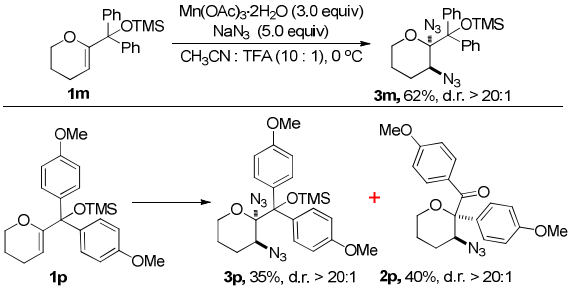
Table 2 Substrate scope of the azidation/1,2-migration reaction[a, b, c]





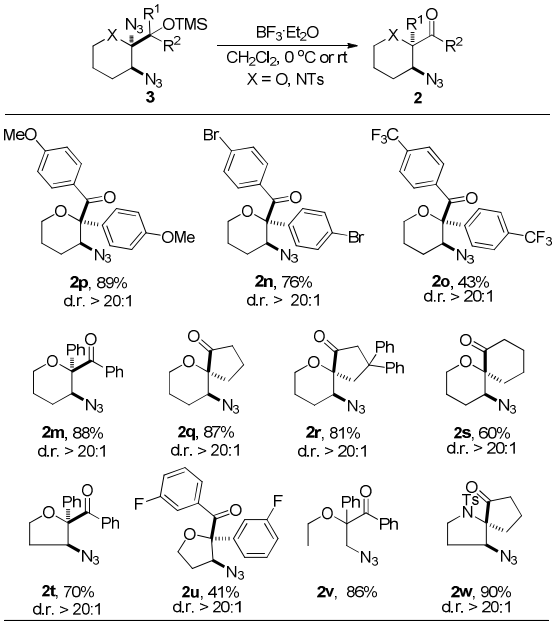
[a]Reaction conditions, please see the SI. [b]Yields of **2** and **2′**. [c]Diastereoisomeric ratio was determined by ^1H NMR. [d]Determined by the weight of isolated product.

applicable, and the corresponding products **2b** and **2c** could be obtained respectively in 69% and 84% yields with moderate diastereoselectivity. Also, the *p*-OMe-phenyl- and 2-naphthyl-substituted substrates were also suitable for this transformation (**2d**, **2e**). Compared with **1a**, substrates **1f-g** with an alkyl and an aryl substituent exhibited relatively low reactivities, affording the desired products with exclusive migration of aryl groups in 67% and 61% yields, respectively. Furthermore, silyl ether substrate **1h** derived from corresponding secondary alcohol was also amenable to the protocol, furnishing the products **2h** and **2h′** in 64% yield, which could provide an alternative strategy for the synthesis of (±)-crinane.[13] To our delight, the substrate bearing a cyclobutanol motif **1i** also went through smoothly under the stated conditions, albeit in lower diastereoselectivity and yield. Finally, some acyclic substrates were examined and successfully afforded **2j**, **2k**, and **2l** in good to excellent yields. It should be noted that the relative configuration of **2a-i** was assigned by X-ray crystallography of **2a** as a representative.[14]



Scheme 2 Reaction results of dihydropyran-type allylic silyl ethers **1m** and **1p**.

Table 3 Substrate scope of the deazidation/1,2-carbon migration.

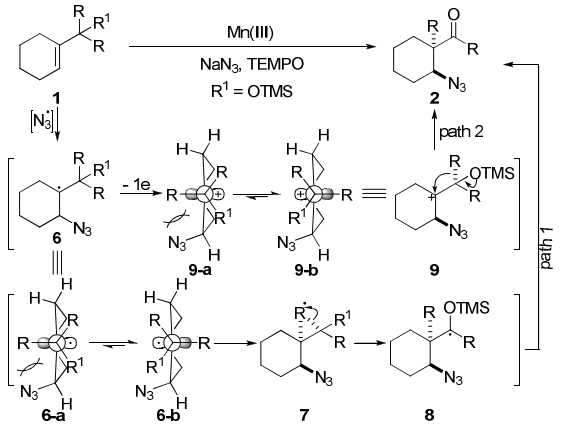


To further expand the scope of this tandem reaction, the dihydropyran-type allylic silyl ether **1m** was subjected to the standard conditions. Different from the substrates in Table 2, the diazide addition product **3m** was obtained in 30% yield with excellent *anti*-selectivity. Although no desired β-azidyl ketone was observed, this result also supported a possible azide radical

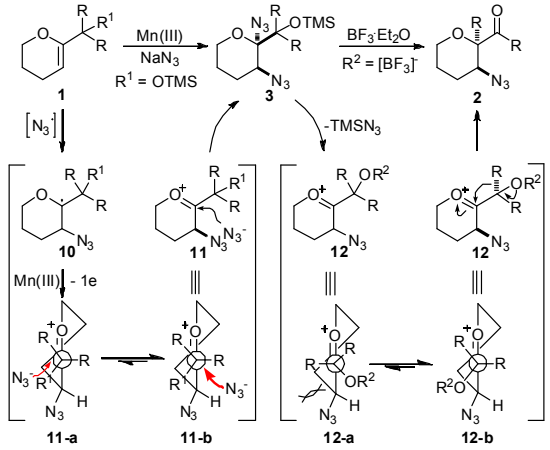
initiated process, which prompted us to further optimize the conditions for this type of substrates. After some unsuccessful attempts, we accidentally found that the yield of **3m** was notably improved to 62% without using TEMPO (Scheme 2). Considering the valuable synthetic utility of bisazido compounds,[12,15] we then applied a variety of activated allylic silyl ethers to this diazidation reaction (**1m-w**). All the substrates were well tolerated under the same conditions and produced the corresponding diazide addition products **3m-w** in moderate to good yields with excellent diastereoselectivity (35%-82%).[16] The relative configuration of **3m-w** was deduced by X-ray crystallography of **3m**.[14] It is worth mentioning that the reaction of **1p** with electron-donating groups at the *para*-position of the phenyl moiety not only gave the diazide addition product **3p** in 35% yield, but also produced the rearrangement product **2p** in 40% yield, which promoted us to further investigate the possibility of a semipinacol rearrangement with bisazido compounds **3** to afford α-quaternary β-azidyl ketones (Scheme 2). Fortunately, under the promotion of $BF_3{\cdot}Et_2O$, a common Lewis acid, the expected rearrangement reaction of **3m-w** went through smoothly to give the desired β-azidyl ketones **2m-w** in moderate to excellent yields with excellent diastereoselectivity (Table 3). The relative configuration of **2m-w** was confirmed by single crystal X-ray analysis of **2m**.[14]

Next, some additional experiments were conducted in order to get a better understanding of the azidation/1,2-migration reaction. When 1.0 equiv of the radical-trapping reagent BHT (2,6-di-*tert*-butyl-*p*-cresol) was added instead of TEMPO, the reaction was messy and no desired product but BHT-N_3 could be detected by GC-MS.[17] The result suggested the existence of an azidyl radical during this transformation. On the basis of the above experimental results and previous literatures, a proposed reaction mechanism is depicted in Scheme 3. Initially, an azidyl radical generated from the oxidation of sodium azide by manganese(III) acetate would add to allylic silyl ether **1** to provide radical intermediate **6**. Next, two possible pathways for the transformation could take place. In path 1, carbon radical species **6** could directly undergo a 1,2-rearrangement to give radical intermediate **8**, which would be further oxidized by manganese(III) acetate to produce the desired product **2** after eliminating a TMS.[18] In path 2, carbon radical species **6** might first be oxidized by manganese(III) to a carbon cation intermediate **9**, which would subsequently undergo a 1,2-migration to afford the corresponding product **2**. At the moment, it is still unclear which path is dominant based on our preliminary experiments, although we hypothesized that the effect of TEMPO is beneficial to accelerate the rate of path 1.[16] Also, since the difference between conformation **6-a** and **6-b** was not very significant, the corresponding diastereoselectivity was not excellent. In contrast, the diazidation reaction might proceed through only one possible way.[19] As shown in Scheme 4, azidyl radical reacted with activated allylic silyl ether to give carbon radical intermediate **10**, and further oxidation of **10** would produce the cyclic oxonium intermediate **11**, which could go through a sterically favored *anti*-addition with azide anion to give product **3**. While in the presence of $BF_3{\cdot}Et_2O$, intermediate **12** would be generated upon the release of $TMSN_3$. Accordingly, a subsequent semipiancol rearrangement would afford product **2** with excellent diastereoselectivity, which could be explained by the clear difference between conformation **12-a** and **12-b**.

In summary, we have developed a novel and mild Mn(III)/TEMPO-co-mediated tandem azidation/1,2-carbon migration reaction of allylic silyl ethers for the first time. This tandem transformation enables the difunctionalization of unactivated alkenes through simultaneous construction of an alkyl azide and an all-carbon quaternary center and is synthetically valuable since a variety of α-quaternary β-azidyl carbonyl derivatives were obtained in moderate to excellent yields. In addition, the diazidation reaction of activated allylic silyl ethers has also been achieved and the 1,2-diazides could further undergo a novel semipinacol rearrangement to produce α-quaternary β-azidyl ketones with the loss of an azide leaving group.



Scheme 3 Proposed mechanism for the azidation/1,2-migration reaction.



Scheme 4 Proposed mechanism for the deazidation/1,2-migration.

Acknowledgements

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Notes and references

State Key Laboratory of Applied Organic Chemistry; School of Pharmacy, Lanzhou University, Lanzhou; and Collaborative Innovation Center of Chemical Science and Engineering, Tianjin, (P. R. China); E-mail: tuyq@lzu.edu.cn; wangshh@lzu.edu.cn.

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