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COMMUNICATION

Diprotonative stabilization of ring-opened carbocationic intermediate: conversion of tetrahydroisoquinoline to triarylmethanes

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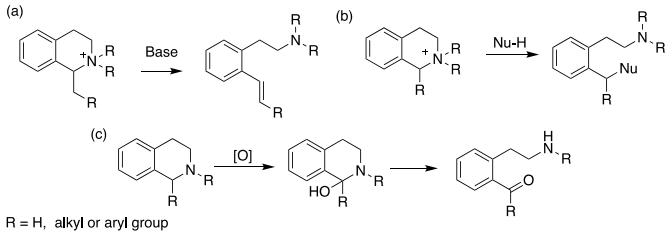
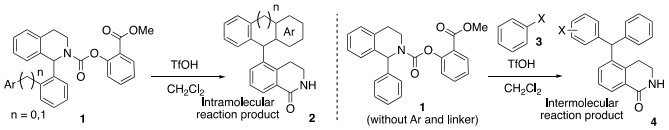
Superacid-promoted conversion of tetrahydroisoquinolines to triarylmethanes via tandem reactions of C–N bond scission, Friedel-Crafts alkylation, C–O bond scission, and electrophilic aromatic amidation was developed. Dication formation was important for stabilizing the ring-opened carbocationic intermediate, which is a new role for diprotonation in reaction mechanisms.

Tetrahydroisoquinoline derivatives are major structures found in various natural products and pharmaceuticals.[1] They have not only unique structures and functions, but also synthetic utility as precursors to valuable compounds such as isoquinolines,[2] benzazepines,[3] and protopines.[4] Transformation of tetrahydroisoquinolines via scission of the C–N bond, while rare, typically takes place via Hoffmann elimination,[4,5] oxidative hemiaminal formation,[4,6] or nucleophilic substitution (Scheme 1).[7]



Scheme 1. Ring-opening reactions of tetrahydroisoquinoline skeletons: (a) Hoffmann-type elimination, (b) nucleophilic substitution, and (c) oxidative hemiaminal formation.

Acid-catalyzed activation of the tetrahydroisoquinoline C–N bond would be expected to generate a carbocation, which is an important electrophile in synthesizing functionalized aromatic molecules such as polyaromatic rings and triarylmethanes,[8] which are used as medicines, dyes, and fluorophores.[9] However, the C–N bond of tetrahydroisoquinoline is relatively stable under acidic conditions. Because of the acid stability of the C–N bond, the Pictet-Spengler reaction has been employed as a remarkably important method in biological and chemical syntheses.[10] Even a superacid media could be used for catalyzing the reaction at 120 °C,[11] indicating the necessity of further activation of the C–N bond for its cleavage. Therefore, C–N bond scission-initiated electrophilic aromatic substitution reactions of tetrahydroisoquinoline have not been reported.



Scheme 2. Conversion of tetrahydroisoquinoline compounds to triarylmethanes which have a dihydroisoquinolone structure (Ar: Aryl group).

In this study, a new series of triarylmethanes **2**, which have a dihydroisoquinolone structure, were synthesized from tetrahydroisoquinolines **1** via a tandem reaction sequence triggered by C–N bond scission using trifluoromethanesulfonic acid (TfOH) (Scheme 2). A previously developed method for activating a carbamate at room temperature was utilized to form the dihydroisoquinolone moiety under mild conditions.[12] Historically, diprotonation of substrates has been used to enhance electrophilicity.[13] In this study, however, diprotonation of the substrate also had an important role in *stabilizing* the reactive ring-opened carbocation for successive electrophilic aromatic substitution. The proposed reaction mechanism is shown in Figure 1.

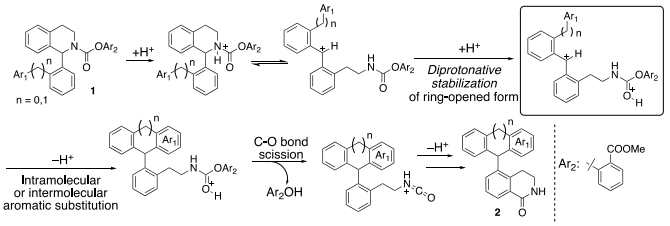


Figure 1. Proposed mechanism of the reaction (Ar_1: Aryl group).

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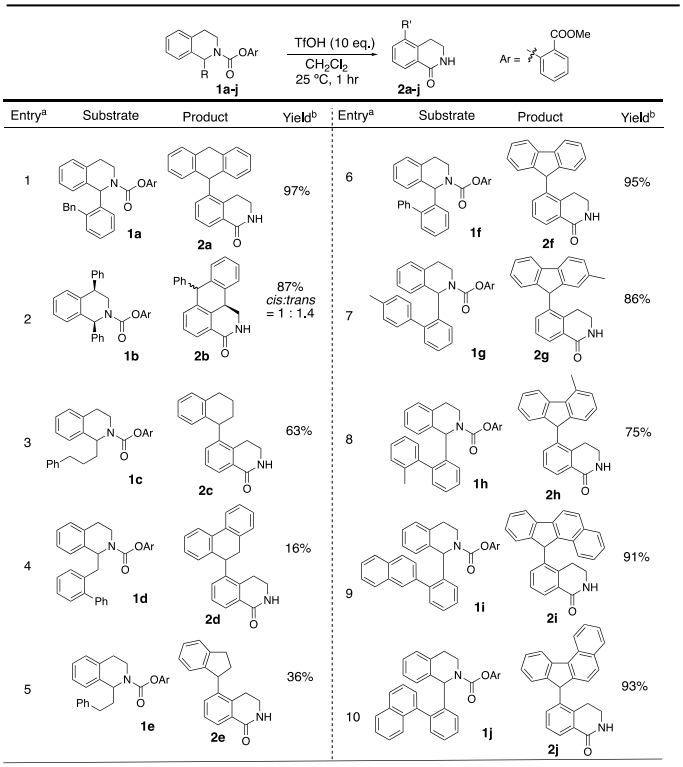
Table 1. Substrate scope of the intramolecular reaction

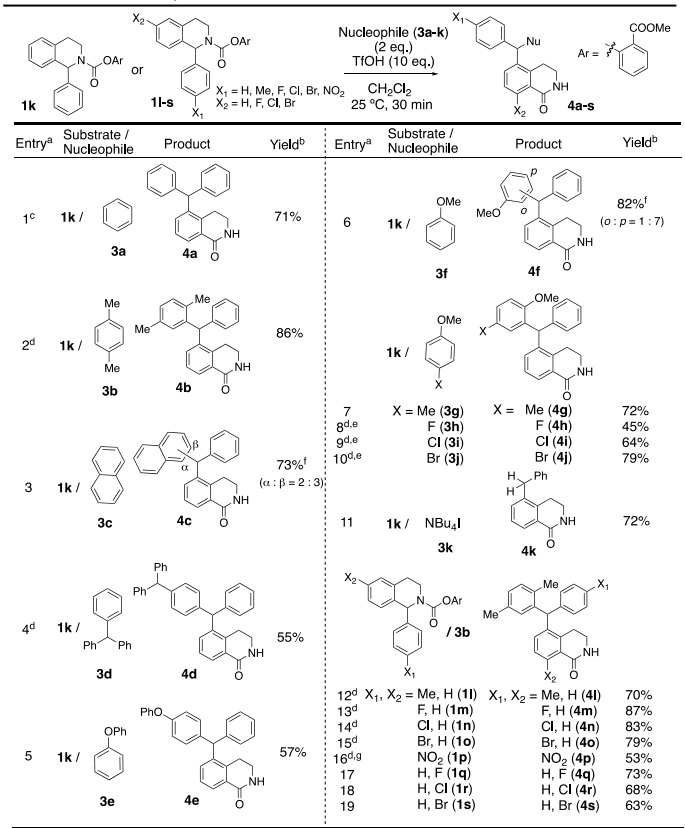


[a] Reaction conditions: TfOH (10 equiv.) was added to a solution of **1** (0.30 mmol) in dichloromethane (1.5 mL) at 0 °C. The reaction mixture was stirred at 25 °C for 1 h. [b] Isolated yield.

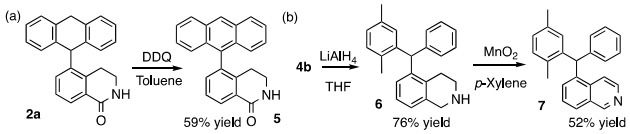
The substrate generality of the reaction was initially verified with intramolecular cyclization reactions. Dihydroisoquinolones bearing fluorophores or a fluorophore precursor were obtained in moderate to high yields (Table 1). Dihydroanthracenes were successfully introduced to the C-5 carbon of the dihydroisoquinolone moiety in high yields (Entry 1). Because of the generation of the carbocationic intermediate by C–N bond cleavage, **2b** was a mixture of cis and trans diastereomers (Entry 2). A tetrahydronaphthalene derivative (**2c**) and a dihydrophenanthlene derivative (**2d**) were also obtained (Entries 3 and 4). In these reactions, intramolecular cyclization proceeded less efficiently in comparison with Entries 1 and 2 because aromatic rings at the C-1 position of the tetrahydroisoquinoline substrates play an important role in stabilizing the carbocation center to facilitate C–N bond cleavage. Dihydroisoquinolones bearing fluorene and its derivatives were also achieved (Entries 5-10). The intramolecular reaction of a naphthalene moiety was highly selective (Entries 9 and 10).

The substrate generality of the intermolecular reaction was also investigated using 2 equivalents of a nucleophile (Table 2). Various triarylmethane derivatives were obtained in moderate to good yields. Optimization details are discussed in the ESI. Benzene (**3a**), *p*-xylene (**3b**), and naphthalene (**3c**) reacted well with substrate **1k** to afford the corresponding triarylmethanes (Entries 1-3). Contrary to some previous studies of electrophilic substitution reactions,[14] naphthalene reacted at its β-position rather than α-position, presumably for steric reasons as the electrophile is bulkier than the cations generated in typical electrophilic aromatic substitution reactions. The use of triphenylmethane (**3d**) and diphenylether (**3e**) afforded products **4d** and **4e** in moderate yields (Entries 4 and 5). Anisole (**3f**) and its derivatives (**3g-j**) also afforded triarylmethanes **4f** to **4j** in moderate to good yields (Entries 6-10). The possibility of attack by a halogen was also examined (Entry 11). Tetrabutylammonium iodide (**3k**) reacted with the substrate but did not afford the expected iodine adduct; instead, reduction of the carbocation afforded **4k**.[15] Substitution on the tethered aromatic ring and tetrahydroisoquinoline was also examined. Substrates **1l-p** afforded triarylmethanes **4l**-**4s** in good to high yields (Entries 12-16). Substrates which had a halogen atom at the 6-position of the tetrahydroisoquinoline ring afforded a dihydroisoquinolone moiety with a halogen at the 8-position, which is difficult to access using other synthetic methods (Entries 17-19).

Table 2. Substrate scope of the intermolecular reaction

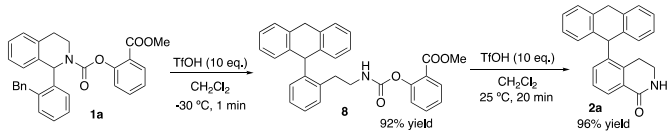


[a] Reaction conditions: TfOH (10 equiv.) was added to a solution of **1k** (0.30 mmol) and **3** (0.60 mmol) in dichloromethane (1.5 mL) at 0 °C. The reaction mixture was stirred at 25 °C for 30 min. [b] Isolated yield. [c] Excess amount of **3a** (57 equiv.) was used as the solvent instead of CH_2Cl_2. [d] 5 equiv. of the nucleophile was used. [e] 15 equiv. of TfOH was used. [f] The ratio was determined by ^{1}H NMR. [g] The reaction mixture was stirred for 2 h.



Scheme 3. (a) Oxidation of **2a** to form anthracene **5**. (b) Conversion of dihydroisoquinolone **4b** to isoquinoline **7**.

The obtained triarylmethanes could be derivatized (Scheme 3). Dihydroanthracene **2a** was oxidized to an anthracene **5** (Scheme 3a).[16] Dihydroisoquinolone **4b** was converted to an isoquinoline derivative **7** via tetrahydroisoquinoline **6** (Scheme 3b).[17]



Scheme 4. Isolation of intermediate **8** and its conversion to **2a**.

To verify the mechanism, we tried isolating the initially formed intermediate and then converting it to **2a**. By running the reaction of **1a** at -30 °C for 1 min, intermediate **8** with a dihydroanthracene ring was obtained in 92% yield, and **8** was then transformed to **2a** in 96% yield (Scheme 4). This is clear evidence that C–N bond cleavage proceeds prior to C–O bond cleavage of the carbamate. The rate of the conversion from **1a** to **8**, with a half-life presumed to be shorter than 10 s at -30 °C, indicated that the energy barrier from substrate **1a** to **8** is less than 16 kcal/mol based on Eyring's absolute rate theory.[18]

To characterize the protonation state of the substrate in the presence of excess amount of TfOH, model substrates **9a-c** were studied by ^{1}H and ^{13}C NMR in TfOH at 0 °C. The tetrahydroisoquinoline structure was completely opened and two dication rotamers (**9a-2H^{+}-Open**) with respect to amide bond rotation were observed (Figure 2a). The proton peaks of the benzhydryl cation moiety were observed at around 10 ppm and the carbon peaks were observed at around 190 ppm. These chemical shifts are in good agreement with the values reported by Olah et al. (9.8 ppm for ^{1}H and 191.1 ppm for ^{13}C).[19] The carbon peaks of the carbamate also shifted to a lower region (~162 ppm), indicating further protonation on the carbamate moiety. Proton exchange of the acid media was suppressed by the addition of SbF_5 to confirm of the protonation state of the carbamate. The OH group derived from the carbamate was directly observed at 10.3 ppm (Figure 2b), although other ^{1}H and ^{13}C chemical shifts did not significantly change. Weaker acids than TfOH such as trifluoroacetic acid (TFA) and methanesulfonic acid ($MeSO_3H$) were also examined. The ring-opened dication was not observed in these acids even though the carbonyl carbon shifted to a lower field, indicating monoprotonation or strong hydrogen bond formation (Figure 2c).

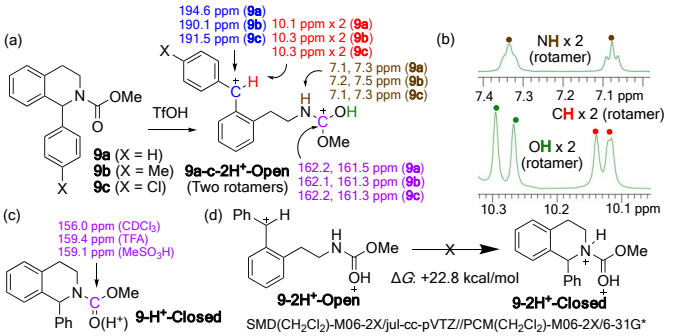


Figure 2. (a) ^{1}H and ^{13}C NMR chemical shifts of **9a-c** in TfOH at 0 °C. (b) Observed protons of the dication **9a-2H^{+}-Open** in a mixture of TfOH and SbF_5 (89:11 (w/w)). (c) ^{13}C chemical shift of **9** in $CDCl_3$, TFA, and $MeSO_3H$. (d) Free energy difference of **9-2H^{+}-Open** and **9-2H^{+}-Closed** calculated by DFT.

Why does the dication exist as a stable ring-opened intermediate even though the monocation has a ring-closed structure? One of the major reasons is electric repulsion between the protonated carbamate and the benzhydryl cation, which avoids the formation of a *gitonic* dication (Figure 2d).[13] Density functional theory (DFT) calculations indicated that **9-2H^{+}-Open** is 22.8 kcal/mol more stable in Gibbs free energy than the closed form (**9-2H^{+}-Closed**). As a result, the reverse ring-closing reaction is prohibited by *diprotonative stabilization* of the carbocationic intermediate. See ESI for details of the DFT calculation.

The reaction profile of the transformation of **1a** was calculated to further clarify the reaction mechanism (Figure 3). The reaction path was initially calculated as the monocation because the high acidity of TfOH enables complete protonation of the carbamate group of **1a**. (See ESI for details.)

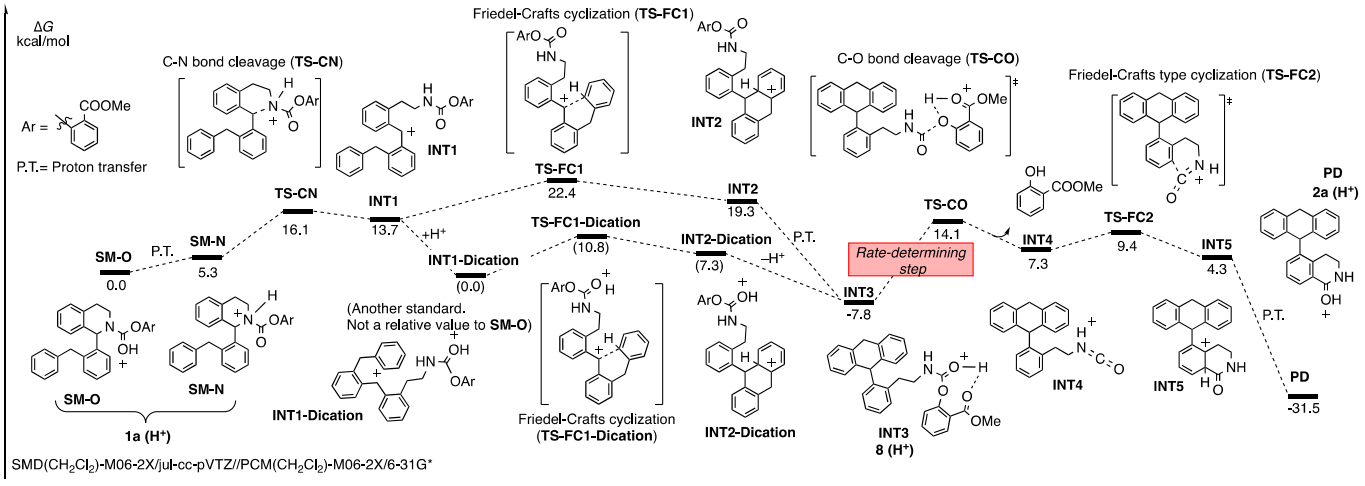


Figure 3. Energy profile of the reaction (298.15 K). The free energy values of the monocations are relative to **SM-O**. The free energy values of the dications are shown in parenthesis and are relative to **INT1-Dication**, not to **SM-O**. See ESI for an explanation of why another standard was used.

The protonated reactant (**1a(H$^+$)**) is in equilibrium between the O-protonated form **SM-O** and N-protonated form **SM-N**. C–N bond cleavage of **SM-N** proceeds quickly, with a barrier of 16.1 kcal/mol. Because the next transition state of the Friedel-Crafts cyclization, **TS-FC1**, has a higher energy barrier than the reverse reaction of **INT1** via **TS-CN**, the C–N bond cleavage process for the monoprotonated form is reversible.[20]

The Friedel-Crafts cyclization and succeeding proton transfer process forms **INT3**. The calculated monocationic pathway via **TS-FC1** has an energy barrier of 22.4 kcal/mol, which is the highest barrier in the entire process. When compared with the experimental results shown in Scheme 4, the DFT-calculated energy barrier is overestimated by more than 6 kcal/mol. This suggests that a monocationic pathway does not suitably explain the rate of the Friedel-Crafts cyclization. As previously seen in the NMR studies, the carbamate substrate forms a stabilized dication. The open dication **INT1-Dication** is expected to be more stable in free energy than **SM-O** in the presence of excess TfOH. The reaction rate of the Friedel-Crafts cyclization should therefore be assumed from the energy barrier between **INT-1-Dication** and **TS-FC1-Dication**, which is 10.8 kcal/mol. The barrier of the dicationic pathway is consistent with the experimental reaction rate. After the dicationic cyclization, deprotonation of **INT2-Dication** immediately proceeds to afford monocationic **INT3** because the dihydroanthracene moiety cannot be fully protonated in TfOH.

The rate-determining step of the entire process is the activation of the carbamate moiety to form **INT4**, which has an activation free energy from **INT3** of 21.9 kcal/mol. This is in good agreement with a previously reported monocationic intramolecular hydrogen bond-activated C–O bond cleavage mechanism.[12a] The cyclization process then proceeds smoothly to afford the final product (**PD**).[21]

In conclusion, we investigated a new type of transformation of tetrahydroisoquinoline to functionalized dihydroisoquinolone derivatives in the presence of TfOH. The reaction is initiated by carbocation generation via C–N bond cleavage of the tetrahydroisoquinoline, then diprotonation prohibits the reverse reaction. The succeeding tandem reaction then proceeds smoothly. The proposed concept of *diprotonative stabilization* is expected to be applicable to the generation of new types of carbocations from complex molecules, such as isoquinoline alkaloids.

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Conflicts of interest

There are no conflicts to declare.

Notes and references

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21 The discussion about the mechanism is explained in details in ESI.