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$PhI(OAc)_2$-mediated iminobromination for synthesis of bromomethyl cyclic imines starting from alkenyl carbonitriles and Grignard reagents

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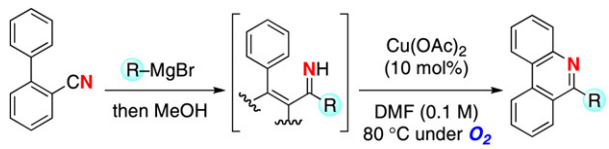
ABSTRACT

$PhI(OAc)_2$-mediated iminobromination was developed starting from alkenyl carbonitriles and Grignard reagents. The present transformation is carried out by a sequence of nucleophilic addition of Grignard reagents to alkenyl carbonitriles to form *N*–H imines and their iminohalogenation by subsequent treatment with $PhI(OAc)_2$.

1. Introduction

Molecular transformations that allow the construction of functionalized organic frameworks from simple and ubiquitous starting materials through multi-formation of chemical bonds in one-pot fashion is an ideal process in organic synthesis from the atom-[1] and step-economical[2] point of views. Electrophilic halocyclization of alkenes has been utilized as one of the most convenient methods to access molecular complexity, where halogenating reagents effect cyclization of alkenes bearing intramolecular nucleophilic parts, such as carboxy, hydroxy, amino, and amido as well as carbonyl oxygen.[3]

We have been interested in use of ubiquitous carbonitriles as a nitrogen source for synthesis of azaheterocycles. We recently disclosed the copper-catalyzed synthesis of phenanthridine derivatives from biaryl-2-carbonitriles and Grignard reagents under an oxygen atmosphere,[4] in which putative iminyl copper species derived from the *N*–H imine intermediate might undergo intramolecular C–N bond formation on the aromatic C–H bond (Scheme 1).



Scheme 1.

Our attention was turned to utilize alkenyl carbonitriles with Grignard reagents to develop a C–N bond forming process on the C=C bond via the *N*–H imine intermediate. Herein, we wish to report $PhI(OAc)_2$-mediated iminobromination starting from alkenyl carbonitriles and Grignard reagents, providing functionalized cyclic imines, such as bromomethyl dihydropyrroles and dihydroisoquinolines with one-pot formation of C–C, C–N, and C–Br bonds. The present transformation is carried out by a sequence of nucleophilic addition of Grignard reagents (R–MgBr) to alkenyl carbonitriles to form *N*–H imines and their iminobromination by subsequent treatment with $PhI(OAc)_2$, where the bromine atom of the counter anion of the Grignard reagents was incorporated into the final products without utilizing additional bromine sources, such as elemental bromine, *N*-bromosuccinimide (NBS),[5] *N*-bromoacetamide (NBA), bromodimethylsulfonium bromide.[6,7]

2. Results and discussion

First of all, 2,2,4-trimethylpent-4-enenitrile (**1a**) and *p*-tolylmagnesium bromide (**2a**) were chosen, and their intermolecular addition reaction to form the *N*–H imine and its cyclization was investigated. Addition of *p*-tolylmagnesium bromide (**2a**) to carbonitrile **1a** occurred smoothly in Et_2O at 60 °C (in sealed tube). After protonation with MeOH,[8] DMF (the reaction was diluted to 0.1 M) and $Cu(OAc)_2$ (20 mol %) were subsequently added, and the reaction mixture was stirred at 80 °C under an oxygen atmosphere (1 atm) (Table 1, entry 1). After 8 h, a hydroimination product, cyclic imine **3**, was isolated in 43% yield. In addition to the formation of **3**,

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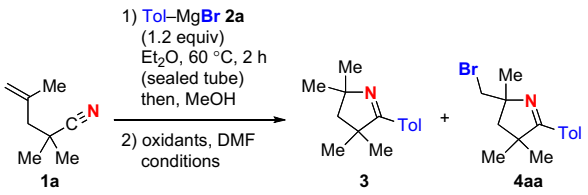
cyclic imine **4aa** bearing a C–Br bond was isolated in 6% yield. When 1.1 equiv of $Cu(OAc)_2$ was utilized without oxygen (under a N_2 atmosphere), the yield of **4aa** was increased to 40% (entry 2). It was found that treatment with $PhI(OAc)_2$ (1.5 equiv) provided brominated cyclic imine **4aa** exclusively in 88% yield at room temperature (entry 3). Oxone[9] also worked well providing a slightly lower yield (76%, entry 4), while the other oxidants, such as $NaIO_4$[10] and $NaClO_2$ did not form **4aa** at all (entries 5 and 6).

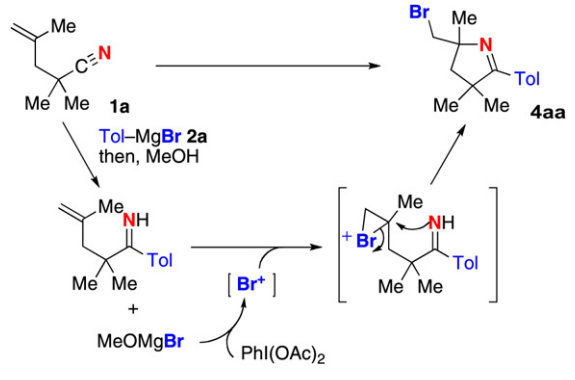
Table 1
Optimization of reaction conditions[a]



Entry	Oxidants	Conditions	Yield (%)[b]	
			3	**4aa**
1	$Cu(OAc)_2$ (20 mol %) under O_2 (1 atm)	80 °C, 8 h	43	6
2	$Cu(OAc)_2$ (1.1 equiv) under N_2 (1 atm)	80 °C, 6 h	49	40
3	**$PhI(OAc)_2$ (1.5 equiv)**	**rt, 0.5 h**	**0**	**88**
4	Oxone (1.5 equiv)	rt, 0.5 h	0	73
5	$NaIO_4$ (1.5 equiv)	rt, 0.5 h	0	0 (97)[c]
6	$NaClO_2$ (1.5 equiv)	rt, 0.5 h	0	0 (73)[c]

Entry 3 was optimized (best) conditions represents in bold.
[a] Reactions were carried out using 0.35–0.4 mmol of carbonitrile **1a**.
[b] Isolated yields.
[c] Isolated yield of 2,2,4-trimethyl-1-*p*-tolylpent-4-en-1-one formed via hydrolysis of the *N*–H imine.

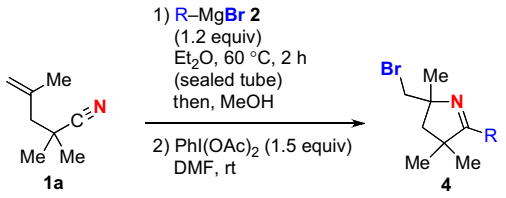
A proposed reaction course of formation of bromomethyl cyclic imine **4aa** was outlined in Scheme 2. Addition of Grignard reagent **2a** to carbonitrile **1a** followed by protonation with MeOH provides the *N*–H imine and MeOMgBr that was oxidized by $PhI(OAc)_2$ to generate Br^+ species. Formation of bromonium cation followed by intramolecular nucleophilic attack of imine affords cyclic imine **4aa**.[11,12]

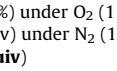


Scheme 2.

By utilizing $PhI(OAc)_2$ as the oxidant (entry 3 in Table 1), we examined the generality of this method for synthesis of bromomethyl dihydropyrroles starting from 4-pentenenitrile derivatives **1**. First, the scope of Grignard reagents **2** was examined using nitrile **1a** (Table 2). Aryl Grignard reagents bearing both electron-donating and -withdrawing groups on the benzene ring as well as 2-thienylmagnesium bromide provided the desired dihydropyrroles **4** in good yields except for the reaction with the sterically hindered 2,6-dimethylphenylmagnesium bromide **2d** (entries 1–6). The reactions of alkenyl Grignard reagents afforded the corresponding dihydropyrroles **4ag** in 55% yield (entry 7), whilst no desired product was observed from alkyl Grignard reagents, such as **2i** probably due to the instability of the resulting *N*–H imine intermediate (entry 8).

Table 2
Scope of Grignard reagents[a]

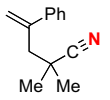
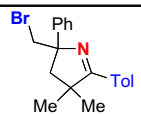
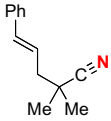
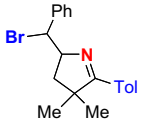
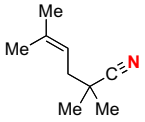
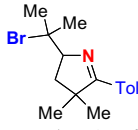


Entry	R–MgBr **2**	Dihydropyrroles **4** (yield/%)[b]
1	**2a**: R=4-Me–C_6H_4	**4aa** (88)
2	**2b**: R=4-MeO–C_6H_4	**4ab** (92)
3	**2c**: R=2-Me–C_6H_4	**4ac** (78)
4	**2d**: R=2,6-Me_2–C_6H_3	**4ad** (12)
5	**2e**: R=4-Cl–C_6H_4	**4ae** (70)
6	**2f**: R=2-thienyl	**4af** (61)
7[c]	**2g**: R = 	**4ag** (55)
8[d]	**2i**: R=$PhCH_2CH_2$	**4ah** (0)

[a] Reactions were run by treatment of carbonitrile **1a** (0.35–0.4 mmol) with 1.2 equiv of Grignard reagents **2** in Et_2O (sealed tube) at 60 °C followed by the addition of MeOH (3 equiv), DMF (reaction diluted to 0.1 M) and $PhI(OAc)_2$ (1.5 equiv) at room temperature.
[b] Isolated yields.
[c] Nitrile **1a** was treated with 2 equiv of alkenyl Grignard reagent **2g** at 80 °C for 6.5 h.
[d] 18 h were required to consume nitrile **1a** with Grignard reagent **2i**.

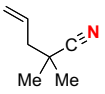
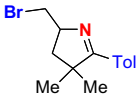
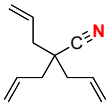
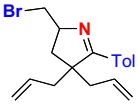
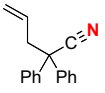
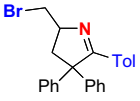
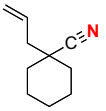
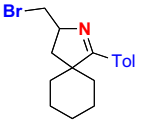
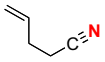
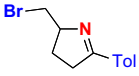
The effects of substituents on the alkenyl carbonitriles **1** were examined using *p*-tolylmagnesium bromide (**2a**) (Table 3). The reaction of 4-phenyl substituted **1b** provided dihydropyrrole **4ba** in good yield (entry 1). From 5-phenyl and 5,5-dimethyl derivatives **1c** and **1d**, only 5-*exo*-cyclization was observed exclusively (entries 8 and 9). 2,2-Dimethyl-, 2,2-diallyl-, and 2,2-diphenyl-4-pentenenitriles (**1e**–**g**) could be utilized to access 4,4-disubstituted dihydropyrroles (entries 4–6). A 2-azaspiro[4.5]dec-1-ene structure **4ha** was efficiently constructed from 1-allylcyclohexanecarbonitrile (**1h**) (entry 7). The reaction of 4-pentenenirile (**1i**) also proceeded to give dihydropyrrole **4ia** while 8% yield of α-brominated compound was isolated as a side product (entry 8).

Table 3
Scope on the substituents of alkenyl carbonitriles **1**[a]

Entry	Nitriles **1**		Dihydropyrroles **4** (yield/%)[b]	
1		**1b**		**4ba** (76)
2		**1c**		**4ca** (87) (dr = 76:11)[c]
3		**1d**		**4da** (65)

(*continued on next page*)

Table 3 (*continued*)

Entry	Nitriles **1**	Dihydropyrroles **4** (yield/%)[b]
4	 **1e**	 **4ea** (75)
5	 **1f**	 **4fa** (71)
6	 **1g**	 **4ga** (57)
7	 **1h**	 **4ha** (83)
8	 **1i**	 **4ia** (64)[d]

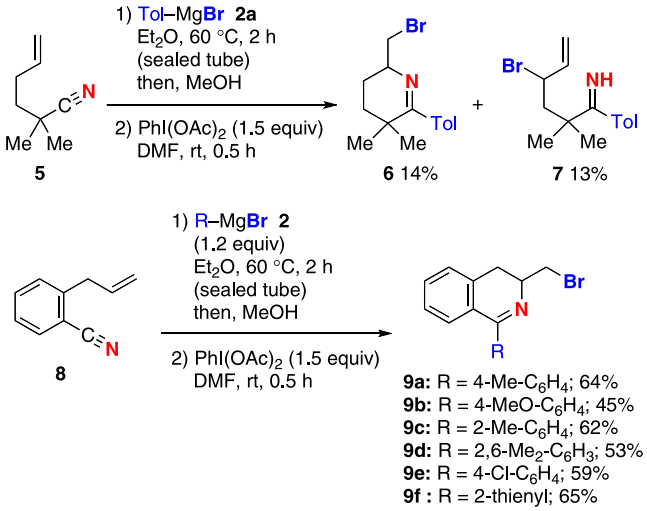
[a] Reactions were run by treatment of carbonitrile **1a** (0.35–0.4 mmol) with 1.2 equiv of Grignard reagents **2** in Et_2O (sealed tube) at 60 °C followed by the addition of MeOH (3 equiv), DMF (reaction diluted to 0.1 M) and $PhI(OAc)_2$ (1.5 equiv) at room temperature.

[b] Isolated yields.

[c] The ratio was determined by weight after separation of two isomers by column chromatography. The relative stereochemistry was not determined.

[d] α-Brominated product **4ia-Br** was isolated in 8% yield.

Having a protocol to prepare bromomethyl dihydropyrroles **4**, we envisioned the construction of six-membered azaheterocycles (Scheme 3). The reaction of 2,2-dimethylhex-5-enenitrile (**5**) with *p*-tolylmagnesium bromide (**2a**) afforded the desired bromomethyl tetrahydropyridine **6**[13] in only 14% yield along with acyclic brominated *N*–H imine **7**[14] in 13% yield. On the contrary, it was found that the reactions of 2-allylbenzonitrile (**8**) with aryl Grignard reagents could provide 3-bromomethyl-3,4-dihydroisoquinolines **9** smoothly in good to moderate yields.



Scheme 3.

3. Conclusion

In conclusion, a synthetic method for the preparation of bromomethyl cyclic imines has been developed starting from a variety of alkenyl carbonitriles and Grignard reagents via $PhI(OAc)_2$-mediated iminobromination. Continuous studies on the scope and synthetic applications of the present method toward various heterocycles are in progress.

4. Experimental section

4.1. General

^1H NMR (400 MHz) spectra were recorded on a Bruker Avance 400 spectrometer in $CDCl_3$ [using tetramethylsilane (for ^1H, δ=0.00) as internal standard]. ^{13}C NMR (100 MHz) spectra on a Bruker Avance 400 spectrometer in $CDCl_3$ [using $CHCl_3$ (for ^{13}C, δ=77.0) as internal standard]. The following abbreviations were used to explain the multiplicities: s=singlet, d=doublet, t=triplet, m=multiplet, br=broad. IR spectra were recorded on a Shimadzu IR Prestige-21 FTIR Spectrometer. High-resolution mass spectra were obtained with a Finnigan MAT 95 XP mass spectrometer (Thermo Electron Corporation). Melting points were uncorrected and were recorded on a Buchi B-54 melting point apparatus.

Flash column chromatography was performed using Merck silica gel 60 with distilled hexane and ethyl acetate. Diisopropylamine was purchased from Alfa Aesar, distilled from KOH and stored over KOH. Tetrahydrofuran (THF), acetonitrile, and diethyl ether (Et_2O) were taken from a solvent purification system (PS-400-5, Innovative Technology, Inc.). Methanol (MeOH) was distilled from sodium and stored over MS 3A. *N*,*N*,-Dimethylformamide (DMF) was purchased from Sigma–Aldrich, Pte. Ltd. Acetone (HPLC grade) was purchased from Tedia Company, Inc.

All liquid starting materials were Kugelrohr distilled before use. 4-Pentenenitrile (**1i**) was purchased from Sigma–Aldrich, Pte. Ltd., and was distilled with Kugelrohr before use (27 mm Hg/50 °C). All solid products were recrystallized from hexane and ethyl acetate.

4.2. Synthesis of alkenyl carbonitriles

*4.2.1. Synthesis of **1a**–**e**, **1g**–**h**, and **5**:*[15] *a typical procedure for synthesis of **1d**[16].* To a 100 mL round-bottom flask was added diisopropylamine (2.2 mL, 15.4 mmol) and *n*-BuLi (9.2 mL, 14.7 mmol) in THF (18 mL), and the reaction mixture was stirred at 0 °C for 30 min. The mixture was then cooled down to −78 °C and isobutyronitrile (1.3 mL, 14.0 mmol) was slowly added. After stirring for 1 h, 1-bromo-3-methylbut-2-ene (1.8 mL, 15.4 mmol) was added dropwise and the reaction mixture was allowed to warm up to room temperature while stirring overnight. The reaction was quenched with saturated aqueous NH_4Cl solution. Organic materials were then extracted three times with 50 mL of Et_2O. The organic phase was washed with water and brine, and dried over $MgSO_4$. After filtration, the solvent was evaporated to give a crude mixture, which was purified by Kugelrohr distillation to provide 2,2,5-trimethylhex-4-enenitrile (**1d**) (1.52 g, 11.1 mmol) for 79% yield (5 mm Hg/86–88 °C).

Colorless oil; ^1H NMR (400 MHz, $CDCl_3$) δ 1.32 (6H, s), 1.65 (3H, s), 1.77 (3H, s), 2.23 (2H, d, J=7.6 Hz), 5.25 (1H, ddt, J=1.3, 1.3, 7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.1, 25.9, 26.2, 32.8, 39.1, 118.2, 125.3, 136.4; distillation: 5 mm Hg/86–88 °C.

*4.2.1.1. 2,2,4-Trimethylpent-4-enenitrile (**1a**)*[17]. Yield 90%; Colorless oil; ^1H NMR (400 MHz, $CDCl_3$) δ 1.36 (6H, s), 1.90 (3H, s), 2.26 (2H, s), 4.84 (1H, s), 4.98 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.6, 27.0, 31.3, 48.5, 116.1, 125.4, 140.6; distillation: 26 mm Hg/70–72 °C.

*4.2.1.2. 2,2-Dimethyl-4-phenylpent-4-enenitrile (**1b**)*[18]. Yield 24%; Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.28 (6H, s), 2.80 (2H, s), 5.32 (1H, s), 5.47 (1H, s), 7.28–7.43 (5H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.1, 33.1, 45.5, 118.5, 124.6, 126.5, 127.8, 128.5, 141.6, 144.0; distillation: 0.9 mm Hg/105–110 °C.

*4.2.1.3. (E)-2,2-Dimethyl-5-phenylpent-4-enenitrile (**1c**)*[19]. Yield 91%; White solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.39 (6H, s), 2.44 (2H, dd, J=1.2, 7.5 Hz), 6.26 (1H, td, J=7.5, 15.7 Hz), 6.51 (1H, d, J=15.7 Hz), 7.23–7.25 (1H, m), 7.30–7.34 (2H, m), 7.38–7.40 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.3, 32.6, 44.3, 123.5, 124.8, 126.3, 127.7, 128.6, 134.8, 136.7; recrystallized from hexane and ethyl acetate.

*4.2.1.4. 2,2-Dimethylpent-4-enenitrile (**1e**)*[15]. Yield 60%; Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.34 (6H, s), 2.28 (2H, d, J=7.3 Hz), 5.16–5.24 (2H, m), 5.82–5.92 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.2, 32.1, 45.0, 119.9, 124.7, 132.2; distillation: 26 mm Hg/70–75 °C.

*4.2.1.5. 2,2-Diphenylpent-4-enenitrile (**1g**)*[15]. Yield 82%; Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.14 (2H, d, J=7.0 Hz), 5.16–5.23 (2H, m), 5.66–5.76 (1H, m), 7.27–7.40 (10H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 43.9, 51.7, 120.4, 121.9, 127.0, 127.9, 128.8, 131.8, 139.7; distillation: 1.6 mm Hg/147–148 °C.

*4.2.1.6. 1-Allylcyclohexanecarbonitrile (**1h**)*[15]. Yield 87%; Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.12–1.28 (3H, m), 1.56–1.64 (2H, m), 1.66–1.75 (3H, m), 1.96 (2H, d, J=12.9 Hz), 2.28 (2H, d, J=7.4 Hz), 5.15–5.22 (2H, m), 5.84–5.94 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.0, 25.3, 35.3, 38.8, 44.6, 119.6, 123.3, 131.9; distillation: 5 mm Hg/95–100 °C.

*4.2.1.7. 2,2-Dimethylhex-5-enenitrile (**5**)*[19]. Yield 75%; Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.36 (6H, s), 1.60–1.64 (2H, m), 2.22–2.28 (2H, m), 5.01 (1H, d, J=10.2 Hz), 5.08 (1H, d, J=17.1 Hz), 5.77–5.87 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.7, 29.5, 32.2, 40.2, 115.5, 124.9, 137.0; distillation: 26 mm Hg/90–95 °C.

*4.2.2. Synthesis of 2,2-diallylpent-4-enenitrile (**1f**)*[20]. To a 200 mL round-bottom flask was added diisopropylamine (11.3 mL, 80.6 mmol) and *n*-BuLi (50 mL, 80 mmol) in THF (120 mL) and the reaction mixture was stirred at 0 °C. The lithium diisopropylamide (LDA) formed was used in three portions. Meanwhile, to a 300 mL round-bottomed flask was added acetonitrile (1.4 mL, 26 mmol) in THF (15 mL) and cooled down to −78 °C. After the first 1/3 portion of LDA was added dropwise, the mixture was stirred for 15 min. Allyl bromide (2.4 mL, 27.3 mmol) was then added dropwise and stirred for 30 min and allowed to warm up to room temperature. The reaction mixture was again cooled down to −78 °C for second addition. Second 1/3 portion of LDA was added and the mixture was stirred for 15 min. Allyl bromide (2.4 mL, 27.3 mmol) was then added dropwise and stirred for 30 min and allowed to warm up to room temperature. The reaction mixture was again cooled down to −78 °C for third addition. The last 1/3 portion of LDA was added and stirred for 15 min. Allyl bromide (2.4 mL, 27.3 mmol) was then added dropwise and the mixture was stirred overnight while warming up to room temperature.

The reaction may not have completed as two spots were observed on TLC after being stained with $KMnO_4$. A fourth 1/3 equivalent of LDA mixture was prepared as stated above [diisopropylamine (4.0 mL, 28.6 mmol) and *n*-BuLi (17.1 mL, 27.3 mmol, 1.6 M in hexane) in THF (25 mL)] and added to the reaction mixture at −78 °C. Allyl bromide (2.4 mL, 27.3 mmol) was then added dropwise and stirred for 1 h and allowed to warm up to room temperature. The reaction mixture was quenched with saturated aqueous NH_4Cl solution at room temperature. Organic materials were then extracted three times with 100 mL of Et_2O. The organic phase was washed with water and brine, and dried over $MgSO_4$. After filtration, the solvent was evaporated to give a crude mixture, which was purified by Kugelrohr distillation, affording product **1f** (3.41 g, 21.1 mmol) for 81% yield.

Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.27 (6H, d, J=7.3 Hz), 5.20 (3H, d, J=17.0 Hz), 5.25 (3H, d, J=10.2 Hz), 5.85 (ddd, J=7.3, 10.2, 17.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 40.0, 40.2, 120.3, 122.6, 131.6; distillation: 5 mm Hg/90–95 °C.

*4.2.3. Synthesis of 2-allylbenzonitrile (**8**)*[21,22]. To a 100 mL round-bottomed flask was added *n*-BuMgBr (10 mL, 1.2 M in THF, 12 mmol) and *n*-BuLi (15 mL, 1.6 M in hexane, 24 mmol) at 0 °C in THF (20 mL), and stirred for 10–15 min. The mixture was then cooled down to −78 °C and 2-bromobenzonitrile (1.82 g, 10 mmol) in THF (20 mL) was added dropwise. It was then allowed to stir at −78 °C for 1 h. Meanwhile, CuCN (269.6 mg, 3.01 mmol) and LiCl (254.3 mg, 6.00 mmol) in THF (3 mL) were added to a 15 mL round-bottomed flask and stirred at room temperature until all solids were dissolved and the mixture turned to blue color. The resulting CuCN•2LiCl solution and allyl bromide (3.5 mL, 40 mmol) were then added onto the reaction mixture at −78 °C, respectively. After 1 h stirring, the reaction mixture was then quenched with saturated aqueous NH_4Cl at room temperature. Organic materials were then extracted three times with 50 mL of Et_2O. The organic phase was washed with water and brine, and dried over $MgSO_4$. After filtration, the solvent was evaporated to give crude mixture, which was purified by Kugelrohr distillation to provide **1f** (0.93 g, 6.49 mmol) for 65% yield.

Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.62 (2H, d, J=6.6 Hz), 5.12 (1H, dd, J=1.4, 16.8 Hz), 5.16 (1H, dd, J=1.4, 8.6 Hz), 5.91–5.99 (1H, m), 7.28 (1H, d, J=7.7 Hz), 7.33 (1H, dd, J=7.7, 7.7 Hz), 7.53 (1H, dd, J=7.7, 7.7 Hz), 7.63 (1H, d, J=7.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 38.5, 112.5, 117.4, 117.9, 126.8, 129.7, 132.8 (2C overlapped), 134.9, 143.8; distillation: (4 mm Hg/93–95 °C).

4.3. Synthesis of bromomethyl cyclic imines: a typical procedure for synthesis of 4aa (Table 1, entry 3)

To a 10 mL Schlenk tube was added nitrile **1a** (41.6 mg, 0.338 mmol) in Et_2O (1.0 mL) and *p*-tolylmagnesium bromide (0.40 mL, 0.354 mmol, 0.89 M in Et_2O) was added slowly. The reaction was then heated at 60 °C for 1 h. After no starting material spot was observed on TLC, the mixture was quenched with distilled MeOH (60 μL) at 0 °C. DMF (4 mL) and $PhI(OAc)_2$ (165.0 mg, 0.512 mmol) was then added immediately. The mixture was further stirred at rt for 30 min. The mixture was then poured into 20 mL of saturated aqueous NH_4Cl upon completion and extracted three times with 30 mL of Et_2O. The organic phase was then washed with water, brine, and finally dried over $MgSO_4$. The organic extract was filtered and the solvent was evaporated to give crude mixture, which was purified by flash column chromatography (hexane/ethyl acetate=95:5) to provide product **4aa** (87.6 mg, 0.298 mmol) for 88% yield.

R_f=0.31 (hexane/ethyl acetate=9:1); yellow oil; FTIR (NaCl) 3028, 2965, 2930, 1605, 1564, 1466, 1450, 664 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.36 (3H, s), 1.45 (3H, s), 1.49 (3H, s), 1.82 (1H, d, J=13.3 Hz), 2.21 (1H, d, J=13.3 Hz), 2.37 (3H, s), 3.57 (2H, s), 7.18 (2H, d, J=8.1 Hz), 7.61 (2H, d, J=8.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.3, 27.5, 28.0, 29.3, 44.7, 50.5, 51.8, 71.9, 128.1, 128.9, 131.7, 139.7; ESIMS: found: m/z 294.0864. Calcd for $C_{15}H_{21}{}^{79}BrN$: $(M+H)^+$ 294.0857.

*4.3.1. 2,2,4,4-Tetramethyl-5-p-tolyl-3,4-dihydro-2H-pyrrole (**3**) (Table 1, entries 1 and 2).* R_f=0.35 (hexane/ethyl acetate=9:1); 49%

(38.5 mg); yellow oil; FTIR (NaCl) 3010, 2967, 2934, 1605, 1564, 1468, 1452 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.35 (6H, s), 1.37 (6H, s), 1.87 (2H, s), 2.36 (3H, s), 7.16 (2H, d, J=8.2 Hz), 7.59 (2H, d, J=8.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.3, 28.9, 30.8, 51.6, 54.5, 68.7, 128.0, 128.7, 132.2, 139.1, 176.1; ESIMS: found: m/z 216.1743. Calcd for $C_{15}H_{22}N$: $(M+H)^+$ 216.1752.

4.3.2. 2,2,4-Trimethyl-1-p-tolylpent-4-en-1-one (Table 1, entries 5 and 6). R_f=0.70 (hexane/ethyl acetate=9:1); 97% (78.0 mg); yellow oil; FTIR (NaCl) 3019, 2968, 2926, 1670, 1607, 1570, 1468, 1449 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.33 (6H, s), 1.62 (3H, s), 2.37 (3H, s), 2.58 (2H, s), 4.64 (1H, d, J=1.2 Hz), 4.80 (1H, d, J=1.2 Hz), 7.19 (2H, d, J=8.1 Hz), 7.66 (2H, d, J=8.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.3, 24.2, 26.8, 47.4, 48.5, 114.4, 128.3, 128.6, 135.8, 141.4, 142.4, 207.9; ESIMS: found: m/z 217.1596. Calcd for $C_{15}H_{21}O$: $(M+H)^+$ 217.1592.

*4.3.3. 2-(Chloromethyl)-2,4,4-trimethyl-5-phenyl-3,4-dihydro-2H-pyrrole (**4aa-Cl**) (Ref. 12; the product from **1a** and PhMgCl).* R_f=0.31 (hexane/ethyl acetate=9:1); 41% (34.0 mg); colorless oil; FTIR (NaCl) 3017, 2997, 1665, 1572, 1495, 1468, 1445, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.35 (3H, s), 1.44 (3H, s), 1.45 (3H, s), 1.80 (1H, d, J=13.3 Hz), 2.22 (1H, d, J=13.3 Hz), 3.65 (2H, dd, J=10.7, 13.7 Hz), 7.34–7.42 (3H, m), 7.65–7.68 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.9, 27.9, 29.2, 49.4, 52.0, 54.0, 72.7, 128.0, 128.2, 129.5, 134.7, 179.5; ESIMS: found: m/z 236.1201. Calcd for $C_{14}H_{19}ClN$: $(M+H)^+$ 236.1206.

*4.3.4. 2-(Bromomethyl)-5-(4-methoxyphenyl)-2,4,4-trimethyl-3,4-dihydro-2H-pyrrole (**4ab**).* R_f=0.40 (hexane/ethyl acetate=9:1); 92% (107.4 mg); white solid; mp 65–67 °C; FTIR (NaCl) 3017, 2965, 2936, 1609, 1568, 1464, 1443, 1169, 667 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.38 (3H, s), 1.47 (3H, s), 1.48 (3H, s), 1.82 (1H, d, J=13.3 Hz), 2.20 (1H, d, J=13.3 Hz), 3.56 (2H, s), 3.83 (3H, s), 6.89 (2H, d, J=8.7 Hz), 7.71 (2H, d, J=8.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.5, 28.1, 29.4, 44.8, 50.8, 51.6, 55.3, 71.6, 113.6, 126.9, 129.8, 160.8, 178.2; ESIMS: found: m/z 310.0811. Calcd for $C_{15}H_{21}{}^{79}BrNO$: $(M+H)^+$ 310.0807.

*4.3.5. 2-(Bromomethyl)-2,4,4-trimethyl-5-o-tolyl-3,4-dihydro-2H-pyrrole (**4ac**).* R_f=0.30 (hexane/ethyl acetate=9:1); 78% (85.9 mg); pale yellow solid; mp 53–55 °C; FTIR (NaCl) 3010, 2965, 2940, 1632, 1601, 1491, 1468, 1450, 665 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.24 (3H, s), 1.27 (3H, s), 1.52 (3H, s), 1.83 (1H, d, J=13.4 Hz), 2.24 (1H, d, J=13.4 Hz), 2.35 (3H, s), 3.60 (2H, dd, J=10.0, 19.4 Hz), 7.12–7.25 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.1, 27.3, 27.8, 28.4, 44.2, 48.0, 54.0, 73.4, 124.8, 127.6, 128.2, 130.5, 134.7, 136.2, 180.0; ESIMS: found: m/z 294.0858. Calcd for $C_{15}H_{21}{}^{79}BrN$: $(M+H)^+$ 294.0857.

*4.3.6. 2-(Bromomethyl)-5-(2,6-dimethylphenyl)-2,4,4-trimethyl-3,4-dihydro-2H-pyrrole (**4ad**).* R_f=0.31 (hexane/ethyl acetate=9:1); 12% (13.1 mg); colorless oil; FTIR (NaCl) 3019, 2965, 2932, 1632, 1599, 1468, 1447, 667 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.35 (3H, s), 1.44 (3H, s), 1.49 (3H, s), 1.82 (1H, d, J=13.3 Hz), 2.20 (1H, d, J=13.3 Hz), 2.33 (6H, s), 3.57 (2H, s), 7.03 (1H, br s), 7.26 (2H, br s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.3, 27.4, 27.9, 29.3, 44.6, 50.2, 52.0, 71.9, 125.8, 131.2, 134.6, 137.7, 179.8; ESIMS: found: m/z 308.1012. Calcd for $C_{16}H_{23}{}^{79}BrN$: $(M+H)^+$ 308.1014.

*4.3.7. 2-(Bromomethyl)-5-(4-chlorophenyl)-2,4,4-trimethyl-3,4-dihydro-2H-pyrrole (**4ae**).* R_f=0.38 (hexane/ethyl acetate=9:1); 70% (82.2 mg); white solid; mp 63–66 °C; FTIR (NaCl) 3019, 2965, 2930, 1638, 1522, 1476, 1423, 669 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.35 (3H, s), 1.44 (3H, s), 1.49 (3H, s), 1.83 (1H, d, J=13.3 Hz), 2.21 (1H, d, J=13.3 Hz), 3.57 (2H, dd, J=10.0 Hz, 19.1 Hz), 7.35 (2H, d, J=8.5 Hz), 7.64 (2H, d, J=8.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.4, 27.8, 29.2, 44.4, 50.3, 51.9, 72.1, 128.5, 129.5, 133.0, 135.7, 178.1; ESIMS: found: m/z 314.0307. Calcd for $C_{14}H_{18}{}^{79}Br{}^{35}ClN$: $(M+H)^+$ 314.0311.

*4.3.8. 2-(Bromomethyl)-2,4,4-trimethyl-5-(thiophen-2-yl)-3,4-dihydro-2H-pyrrole (**4af**).* R_f=0.50 (hexane/ethyl acetate=9:1); 61% (62.3 mg); colorless oil; FTIR (NaCl) 3019, 2967, 2930, 1593, 1466, 1450, 1431, 665 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.47 (3H, s), 1.49 (3H, s), 1.50 (3H, s), 1.83 (1H, d, J=13.4 Hz), 2.22 (1H, d, J=13.4 Hz), 3.54 (2H, dd, J=10.0, 17.8 Hz), 7.06 (1H, dd, J=3.6, 5.0 Hz), 7.38 (1H, d, J=5.0 Hz), 7.49 (1H, d, J=3.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.7, 28.3, 29.2, 44.3, 50.8, 51.5, 72.6, 127.4, 128.2, 128.7, 137.7, 172.6; ESIMS: found: m/z 286.0269. Calcd for $C_{12}H_{17}{}^{79}BrNS$: $(M+H)^+$ 286.0265.

*4.3.9. (E)-2-(Bromomethyl)-2,4,4-trimethyl-5-styryl-3,4-dihydro-2H-pyrrole (**4ag**).* R_f=0.40 (hexane/acetone=85:15); 55% (65.7 mg, purified with hexane/acetone=9:1); colorless oil; FTIR (NaCl) 3019, 2961, 2932, 1639, 1589, 1495, 1449, 696 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.32 (3H, s), 1.33 (3H, s), 1.46 (3H, s), 1.75 (1H, d, J=13.4 Hz), 2.12 (1H, d, J=13.4 Hz), 3.53 (2H, dd, J=10.0, 17.5 Hz), 6.68 (1H, d, J=16.3 Hz), 7.31–7.38 (3H, m), 7.49–7.53 (3H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.5, 27.8, 28.5, 44.4, 49.1, 50.7, 72.7, 119.5, 127.3, 128.7, 129.0, 136.0, 137.7, 177.3; ESIMS: found: m/z 306.0855. Calcd for $C_{16}H_{21}{}^{79}BrN$: $(M+H)^+$ 306.0857.

*4.3.10. 2-(Bromomethyl)-4,4-dimethyl-2-phenyl-5-p-tolyl-3,4-dihydro-2H-pyrrole (**4ba**).* R_f=0.63 (hexane/ethyl acetate=9:1); 76% (93.3 mg); white solid; mp 85–87 °C; FTIR (NaCl) 3019, 2965, 2930, 1634, 1522, 1476, 1423, 669 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.12 (3H, s), 1.41 (3H, s), 2.34 (1H, d, J=13.0 Hz), 2.39 (3H, s), 2.59 (1H, d, J=13.0 Hz), 3.75 (1H, d, J=10.2 Hz), 3.90 (1H, d, J=10.2 Hz), 7.22 (2H, d, J=8.1 Hz), 7.25–7.27 (1H, m), 7.31–7.35 (2H, m), 7.49 (2H, d, J=7.4 Hz), 7.71 (2H, d, J=8.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.4, 26.9, 27.7, 45.3, 50.7, 51.7, 76.2, 126.2, 127.1, 128.2, 128.3, 128.9, 131.7, 139.8, 145.6, 179.8; ESIMS: found: m/z 356.1013. Calcd for $C_{20}H_{23}{}^{79}BrN$: $(M+H)^+$ 356.1014.

*4.3.11. 2-(Bromo(phenyl)methyl)-4,4-dimethyl-5-p-tolyl-3,4-dihydro-2H-pyrrole (**4ca**-major).* R_f=0.48 (hexane/ethyl acetate=9:1); 76% (95.7 mg); colorless oil; FTIR (NaCl) 3028, 2959, 2926, 1601, 1562, 1495, 1452, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.24 (3H, s), 1.36 (3H, s), 1.60 (1H, dd, J=9.3, 12.8 Hz), 1.88 (1H, dd, J=6.9, 12.8 Hz), 2.37 (3H, s), 4.64 (1H, ddd, J=6.9, 7.3, 9.3 Hz), 4.97 (1H, d, J=7.3 Hz), 7.19 (2H, d, J=8.1 Hz), 7.27–7.31 (1H, m), 7.33–7.38 (2H, m), 7.55–7.57 (2H, m), 7.67 (2H, d, J=8.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.4, 26.3, 26.8, 46.4, 50.7, 58.7, 73.5, 128.1, 128.3, 128.5, 128.9, 131.4, 139.9, 140.0, 180.6; ESIMS: found: m/z 356.1018. Calcd for $C_{20}H_{23}{}^{79}BrN$: $(M+H)^+$ 356.1014.

*4.3.12. 2-(Bromo(phenyl)methyl)-4,4-dimethyl-5-p-tolyl-3,4-dihydro-2H-pyrrole (**4ca**-minor).* R_f=0.38 (hexane/ethyl acetate=9:1); 11% (14.7 mg); colorless oil; FTIR (NaCl) 3028, 2959, 2926, 1601, 1562, 1495, 1452, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.35 (3H, s), 1.39 (3H, s), 2.09 (2H, dd, J=2.1, 8.5 Hz), 2.36 (3H, s), 4.52 (1H, ddd, J=5.4, 7.8, 7.8 Hz), 5.49 (1H, d, J=5.4 Hz), 7.18 (2H, d, J=7.9 Hz), 7.26–7.37 (3H, m), 7.49 (2H, dd, J=1.2, 8.2 Hz), 7.63 (2H, d, J=8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.4, 26.7, 45.4, 50.5, 60.6, 73.1, 128.1, 128.2, 128.3, 128.5, 128.9 (2C, overlapped), 131.2, 140.1, 180.9; ESIMS: found: m/z 356.1018. Calcd for $C_{20}H_{23}{}^{79}BrN$: $(M+H)^+$ 356.1014.

*4.3.13. 2-(2-Bromopropan-2-yl)-4,4-dimethyl-5-p-tolyl-3,4-dihydro-2H-pyrrole (**4da**).* R_f=0.63 (hexane/ethyl acetate=9:1); 65% (73.4 mg); white solid; mp 105–107 °C; FTIR (NaCl) 3019, 2968, 2928, 1634, 1605, 1562, 1464, 669 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.36 (3H, s), 1.44 (3H, s), 1.89 (3H, s), 1.93–1.99 (3H, s, 1H,

overlapped), 2.08 (1H, dd, *J*=6.9, 12.6 Hz), 2.39 (3H, s), 4.03 (1H, dd, *J*=6.9, 9.3 Hz), 7.20 (1H, d, *J*=8.1 Hz), 7.66 (2H, d, *J*=8.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.3, 26.6, 26.7, 31.0, 32.3, 45.3, 50.5, 70.8, 77.9, 128.0, 128.9, 131.8, 139.7, 180.3; ESIMS: found: *m*/*z* 308.1024. Calcd for $C_{16}H_{23}{}^{79}BrN$: $(M+H)^+$ 308.1014.

*4.3.14. 2-(Bromomethyl)-4,4-dimethyl-5-p-tolyl-3,4-dihydro-2H-pyrrole (**4ea**).* R_f=0.20 (hexane/ethyl acetate=9:1); 75% (80.1 mg); yellow oil; FTIR (NaCl) 3030, 2959, 2928, 1599, 1560, 1464, 1452, 665 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.38 (3H, s), 1.39 (3H, s), 1.78 (1H, dd, *J*=8.7, 12.7 Hz), 2.14 (1H, dd, *J*=6.9, 12.7 Hz), 2.37 (3H, s), 3.59 (1H, dd, *J*=7.4, 9.8 Hz), 3.79 (1H, dd, *J*=4.2, 9.8 Hz), 4.31–4.36 (1H, m), 7.18 (2H, d, *J*=8.0 Hz), 7.62 (2H, d, *J*=8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.4, 26.4, 27.0, 38.0, 46.6, 50.9, 68.2, 127.9, 128.9, 131.4, 139.9, 181.1; ESIMS: found: *m*/*z* 280.0712. Calcd for $C_{14}H_{19}{}^{79}BrN$: $(M+H)^+$ 280.0701.

*4.3.15. 4,4-Diallyl-2-(bromomethyl)-5-p-tolyl-3,4-dihydro-2H-pyrrole (**4fa**).* R_f=0.21 (hexane/ethyl acetate=9:1); 71% (83.4 mg); yellow oil; FTIR (NaCl) 3030, 2959, 2920, 1638, 1601, 1562, 1447, 1418, 665 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.91 (1H, dd, *J*=8.1, 13.2 Hz), 2.12 (1H, dd, *J*=7.7, 13.3 Hz), 2.34–2.44 (2H, m), 2.38 (3H, s), 2.55–2.61 (2H, m), 3.50 (1H, dd, *J*=7.4, 9.7 Hz), 3.74 (1H, dd, *J*=4.4, 9.7 Hz), 4.23–4.28 (1H, m), 5.01–5.15 (4H, m), 5.55–5.66 (1H, m), 5.67–5.77 (1H, m), 7.19 (2H, d, *J*=7.9 Hz), 7.65 (2H, d, *J*=7.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.4, 38.0, 39.2, 43.0, 43.4, 69.5, 118.7, 118.8, 127.9, 129.1, 131.8, 133.6, 134.0, 140.1, 177.8; ESIMS: found: *m*/*z* 332.1018. Calcd for $C_{18}H_{23}{}^{79}BrN$: $(M+H)^+$ 332.1014.

*4.3.16. 2-(Bromomethyl)-4,4-diphenyl-5-p-tolyl-3,4-dihydro-2H-pyrrole (**4ga**).* R_f=0.43 (hexane/ethyl acetate=9:1); 57% (103.1 mg); white solid; mp 158–160 °C; FTIR (NaCl) 3019, 2965, 2936, 1638, 1599, 1493, 1449, 1423, 669 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.25 (3H, s), 2.73 (1H, dd, *J*=9.3, 12.9 Hz), 2.99 (1H, dd, *J*=6.2, 12.9 Hz), 3.76–3.84 (2H, m), 4.18–4.23 (1H, m), 6.94 (2H, d, *J*=7.8 Hz), 7.17–7.40 (10H, m), 7.45 (2H, d, *J*=7.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.3, 37.3, 53.3, 68.2, 68.7, 126.5, 127.0, 128.3, 128.3, 128.6, 128.7, 129.2, 129.6, 131.2, 140.2, 142.0, 144.6, 176.7; ESIMS: found: *m*/*z* 404.1010. Calcd for $C_{24}H_{23}{}^{79}BrN$: $(M+H)^+$ 404.1014.

*4.3.17. 3-(Bromomethyl)-1-p-tolyl-2-azaspiro[4.5]dec-1-ene (**4ha**).* R_f=0.19 (hexane/ethyl acetate=9:1); 83% (94.8 mg); yellow oil; FTIR (NaCl) 3019, 2930, 1601, 1560, 1447, 664 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.14–1.85 (11H, m), 2.37 (3H, s), 2.41 (1H, dd, *J*=7.4, 13.1 Hz), 3.62 (1H, dd, *J*=7.1, 9.9 Hz), 3.79 (1H, dd, *J*=4.0, 9.9 Hz), 4.32–4.37 (1H, m), 7.18 (2H, d, *J*=7.8 Hz), 7.48 (2H, d, *J*=7.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.3, 23.1, 23.3, 25.5, 32.3, 35.4, 38.4, 39.6, 56.9, 68.9, 128.0, 128.8, 132.4, 139.2, 182.2; ESIMS: found: *m*/*z* 320.1013. Calcd for $C_{17}H_{23}{}^{79}BrN$: $(M+H)^+$ 320.1014.

*4.3.18. 2-(Bromomethyl)-5-p-tolyl-3,4-dihydro-2H-pyrrole (**4ia**).* R_f=0.31 (hexane/ethyl acetate=9:1); 64% (61.5 mg); white solid; mp 75–77 °C; FTIR (NaCl) 3019, 2961, 1611, 1568, 1456, 1430, 669 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.86–1.95 (1H, m), 2.22–2.31 (1H, m), 2.39 (3H, s), 2.89–2.98 (1H, m), 3.05–3.13 (1H, m), 3.61 (1H, dd, *J*=6.6, 10.0 Hz), 3.79 (1H, dd, *J*=7.9, 10.0 Hz), 4.54–4.61 (1H, m), 7.22 (2H, d, *J*=8.0 Hz), 7.73 (2H, d, *J*=8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.5, 27.2, 35.5, 38.3, 73.1, 127.8, 129.2, 131.4, 141.1, 174.4; ESIMS: found: *m*/*z* 252.0389. Calcd for $C_{12}H_{15}{}^{79}BrN$: $(M+H)^+$ 252.0388.

*4.3.19. 4-Bromo-2-(bromomethyl)-5-p-tolyl-3,4-dihydro-2H-pyrrole (**4ia**-Br).*[23] R_f=0.20 (hexane/ethyl acetate=9:1); 8% (10.3 mg); white solid; mp 78–80 °C; FTIR (NaCl) 3015, 2980, 2967, 1603, 1566, 1431, 667 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.32–2.40 (1H, m), 2.41 (3H, s), 2.67 (1H, dd, *J*=6.2, 14.7 Hz), 3.76 (1H, dd, *J*=6.2, 10.3 Hz), 3.87 (1H, dd, *J*=4.1, 10.3 Hz), 4.59–4.65 (1H, m), 5.29 (1H, d, *J*=7.0 Hz), 7.25 (2H, d, *J*=8.2 Hz), 7.83 (2H, d, *J*=8.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.5, 36.0, 41.0, 48.2, 70.8, 128.3, 128.4, 129.4, 141.9, 171.9; ESIMS: found: *m*/*z* 329.9492. Calcd for $C_{12}H_{14}{}^{79}Br_2N$: $(M+H)^+$ 329.9493.

*4.3.20. 2-(Bromomethyl)-5,5-dimethyl-6-p-tolyl-2,3,4,5-tetrahydropyridine (**6**).* R_f=0.10 (hexane/ethyl acetate=9:1); 14% (14.7 mg); colorless oil (very unstable and decomposed to a complex mixture at room temperature); FTIR (NaCl) 3010, 2959, 2928, 1632, 1510, 1456, 665 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.12 (3H, s), 1.19 (3H, s), 1.69 (1H, dd, *J*=4.3, 9.7 Hz), 1.73–1.85 (1H, m), 1.90–1.94 (1H, m), 2.34 (3H, s), 3.65 (1H, dd, *J*=6.6, 9.7 Hz), 3.75 (1H, dd, *J*=3.2, 9.7 Hz), 3.78–3.82 (1H, m), 7.13 (2H, d, *J*=7.9 Hz), 7.18 (2H, d, *J*=7.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.2, 23.4, 27.2, 28.3, 35.6, 35.7, 39.8, 58.8, 127.5, 128.4, 137.4, 138.1, 178.0; ESIMS: found: *m*/*z* 294.0851. Calcd for $C_{15}H_{21}{}^{79}BrN$: $(M+H)^+$ 294.0857.

*4.3.21. 4-Bromo-2,2-dimethyl-1-p-tolylhex-5-en-1-imine (**7**).* R_f=0.42 (hexane/ethyl acetate=9:1); 13% (17.0 mg); colorless oil; FTIR (NaCl) 3009, 2961, 2928, 1641, 1599, 1464, 1452, 1420, 1406, 667 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.37 (6H, s), 1.73 (1H, dd, *J*=8.4, 12.5 Hz), 2.14 (1H, dd, *J*=7.2, 12.5 Hz), 2.37 (3H, s), 4.55 (1H, dd, *J*=7.2, 14.9 Hz), 5.14 (1H, ddd, *J*=1.4, 1.4, 10.2 Hz), 5.28 (1H, ddd, *J*=1.4, 1.4, 17.1 Hz), 6.04 (1H, ddd, *J*=6.6, 10.2, 17.1 Hz), 7.18 (2H, d, *J*=8.1 Hz), 7.66 (2H, d, *J*=8.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.3, 25.9, 27.2, 48.0, 50.3, 69.7, 114.8, 128.0, 128.8, 131.5, 139.7, 140.5, 179.9; ESIMS: found: *m*/*z* 294.0861. Calcd for $C_{15}H_{21}{}^{79}BrN$: $(M+H)^+$ 294.0857.

*4.3.22. 3-(Bromomethyl)-1-p-tolyl-3,4-dihydroisoquinoline (**9a**).* R_f=0.20 (hexane/ethyl acetate=9:1); 64% (70.4 mg); white solid (mg); mp 80–82 °C; FTIR (NaCl) 3019, 2959, 1607, 1560, 1425, 669 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.40 (3H, s), 2.77 (1H, dd, *J*=12.7, 15.4 Hz), 3.07 (1H, dd, *J*=4.7, 15.4 Hz), 3.55 (1H, dd, *J*=8.9, 9.3 Hz), 3.78–3.85 (1H, m), 3.88 (1H, dd, *J*=4.8, 9.7 Hz), 7.22–7.31 (5H, m), 7.40 (1H, ddd, *J*=1.3, 7.2, 7.2 Hz), 7.49 (2H, dd, *J*=8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.4, 30.2, 36.9, 58.5, 126.8, 127.9, 128.2, 128.8, 128.9, 129.0, 131.0, 135.5, 137.7, 139.7, 167.5; ESIMS: found: *m*/*z* 314.0546. Calcd for $C_{17}H_{17}{}^{79}BrN$: $(M+H)^+$ 314.0544.

*4.3.23. 3-(Bromomethyl)-1-(4-methoxyphenyl)-3,4-dihydroisoquinoline (**9b**).* R_f=0.41 (hexane/ethyl acetate=9:1); 45% (56.1 mg); yellow oil; FTIR (NaCl) 3011, 2938, 1649, 1605, 1572, 1462, 1425, 1182, 662 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.76 (1H, dd, *J*=12.7, 15.3 Hz), 3.08 (1H, dd, *J*=4.6, 15.3 Hz), 3.55 (1H, dd, *J*=8.9, 9.6 Hz), 3.76–3.84 (1H, m), 3.86 (3H, s), 3.88 (1H, dd, *J*=4.9, 9.6 Hz), 6.95 (2H, d, *J*=8.7 Hz), 7.28 (1H, d, *J*=7.9 Hz), 7.32 (2H, dd, *J*=6.3, 6.3 Hz), 7.42 (1H, dd, *J*=6.3, 7.9 Hz), 7.58 (2H, d, *J*=8.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 30.3, 36.8, 55.4, 58.4, 113.6, 126.8, 127.9, 128.3, 128.8, 130.6, 130.7, 131.0, 137.8, 161.0, 167.0; ESIMS: found: *m*/*z* 330.0495. Calcd for $C_{17}H_{17}{}^{79}BrNO$: $(M+H)^+$ 330.0494.

*4.3.24. 3-(Bromomethyl)-1-o-tolyl-3,4-dihydroisoquinoline (**9c**).* R_f=0.43 (hexane/ethyl acetate=9:1); 62% (69.5 mg); colorless oil; FTIR (NaCl) 3019, 2957, 1612, 1568, 1485, 1454, 1425, 665 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.14 (3H, s), 2.89 (1H, dd, *J*=12.8, 15.6 Hz), 3.11 (1H, dd, *J*=4.9, 15.6 Hz), 3.64 (1H, dd, *J*=8.4, 9.3 Hz), 3.89–3.98 (2H, m), 6.94 (1H, d, *J*=7.7 Hz), 7.18 (1H, dd, *J*=7.5, 7.5 Hz), 7.22–7.34 (5H, m), 7.38 (1H, dd, *J*=7.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.7, 29.9, 37.2, 58.3, 125.8, 127.2, 127.6, 127.9, 128.5, 128.7, 129.3, 130.4, 131.2, 135.8, 136.3, 138.3, 168.8; ESIMS: found: *m*/*z* 314.0550. Calcd for $C_{17}H_{17}{}^{79}BrN$: $(M+H)^+$ 314.0544.

*4.3.25. 3-(Bromomethyl)-1-(2,6-dimethylphenyl)-3,4-dihydroisoquinoline (**9d**).* R_f=0.36 (hexane/ethyl acetate=9:1); 53%

(60.0 mg); brown solid; mp 122–124 °C; FTIR (NaCl) 3017, 2951, 1616, 1570, 1464, 1429, 665 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.04 (3H, s), 2.20 (3H, s), 2.98 (1H, dd, J=12.7, 15.8 Hz), 3.10 (1H, dd, J=5.4, 15.8 Hz), 3.71 (1H, dd, J=7.9, 10.0 Hz), 3.90 (1H, dd, J=4.0, 10.0 Hz), 3.99–4.07 (1H, m), 6.87 (1H, d, J=7.6 Hz), 7.05 (1H, d, J=7.5 Hz), 7.10 (1H, d, J=7.5 Hz), 7.16 (1H, dd, J=7.6, 7.6 Hz), 7.19 (1H, dd, J=7.6, 7.6 Hz), 7.29 (1H, d, J=7.4 Hz), 7.38 (1H, dd, J=7.4, 7.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.4, 19.5, 29.7, 37.6, 57.9, 126.7, 127.5, 127.6, 127.7, 128.0, 128.1, 128.8, 131.4, 135.3, 135.7, 136.1, 137.8, 168.8; ESIMS: found: m/z 328.0706. Calcd for $C_{18}H_{19}{}^{79}BrN$: $(M+H)^+$ 328.0701.

*4.3.26. 3-(Bromomethyl)-1-(4-chlorophenyl)-3,4-dihydroisoquinoline (**9e**).* R_f=0.39 (hexane/ethyl acetate=9:1); 59% (72.0 mg); white solid; mp 81–83 °C; FTIR (NaCl) 3019, 2963, 1607, 1560, 1489, 1427, 669 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.78 (1H, dd, J=12.9, 15.4 Hz), 3.07 (1H, dd, J=4.6, 15.4 Hz), 3.58 (1H, dd, J=8.1, 9.5 Hz), 3.78–3.85 (1H, m), 3.88 (1H, dd, J=4.9, 9.5 Hz), 7.23–7.33 (3H, m), 7.40–7.44 (2H, d, J=8.4 Hz, 1H, m, overlapped), 7.56 (1H, d, J=8.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 30.2, 36.8, 58.7, 127.0, 127.9, 128.0, 128.4, 128.5, 130.4, 131.3, 135.8, 136.8, 137.7, 166.6; ESIMS: found: m/z 334.0000. Calcd for $C_{16}H_{14}{}^{79}Br^{35}ClN$: $(M+H)^+$ 333.9998.

*4.3.27. 3-(Bromomethyl)-1-(thiophen-2-yl)-3,4-dihydroisoquinoline (**9f**).* R_f=0.64 (hexane/ethyl acetate=9:1); 65% (76.0 mg); yellow oil; FTIR (NaCl) 3011, 2957, 1601, 1591, 1557, 1520, 1452, 1429, 664 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.75 (1H, dd, J=12.0, 15.2 Hz), 3.07 (1H, dd, J=4.2, 15.2 Hz), 3.52 (1H, dd, J=8.7, 9.3 Hz), 3.79–3.88 (2H, m), 7.11 (1H, dd, J=3.6, 5.0 Hz), 7.35 (2H, dd, J=7.7, 7.7 Hz), 7.42–7.47 (3H, m), 7.70 (1H, d, J=7.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 30.2, 36.2, 58.1, 127.1 (2C, overlapped), 127.3, 127.6, 128.1, 128.4, 128.5, 130.4, 131.3, 135.8, 136.8, 137.7, 166.6; ESIMS: found: m/z 305.9956. Calcd for $C_{14}H_{13}{}^{79}BrNS$: $(M+H)^+$ 305.9952.

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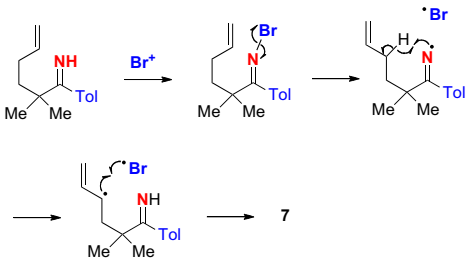
12. When PhMgCl was utilized with carbonitrile **1a** under the present reaction conditions, the desired chloromethyl dihydropyrrole **4aa-Cl** was obtained in only 41% yield.
13. Tetrahydropyridine **6** was found to be very unstable and decompose to a complex mixture at room temperature.
14. Brominated *N*–H imine 7 might be formed via allylic radical bromination, although we are not certain as to the detailed reaction course. For example, it is speculated that formation of *N*-bromoimine followed by its thermal hemolytic cleavage could generate iminyl and bromine radicals as shown below. 1,5-Hydrogen shift by radical abstraction of the allylic hydrogen with the iminyl radical could afford the allylic radical that could be trapped by the resulting bromine radical to give **7**.



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