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Manganese-Catalyzed N−F Bond Activation for Hydroamination and Carboamination of Alkenes

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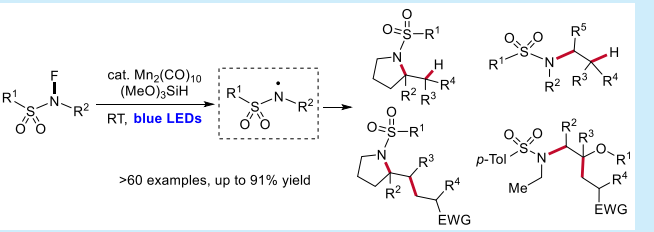
ABSTRACT: A visible-light-promoted method for generating amidyl radicals from *N*-fluorosulfonamides via a manganese-catalyzed N−F bond activation strategy is reported. This protocol employs a simple manganese complex, $Mn_2(CO)_{10}$, as the precatalyst and a cheap silane, $(MeO)_3SiH$, as both the hydrogen-atom donor and the F-atom acceptor, enabling intramolecular/intermolecular hydroaminations of alkenes, two-component carboamination of alkenes, and even three-component carboamination of alkenes. A wide range of valuable aliphatic sulfonamides can be readily prepared using these practical reactions.



Amidyl radicals are valuable reactive intermediates that have found wide applications in the synthesis of N-containing molecules.[1] In general, these radicals can be generated from N-halogenated amides via the thermal or photochemical homolysis of the N−X bonds (X = I, Br).[2] Important contributions by Suárez,[3] Muñiz,[4] Nagib,[5] and others[6] show that amidyl radicals generated from N-iodinated or -brominated amides can initiate the remote C(sp^3)−H activation through a intramolecular 1,5-hydrogen-atom-transfer process, followed by halogenation and cyclization, thereby enabling the construction of various nitrogen heterocycles. Apart from these N-radical precursors, N-chlorinated amides are also used to produce amidyl radicals that can engage in a series of radical transformations, such as remote C−H chlorination[7] and chloramination of alkenes.[8] Compared with the aforementioned haloamides, N-fluorinated amides exhibit much higher air, moisture, and thermal stability.[9] Since the pioneering work of Cook and coworkers in 2016,[10] activating N−F bonds to generate amidyl radicals facilitated by a copper catalyst has been intensively investigated, and many elegant amidyl-radical-directed remote C(sp^3)-H functionalization reactions have been achieved by several groups.[11] In these established radical cascades, the stable N−F bonds (the calculated bond-dissociation energy (BDE) of the N−F bond is 51.8 kcal mol^{-1}) are usually activated through a Cu(I)-promoted single-electron-transfer (SET) pathway. Notwithstanding these advances, developing a complementary N−F bond activation method and exploring the new reactivity of the formed amidyl radicals are still highly desirable.

Manganese is the twelfth most abundant element and the third most abundant transition metal, which has been extensively exploited as a low-cost and low-toxicity catalyst for a variety of practical reactions.[12] Among these transformations, manganese-catalyzed atom-transfer reactions provide a powerful tool for the generation of radical species, which have received considerable attention from the synthetic community.[13] Recently, our group has demonstrated that amidyl radicals can be easily afforded from in situ formed N−Cl bonds by a manganese-catalyzed Cl-atom-transfer reaction.[14] This protocol enables the site-selective chlorination of unactivated C−H bonds of aliphatic amines and chloroaminations of unactivated alkenes. However, besides the Cl atom, other radical capture reagents (e.g., hydrogen atom and olefin) failed to interrupt the C radicals formed by the addition of amidyl radicals to alkenes due to the fact that recombination of the C radicals with the Cl atom to forge C−Cl bonds is rapid. This limitation prompted us to develop a new strategy to address this issue. We envisioned that by taking advantage of simple and low-cost manganese complexes (e.g., $Mn_2(CO)_{10}$) as the catalysts, the stable N−F bonds might be efficiently activated through a manganese-mediated F-atom-transfer process to furnish amidyl radicals. Meanwhile, incorporating a silane as both the hydrogen-atom donor (HAD) and the F-atom acceptor might present the opportunity to trap the C radicals with reagents other than halogens. The key design element for N−F bond activation differentiates this work from all of the previously reported metal-catalyzed amidyl-radical-mediated cascades.[10,11] To our knowledge, activating stable N−F bonds to produce amidyl radicals by a manganese-mediated F-atom-transfer process has not been reported.

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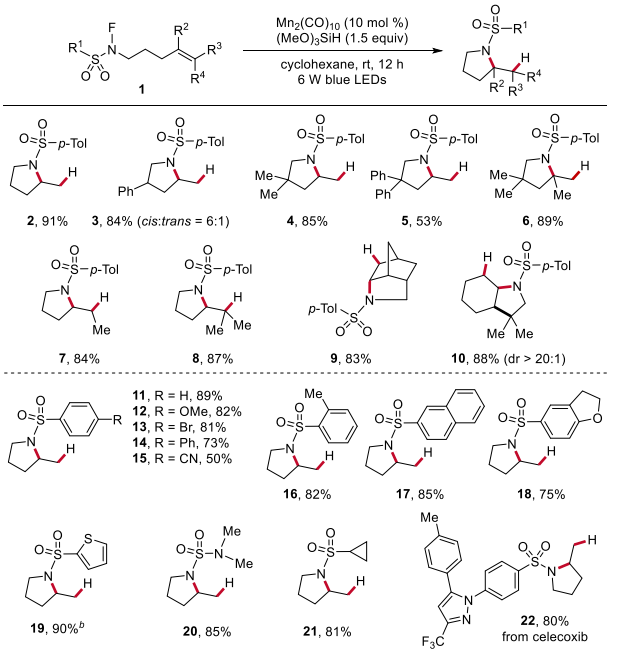
Herein we disclose that the employment of an earth-abundant and inexpensive manganese complex, $Mn_2(CO)_{10}$, as the precatalyst and visible light as the energy input in combination with a cheap silane, $(MeO)_3SiH$, as the HAD and F-atom acceptor can efficiently activate N−F bonds of N-fluorinated sulfonamides to generate amidyl radicals under very mild reaction conditions. In addition, the synthetic utility of amidyl radicals formed by this protocol is demonstrated by a series of useful chemical transformations, including the hydroamination and carboamination of alkenes.

To test our hypothesis, we first investigated the manganese-catalyzed intramolecular and intermolecular hydroaminations of alkenes using readily prepared *N*-fluorosulfonamides as N-radical precursors to access aliphatic sulfonamides, which are prevalent structural motifs in medicinal and agrochemical agents.[15] Notably, some metal and strong acid-catalyzed methods for the intermolecular sulfonamide-based hydroaminations of alkenes have been developed.[16] However, these reactions generally proceed with Markovnikov selectivity. By contrast, fewer studies pertaining to the intermolecular anti-Markovnikov alkene hydroamination reaction have been reported.[17] The groups of Nicewicz[18] and Knowles[19] have recently accomplished photoredox-catalyzed intermolecular anti-Markovnikov hydroaminations of alkenes with sulfonamides. The paucity of intermolecular anti-Markovnikov hydroamination reactions toward the preparation of aliphatic sulfonamides encourages us to exploit new methods.

Our initial study was focused on exploring the viability of the manganese-catalyzed intramolecular hydroamination reaction of alkenes. Extensive optimization studies showed that blue LED light irradiation of a cyclohexane solution of the corresponding *N*-fluorosulfonamide in the presence of $Mn_2(CO)_{10}$ as a precatalyst and $(MeO)_3SiH$ at room temperature afforded the desired hydroaminated product **2** in 91% yield. (For a full list of results, see the Supporting Information (SI).) Under the optimized reaction conditions, we examined the scope of this reaction (Scheme 1). Monosubstituted and gem-disubstituted *N*-fluorosulfonamides were cyclized to afford products **3**−**5**. Substrates possessing diverse alkene substituent patterns, including 1,1-disubstituted (**6**), 1,2-disubstituted (**7**), and trisubstituted alkenes (**8**), underwent successful hydroamination. We show that the construction of bridged and bicyclic ring systems with high levels of diastereoselectivity is possible using this protocol (**9**, **10**). A variety of *N*-fluorosulfonamides containing electron-donating and electron-withdrawing substituents on the aromatic ring all reacted well (**11**−**17**). The reaction also proceeded efficiently with heterocyclic substrates (**18**, **19**). An N-fluorinated dimethylaminosulfamate substrate participated in this cyclization to afford **20**. The substrate scope could be expanded to alkyl-substituted *N*-fluorosulfonamides, as exemplified by the preparation of **21**. Notably, a celecoxib-derived substrate was transformed into **22** in 80% yield.

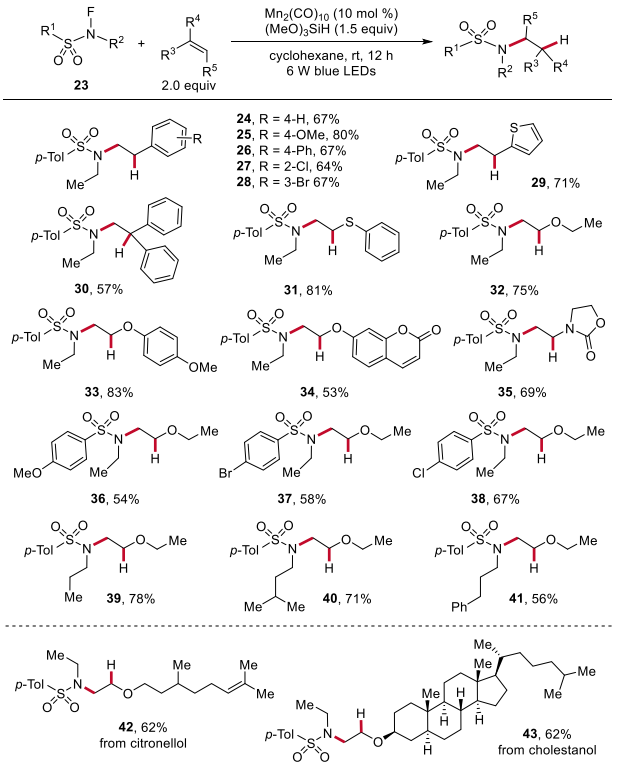
We next evaluated the feasibility of this strategy for intermolecular alkene hydroamination (Scheme 2). We observed that a range of styrene derivatives bearing different electronically and sterically varied phenyl substituents were competent reaction partners, which reacted smoothly to produce the anti-Markovnikov hydroaminated products **24**−**28**. 2-Vinylthiophene proved to be compatible with the applied conditions, delivering product **29**. Ethene-1,1-diyldibenzene could be efficiently hydroaminated (**30**). Because of their electronic match with the electrophilic amidyl radicals, electron-rich alkenes were selected as radical acceptors to further assess the applicability of this reaction. A portfolio of electron-rich olefins, including vinyl sulfides, vinyl ethers, and aryl vinyl ethers, reacted efficiently to afford products **31**−**33**.

Scheme 1. Scope of the Intramolecular Hydroamination of Alkenes[a]



[a]Isolated yields. [b]Using $(Me_3Si)_3SiH$ (1.5 equiv).

Scheme 2. Scope of the Intermolecular Hydroamination of Alkenes[a]



[a]Isolated yields.

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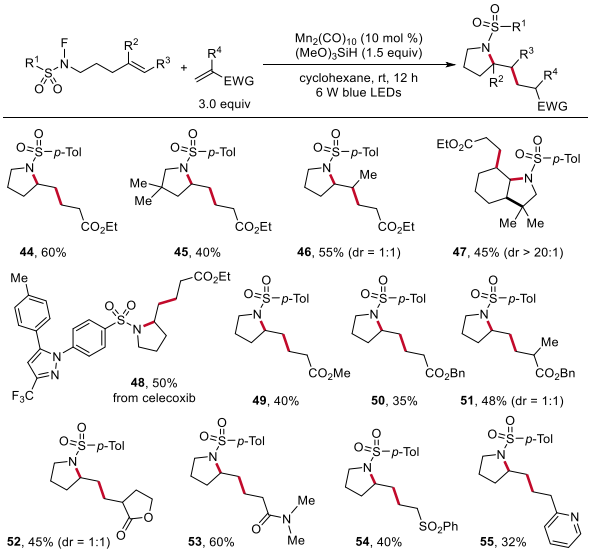
A substrate carrying a coumarin group was tolerated (**34**). *N*-vinyl carbamate was readily converted to product **35**. However, alkyl-substituted alkenes exhibited low reactivity. Moreover, various N-radical precursors were also tested, and we found that a series of *N*-fluorosulfonamides carrying different functional groups on the arene ring as well as those with different alkyl substituents on the nitrogen atom uniformly provided the desired products **36**−**41**. Remarkably, substrates derived from citronellol and cholestanol underwent this transformation smoothly to give products **42** and **43**.

Encouraged by the above results, we reasoned that by using electron-deficient olefins as radical traps to intercept the C-radical intermediate following C−N bond formation, the olefin carboamination reactions could be realized.[20] After extensive investigation, we were delighted to find that a diverse set of amidyl-radical precursors successfully reacted with ethyl acrylate to deliver products **44**−**46**. Highly functionalized bicyclic ring systems were accessed with excellent diastereoselectivity (**47**). A substrate derived from celecoxib was carboaminated to provide **48**. In addition, a wealth of electron-deficient olefins, such as methyl acrylate, benzyl acrylate, benzyl methacrylate, 3-methylenedihydrofuran-2(3*H*)-one, *N*,*N*-dimethylacrylamide, (vinylsulfonyl)benzene, and 2-vinylpyridine, were found to be suitable reaction partners (**49**−**55**).

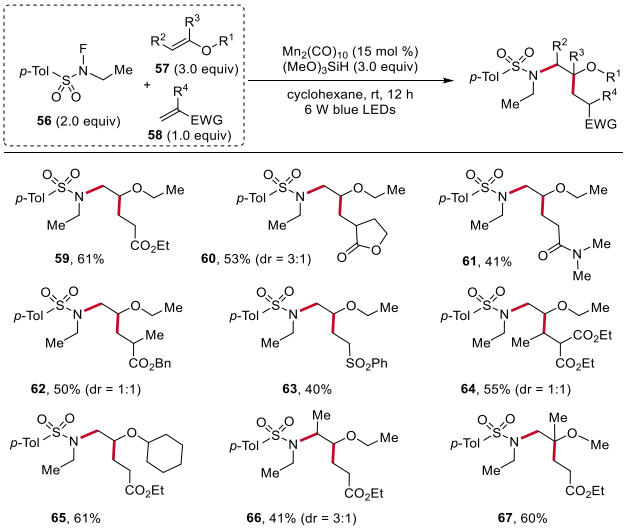
Finally, we demonstrated that more challenging three-component radical conjugate addition reactions involving *N*-fluorosulfonamides and two electronically differentiated alkenes could be accomplished using our manganese-catalyzed N−F bond activation strategy.[21] As illustrated in Scheme 4, a wide range of electron-deficient olefins could successfully couple to the N-radical precursor **56** and ethyl vinyl ether under slightly modified reaction conditions, including ethyl acrylate, 3-methylenedihydrofuran-2(3*H*)-one, *N*,*N*-dimethylacrylamide, benzyl methacrylate, (vinylsulfonyl)benzene, and diethyl 2-ethylidenemalonate (**59**−**64**). Furthermore, electron-rich olefins, such as (vinyloxy)cyclohexane, (*E*)-1-ethoxyprop-1-ene, and 2-ethoxyprop-1-ene, furnished products **65**−**67**. In Schemes 3 and 4, the formation of reduced byproduct

Scheme 3. Scope of the Two-Component Carboamination of Alkenes[a]



[a]Isolated yields.

Scheme 4. Scope of the Three-Component Carboamination of Alkenes[a]

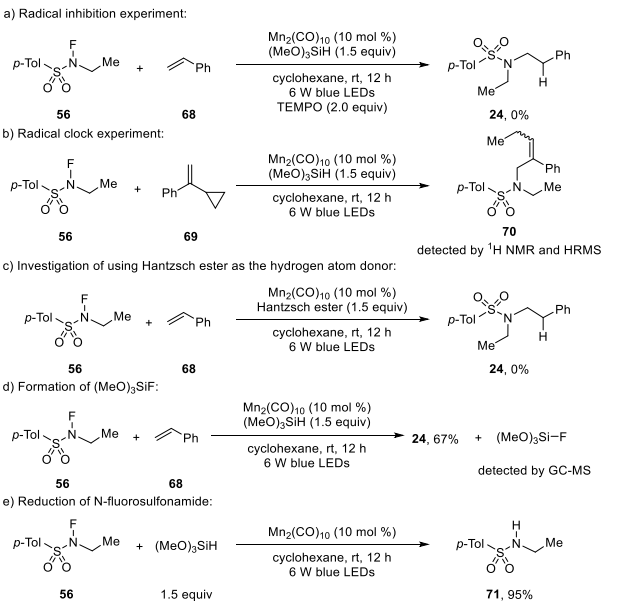


[a]Isolated yields.

sulfonamides was detected, which could account for the missing yield. These results illustrated in Schemes 3 and 4 represent the first examples of the sulfonamidyl-radical-mediated carboaminations of alkenes.

To shed light on the mechanism, we conducted some experiments with *N*-fluorosulfonamide **56**. Performing the reaction in the presence of the radical scavenger TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxy) led to no reaction, and **56** was completely recovered, suggesting that a radical mechanism might be operative (Scheme 5a). The reaction of **56** with radical clock substrate **69** took place to deliver a mixture including ring-opened product **70**, which indicates that a N radical is generated (Scheme 5b). When this reaction was run with Hantzsch ester as the HAD in place of $(MeO)_3SiH$, no product **24** was detected (Scheme 5c). This result implies that $(MeO)_3SiH$ plays a crucial role in the current N−F bond

Scheme 5. Mechanistic Studies



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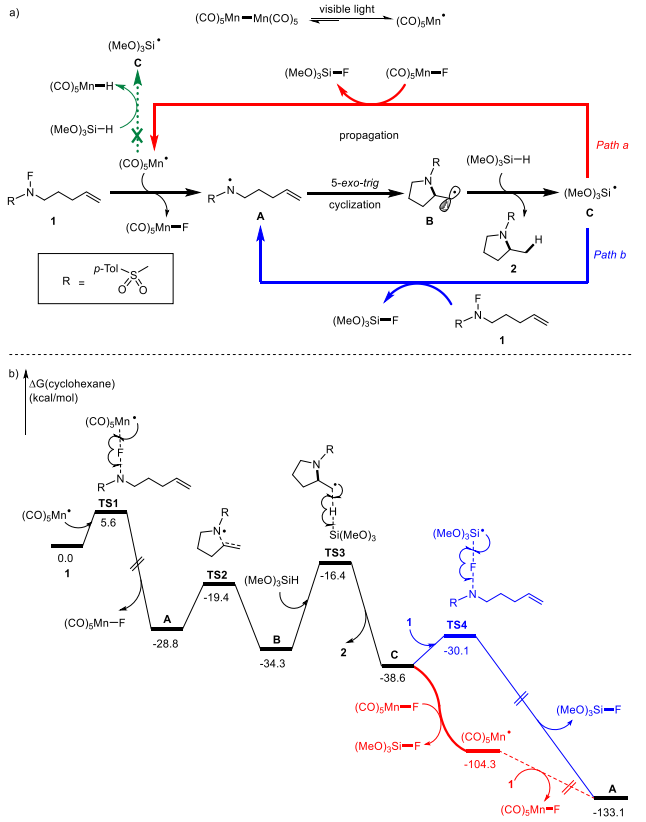
activation process. Additionally, $(MeO)_3SiF$ could be identified by gas chromatography mass spectrometry (GC-MS), which is consistent with F-atom abstraction by the silyl radical (Scheme 5d). When the reaction was carried out in the absence of olefin, sulfonamide **71** was obtained in 95% yield (Scheme 5e). Furthermore, **71** did not add to styrene or ethyl vinyl ether under the standard reaction conditions, thus demonstrating that sulfonamides are not an intermediate on the way to the products.

To gain further mechanistic details of this reaction, we carried out density functional theory (DFT) calculations.[22] The proposed reaction mechanism is depicted in Scheme 6a

Scheme 6. (a) Proposed Reaction Mechanism and (b) Calculated Free-Energy Profile for the Formation of Product



(with the intramolecular alkene hydroamination as a representative), and the corresponding DFT-calculated reaction energy profile is given in Scheme 6b. First, the initiation occurs by visible-light-induced Mn−Mn bond homolysis, thus converting $Mn_2(CO)_{10}$ to $^{\bullet}Mn(CO)_5$.[13j−l,14] Subsequently, the formed $^{\bullet}Mn(CO)_5$ abstracts the F atom from *N*-fluorosulfonamide **1** via **TS1** to generate the amidyl radical **A** while yielding $FMn(CO)_5$. This step proceeds facilely by crossing a free-energy activation barrier of 5.6 kcal mol^{-1} and is exergonic by 28.8 kcal mol^{-1}. In principle, $^{\bullet}Mn(CO)_5$ could also abstract the hydrogen atom from $(MeO)_3SiH$ to generate a silyl radical **C** (the green pathway in Scheme 6a), which might abstract the F atom from *N*-fluorosulfonamide **1**, leading to the amidyl radical **A**. However, this Si−H bond abstraction pathway is excluded based on the predicted highly unfavorable thermodynamics (uphill by 33.8 kcal mol^{-1}; see the SI for details). Next, the N-radical moiety of **A** cyclizes onto the pendant olefin via **TS2**, crossing a free-energy activation barrier of 9.4 kcal mol^{-1} and delivering a more stable C radical **B**, which then abstracts the hydrogen atom from $(MeO)_3SiH$ via **TS3** with a free-energy activation barrier of 17.9 kcal mol^{-1} to provide the product **2** and the silyl radical **C**. This step is thermodynamically favorable by 4.3 kcal mol^{-1}, which is unlike the hydrogen-atom transfer from $(MeO)_3SiH$ to $^{\bullet}Mn(CO)_5$. Finally, the radical regeneration could probably proceed through two pathways. Along *Path a* (the red pathway), **C** accepts the F atom from $FMn(CO)_5$ to produce $(MeO)_3SiF$ with the concurrent regeneration of $^{\bullet}Mn(CO)_5$. Note that all of our efforts to locate the transition state for this step failed, but we found that the F atom is directly transferred from $FMn(CO)_5$ to **C** without an energetic barrier.[23] Alternatively, **1** could also provide the F atom. According to *Path b* (the blue pathway), the transfer of the F atom from **1** to **C** occurs through **TS4** with a free-energy activation barrier of 8.5 kcal mol^{-1}, affording $(MeO)_3SiF$ and regenerating **A**. Although *Path a* could proceed facilely without an energetic barrier, we could not exclude *Path b* because the corresponding activation barrier (8.5 kcal mol^{-1}) was readily accessible, especially when considering that the concentration of **1** is much higher than that of $FMn(CO)_5$. Therefore, we think that quenching **C** by **1** represents a major reaction pathway in the early reaction stage because of the low concentration of $FMn(CO)_5$ compared with that of **1**, whereas in the late reaction stage, when the concentration of **1** is comparable to that of $FMn(CO)_5$, the latter can also effectively provide the F atom to **C**.

In conclusion, we have demonstrated that amidyl radicals can be easily generated from *N*-fluorosulfonamides through a manganese-catalyzed N−F bond activation strategy. Using this strategy, intramolecular/intermolecular hydroaminations of alkenes, two-component carboamination of alkenes, and even three-component carboamination of alkenes can be implemented at room temperature, thereby providing a mild and versatile synthetic platform for a facile access to a wide array of valuable aliphatic sulfonamides. These reactions exhibit a broad substrate scope and high functional-group tolerance and are well suited for the late-stage functionalization of complex molecules. Combining the use of earth-abundant 3d non-noble metals, visible light, and cheap silane makes this strategy highly practical.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c03916.

Experimental procedures and characterization data for all compounds and computational details (PDF)

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[§]Y.-X.J. and J.L. contributed equally.

Notes

The authors declare no competing financial interest.

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(23) The potential energy surface (PES) scanning also supports that this process is barrierless. See the Supporting Information for details.

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