ORGANIC CHEMISTRY FRONTIERS

RESEARCH ARTICLE

View Article Online
View Journal

Cite this: DOI: 10.1039/d5qo00476d

A formal vinylogous Schmidt reaction: nitrogen insertion of *para*-quinone methides†

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Received 21st March 2025,
Accepted 10th May 2025

DOI: 10.1039/d5qo00476d

rsc.li/frontiers-organic

Compared with recent nitrogen addition reactions, which mainly focus on the styrene motif, feasible modification of a conjugated C(sp^2)–C(sp^2) single bond is rare due to its robustness. Herein, we report a facile nitrogen introduction to the conjugated C(sp^2)–C(sp^2) bond of *p*-QMs through a vinylogous Schmidt process, using N-OTs carbamate as a bench-stable ambiphilic nitrogen source. Depending on the electron-donating ability of the *ortho*-substituent on the benzene ring, the reaction underwent the formal vinylogous Schmidt process through an aziridine intermediate or a 1,6-addition/cyclization step delivering benzoxazolidine or dihydroindazole scaffolds, respectively. This study not only expands the application boundary of the Schmidt reaction but also provides a new strategy for nitrogen addition to a C(sp^2)–C(sp^2) bond.

Introduction

Prevalent in nature, nitrogen-containing compounds are widely found in natural products, such as alkaloids. Considering that the nitrogen atom plays a crucial role in the structural scaffold as well as in the resulting biological activity, the facile incorporation of a nitrogen-containing group into organic molecules has been of keen interest to synthetic and medicinal chemists. Notably, skeletal editing[1–5] through nitrogen deletion/addition has been studied intensively.[6–8] Levin,[9] Antonchick,[10] and Lu[11] delivered nitrogen deletion to achieve the formation of a C–C single bond while cleaving two C–N single bonds. Relatedly, Cheng[12] reported the electrochemical direct insertion of ammonia into the C–C double bond of cyclic alkenes for the synthesis of aromatic nitrogen-containing heterocycles. Morandi[13] used *in situ* generated iodonitrene as a nitrogen source to complete the insertion of nitrogen into the C–C double bond of indoles. The key nitrogen insertion step is realized by cleavage of the C–C bond of the aziridine intermediate bearing an electrophilic nitrogen. Notably, both nitrogen insertions undergo an umpolung of a nucleophilic nitrogen to an electrophilic one (Fig. 1a).

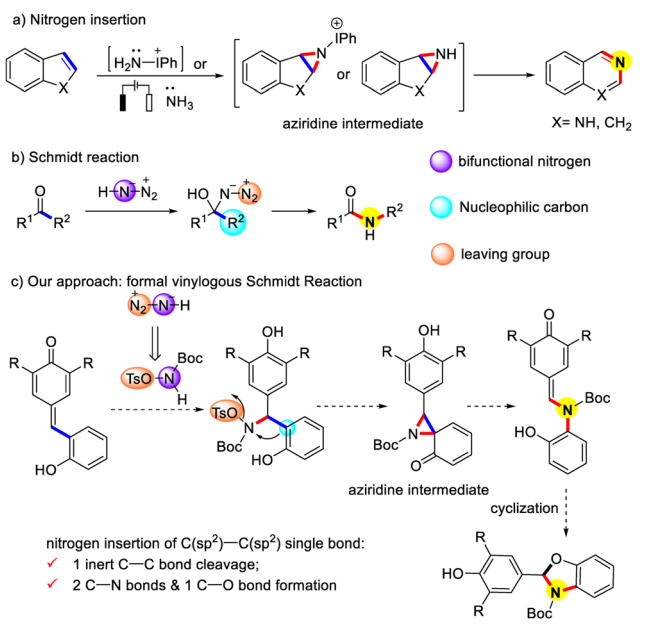

Fig. 1 The first formal vinylogous Schmidt reaction employing N-OTs carbamate as a bifunctional nitrogen source.

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†Electronic supplementary information (ESI) available. CCDC 2323528 and 2323529. For ESI and crystallographic data in CIF or other electronic format see DOI: https://doi.org/10.1039/d5qo00476d

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To the best of our knowledge, reported nitrogen additions have focused mainly on the conjugated C–C double bond, but studies of inert conjugated C(sp^2)–C(sp^2) single bonds are scarce. We understand that the Schmidt reaction can be regarded as a nitrogen insertion process into a C–C single bond, in which hydrogen azide (HN_3) not only shows a nucleophilic character when a proton is ionized but also shows electrophilicity when nitrogen gas leaves, resembling the ambiphilic properties of ammonia or iodonitrene in previous reports (Fig. 1b). Therefore, we propose that it would be feasible to develop a nitrogen addition to a conjugated C(sp^2)–C(sp^2) bond *via* a Schmidt-type transformation.

para-Quinone methides (*p*-QMs) are well-developed Michael addition acceptors represented by two resonance structures possessing a neutral charge and an aromatic zwitterionic property, respectively.[14–20] Over the past decade, our group has focused on the application of *p*-QMs in the construction of natural products or pharmaceutical motifs by applying organic catalytic strategies.[21–24]

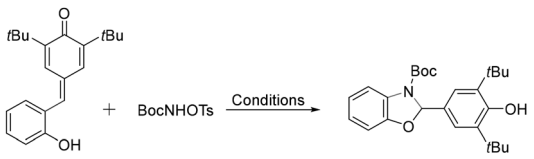
As part of our continuing interest in nucleophilic cascade annulation using *o*-hydroxyl phenyl *p*-QMs, we hypothesized that the hydroxyl group on the benzene ring can be used not only as a nucleophilic group but also as an electron-donating group to enhance the nucleophilicity of *ortho*-carbon, which might suggest the facile migration of aryl motifs to the adjacent electrophilic center. To put this hypothesis into practice, we investigated whether this enhanced nucleophilicity may promote the rearrangement of nucleophilic sp^2 carbon to electrophilic nitrogen, similar to the Schmidt reaction, to incorporate nitrogen functionality into the molecular skeleton. Appreciating the potential explosiveness of azide, we chose bench-stable N-OTs carbamate as a nitrogen source[25,26] with nitrogen substituted with OTs as a labile leaving group. Resembling the classic Schmidt reaction, such electrophilic nitrogen could be attacked by nucleophilic carbon to achieve nitrogen addition (Fig. 1c). Herein, we describe the first formal vinylogous Schmidt reaction employing N-OTs carbamate as an ambiphilic nitrogen source. Compared to the Schmidt reaction, this transformation was carried out under basic conditions. The nitrogen insertion intermediate, which was obtained by the vinylogous Schmidt reaction, would be cyclized spontaneously to afford a dihydrobenzoxazle scaffold. This cascade reaction has demonstrated mild conditions and broad substrate scope. The key to realizing this vinylogous Schmidt reaction is the enhanced nucleophilicity of the migrated carbon atom due to *ortho*-hydroxyl substitution, where such moieties are also within the component of the resulting dihydroindazole. Computational study demonstrated that the nitrogen migration step goes through an aziridine intermediate similar to recent reports on nitrogen addition.[12,13]

Results and discussion

Condition optimization

We initiate our investigation with hydroxyl group substituted *p*-QMs **1a** as a model substrate and *tert*-butyl (tosyloxy)carbamate **2a** as a nitrogen source under basic conditions (Table 1). The desired benzoxazolidine **3a** can be generated successfully in DCM solution in the presence of several inorganic bases (entries 1–7), while organic bases, such as DIPEA, TEA, DABCO, and DBU, showed sluggish efficiency (entry 8). With base screening indicating that Cs_2CO_3 plays a potent role in deprotonation, the solvent was examined next. While haloalkanes demonstrated comparable efficiency (entries 9 and 10), non-protic solvents indicated less reactivity of the substrates (entry 11). To further interrogate the mass balance of the reaction mixture while the reaction is running, we performed real-time thin-layer chromatography, suggesting that lower temperature could lead to less substrate decomposition and smoothly furnish the expected products with dichloroethane as solvent (entries 12–15). It was delightful that product **3a** could be obtained at −20 °C in 75% yield (entry 14).

Table 1 Optimization of reaction conditions[a]



1a 2a 3a

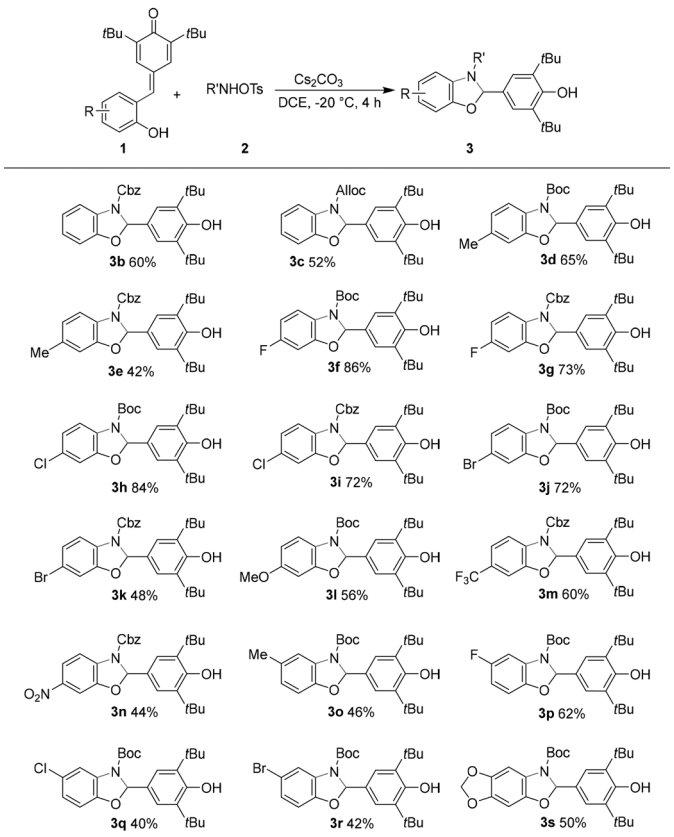
Entry	Base	Solvent	*T* (°C)	Yield[b] (%)
1	Cs_2CO_3	DCM	rt	26
2	Na_2CO_3	DCM	rt	21
3	K_2CO_3	DCM	rt	18
4	$NaHCO_3$	DCM	rt	15
5	KOH	DCM	rt	12
6	NaOH	DCM	rt	<10
7	*t*-BuOK	DCM	rt	<10
8	DIPEA, TEA, DABCO, DBU, *etc.*	DCM	rt	<10
9	Cs_2CO_3	DCE	rt	32
10	Cs_2CO_3	$CHCl_3$	rt	28
11	Cs_2CO_3	Toluene, CH_3CN, DMF, THF, *etc.*	rt	<10
12	Cs_2CO_3	DCE	0	42
13	Cs_2CO_3	DCE	−10	58
14	Cs_2CO_3	DCE	−20	75
15	Cs_2CO_3	DCE	−30	72

[a] The reaction was conducted as follows, unless otherwise noted: all reactions were conducted with 0.2 mmol of **1a** (1 equiv.), 0.24 mmol of **2a** (1.2 equiv.), and 0.24 mmol of base (1.2 equiv.) in the indicated solvent (2.0 mL) for 4 h. [b] Isolated yield.

Substrate scope

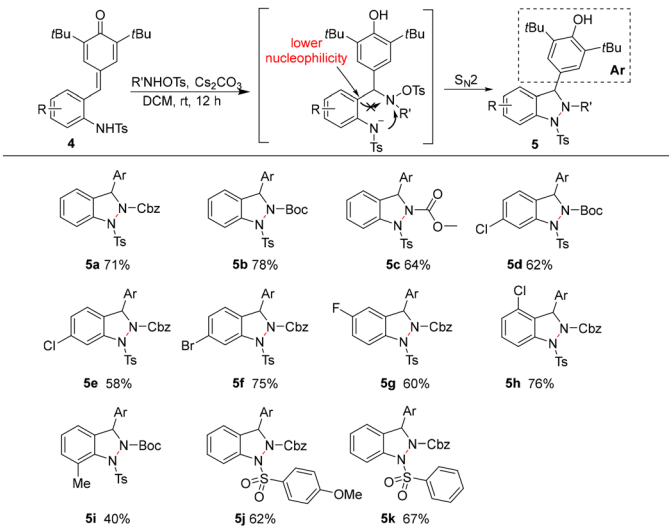
With the optimized conditions in hand, a range of substrates was examined for the vinylogous Schmidt reaction, and the results are illustrated in Table 2. First, we tested various arrays of substituted N-OTs carbamates. *tert*-Butyloxycarbonyl (Boc) group gave a better yield of 75% (**3a**). Meanwhile, benzyloxycarbonyl (Cbz) and allyloxycarbonyl (Alloc) groups can also produce the migrated product in 60% (**3b**) and 52% (**3c**) yields. Notably, this divergence in yield still exists during the screening of *p*-QM substrates (**3d–3k**). We posited that the slightly

Table 2 Evaluation of the substrate scope for vinylogous Schmidt reaction[a]



[a] To a solution of **1** (0.1 mmol) and **2** (0.12 mmol) in DCE (2 mL) at −20 °C was added Cs_2CO_3 (0.12 mmol). The reaction mixture was stirred at −20 °C for 4 h and then directly purified by silica gel chromatography to provide the desired products **3b–3s**.

Table 3 Evaluation of the substrate scope to synthesize dihydroindazoles[a]



[a] To a solution of **4** (0.1 mmol) and **2** (0.12 mmol) in DCM (2 mL) was added Cs_2CO_3 (0.12 mmol). The reaction mixture was stirred at rt for 12 h and then directly purified by silica gel chromatography to provide the desired products **5a–5k**.

decreased efficiency might be due to the vulnerability of benzyl and allyl esters to nucleophilic attack. The following exploration of substituents on migrating aromatic rings demonstrated good functional group tolerance. It is revealed that both electron-donating substituents, such as methyl (**3d**, **3e**) and methoxy (**3l**), and electron-withdrawing substituents, such as trifluoromethyl (**3m**) and nitro (**3n**), can furnish the benzoxazolidine products with moderate to good yields. Notably, *meta*-substituted *para*-QMs gave lower yields of migrated products than *para*-ones. We postulated that substitution at the *para*-position could equally affect the electronic property of arene, working synergistically with *ortho*-hydroxyl to enhance the nucleophilicity of rearranged carbon. It might be interpreted that the existence of a *para*-substituent of the phenol fragment will affect the electron density of the benzene ring, and then influence the nucleophilicity of the migrated carbon, resulting in a decrease in yield.

Inspired by the electron-donating ability of the hydroxyl group influencing the nucleophilicity of the migrated carbon, another hypothesis was proposed that, if the hydroxyl group is replaced by a stronger acidic but poorer electron-donating group, such as the sulfonamide group, the lower nucleophilicity of the aromatic carbon would not drive this vinylogous Schmidt rearrangement reaction, and would be replaced by the 1,6-addition/cyclization reaction *via* S_N2 of the adduct intermediate (Table 3). Consistent with our hypothesis, the proposed dihydroindazole **5a** was obtained in a good yield after optimization of the reaction conditions (see Table S1†).

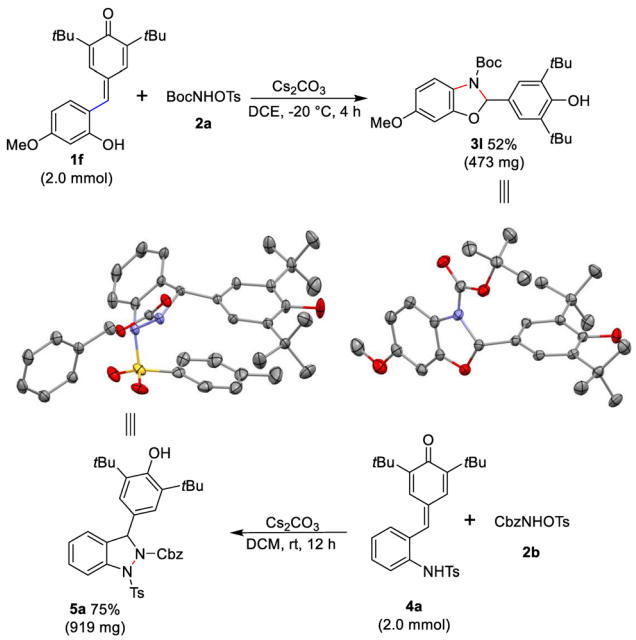


Fig. 2 Gram-scale syntheses and X-ray crystallographic analyses of **3l** and **5a**.

As shown in Table 3, a series of *p*-QM substrates bearing a sulfonamide group gave dihydroindazoles in moderate to good yields. The ester groups of N-OTs carbamate were tested first, and yielded the corresponding products smoothly (**5a–5k**, 64%–78% yield). Next, the examination of substituted position on the phenyl ring exhibited good tolerance, where even the sterically hindered 3-substituted *p*-QMs can give acceptable yields (40% for **5i**). This phenomenon suggested that the intramolecular nucleophilic attack of sulfonamide (NTs) on N-OTs carbamate was affected by steric hindrance, and might be the rate-determining step. Instead, the 6-substitution of *p*-QMs would repel the Ar group and the N-OTs carbamate group because of the steric hindrance, causing the sulfonamide to be closer to the N-OTs carbamate and promoting the intramolecular S_N2 reaction to generate a higher yield of dihydroindazole (76% for **5h**). Finally, benzenesulfonyl and 4-methoxybenzenesulfonyl protected *p*-QM substrates generated the corresponding products **5j** and **5k** in 62% and 67% yields, respectively.

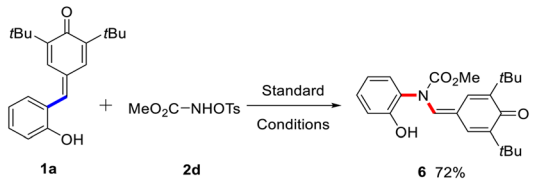


Fig. 3 Isolation of the rearranged intermediate.

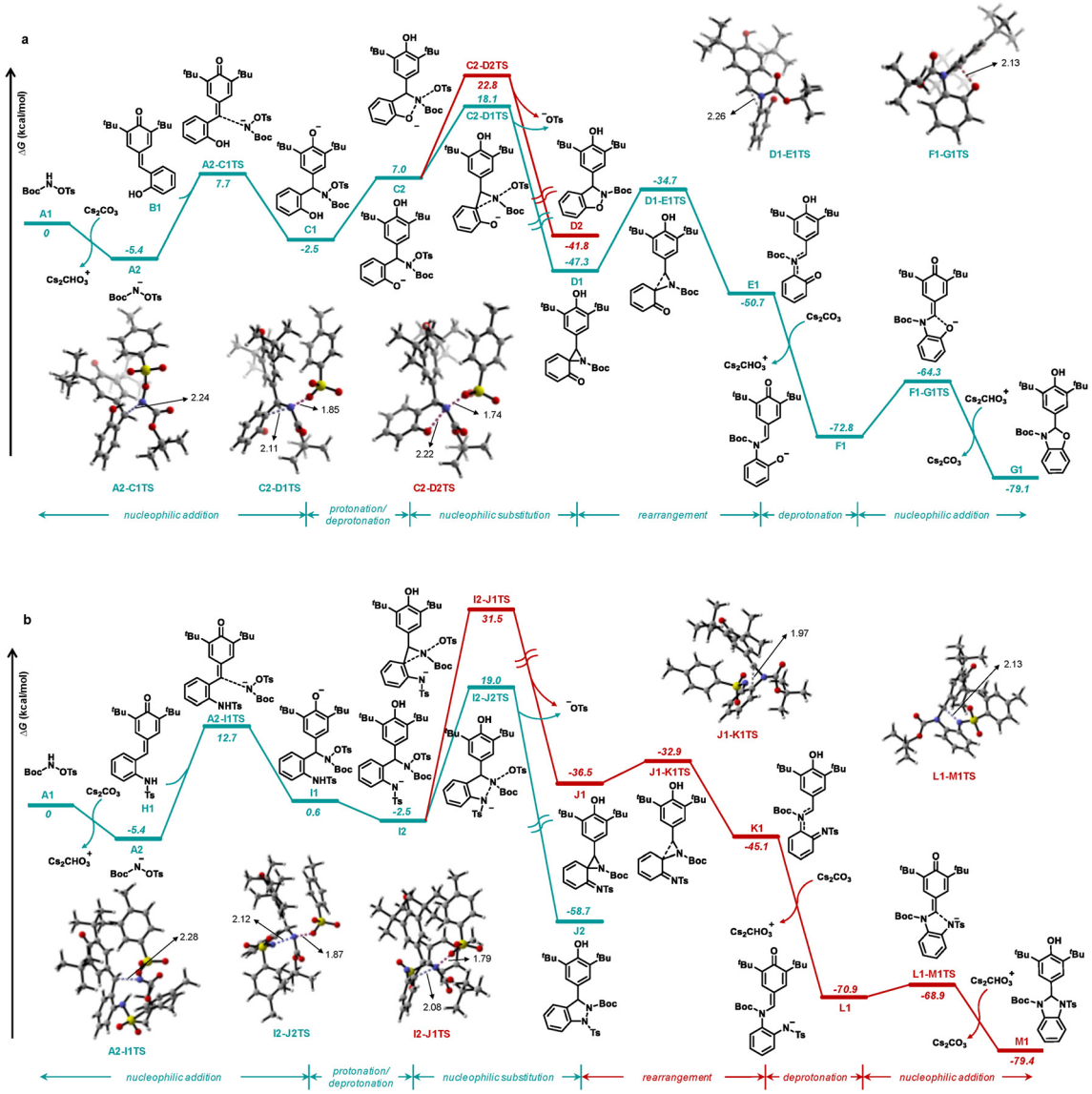


Fig. 4 (a) DFT-computed energy profiles for the formal vinylogous Schmidt reaction employing A1 and B1. (b) DFT-computed energy profiles for the 1,6 addition/cyclization reaction employing A1 and H1. Free energies in solution (in kcal mol^{-1}) calculated at SMD (chloroform)-M06-2X/Def2-TZVPP//ωB97XD/Def2-SVP. DFT optimized geometries of the transition states are shown. Bond lengths are in Å.

Structural analysis

To demonstrate the feasibility and robustness of our reaction, we conducted scaled-up reactions under the optimized conditions for the two reactions (Fig. 2). Both entries can afford the corresponding products in yields comparable to those under batch conditions (52% for **3l** and 75% for **5a**). The structures of **3l** and **5a** were unambiguously determined by single-crystal X-ray crystallographic analysis.[27]

Mechanistic studies

During the examination of the substrate scope, it was found that the vinylogous Schmidt reaction system cannot give the benzoxazolidine product when using methyl *N*-tosyloxycarbamate **2d** as the ambiphilic nitrogen source, but generates nitrogen insertion product **6** with C(aryl)–C(alkenyl) bond cleavage (Fig. 3). Obviously, the benzoxazoline would be obtained if **6** was cyclized, which was speculated to be the key intermediate during rearrangement. Comparison of the structures of **3a**, **3b**, **3c** and **6** suggested that the less sterically hindered methyl carbamate might be unable to push the 2-hydroxyphenyl and *p*-QM partners close enough to accomplish cyclization.

Furthermore, density functional theory (DFT) calculations were performed to elucidate the reaction mechanism of the formal vinylogous Schmidt reaction and the 1,6-addition/cyclization reaction (Fig. 4). These calculations aimed to clarify the differential catalytic pathways resulting from *p*-QM substrates adorned with various functional groups. Computational analysis was conducted at the SMD (chloroform)-M06-2X/Def2-TZVPP//ωB97XD/Def2-SVP level, with detailed computational methods provided in the ESI.†

Initially, we explored the model reaction between carbamate A1 and the *p*-QM substrate B1 bearing hydroxyl group. This reaction commences with the deprotonation of carbamate A1 by cesium carbonate, forming carbamate anion A2. Subsequently, A2 undergoes nucleophilic addition to *p*-QM substrate B1, traversing through transition state A2-C1TS with an energy barrier of 13.1 kcal mol^{-1}. The resultant phenolate intermediate C1 can isomerize into C2, setting the stage for the ensuing substitution reaction. The nucleophilic attack on the electrophilic nitrogen atom by the oxygen anion of C2, *via* S_N2 transition state C2-D2TS, faces an energy barrier of 25.3 kcal mol^{-1}. Alternatively, the enolate carbon of C2 can also attack the nitrogen atom through transition state C2-D1TS, entailing a lower energy barrier of 20.6 kcal mol^{-1}. This enolate carbon nucleophilic attack pathway is favored both kinetically and thermodynamically, marking a crucial juncture in determining the reaction pathway. Subsequently, aziridine ring cleavage occurs, followed by cesium-carbonate-mediated deprotonation. The final step involves the phenolate F1 undergoing nucleophilic cyclization to yield final product G1.

Additionally, we examined the catalytic cycle involving a *p*-QM substrate with a sulfonamide group (H1). Mirroring the earlier cycle, the deprotonated carbamate anion A2 attacks the *p*-QM substrate H1 through transition state A2-I1TS, with an energy barrier of 18.1 kcal mol^{-1}. The resultant phenolate I1 can isomerize into aniline anion I2. Subsequent N–N bond formation occurs *via* nucleophilic attack by the nitrogen atom on the electrophilic nitrogen, proceeding through transition state I2-J2TS with an energy barrier of 21.5 kcal mol^{-1}. Conversely, nucleophilic attack by the enamine carbon presents a prohibitively high energy barrier of 34.0 kcal mol^{-1}, likely due to reduced nucleophilicity compared to the enolate carbon. The N–N bond cyclization pathway emerges as the more kinetically and thermodynamically viable route.

Conclusions

We have developed the facile introduction of a nitrogen-containing group into *p*-QM substrates for the construction of benzoxazolidine and dihydroindazole scaffolds, using the bench-stable N-OTs carbamate as the ambiphilic nitrogen source. Depending on the electron-donating ability of the *ortho*-substituents on the benzene ring, the reaction underwent a formal vinylogous Schmidt process with an aziridine intermediate or 1,6-addition/cyclization step. Further investigations of nitrogen addition using bench-stable nitrogen sources are ongoing in our laboratory.

Author contributions

Bo Wang, Yanhao Dong, Chen Kong, Hanxiao Zhu, Yatong Yang and Xin Zhao experimental investigation and data collection; Chen Zhu computational investigation and data analysis; Tiandi Ding and Guoyue Wei crystallization; Magnus Rueping supervision; Qingqiang Yao conceptualization and supervision; Yan Li and Kun Zhao conceptualization, funding acquisition, supervision, writing-original draft, writing-review & editing; Ying Zhi conceptualization, funding acquisition, supervision, writing-original draft, writing-review & editing. All authors have given approval to the final version of the manuscript.

Data availability

The data supporting this article have been included as part of the ESI.†

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

This work was supported by Shandong Provincial Natural Science Foundation (ZR2021QB038, ZR2022QB069), the Natural Science Foundation of China (22101154), Excellent

Young Scholars of Shandong Provincial Natural Science Foundation (2022HWYQ-008), Taishan Scholar Youth Program of Shandong Province (tsqnz20230623) and Academic Promotion Program of Shandong First Medical University (2019LJ003). We acknowledge the KAUST Supercomputing Laboratory for providing computational resources from the supercomputer Shaheen II.

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27 The X-ray crystallographic coordinates for structures reported in this study have been deposited at the Cambridge Crystallographic Data Centre (CCDC), under deposition numbers CCDC 2323528 (for **3l**) and 2323529 (for **5a**).†