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Catalytic imino Diels–Alder reaction by triflic imide and its application to one-pot synthesis from three components

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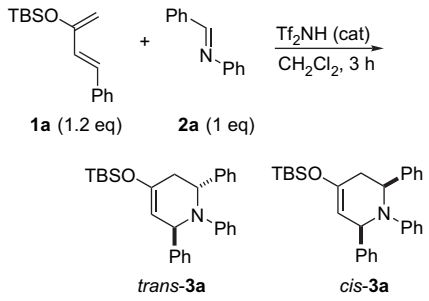
Abstract—An imino Diels–Alder reaction of 2-siloxydienes with aldimines catalyzed by triflic imide (Tf_2NH; 0.1∼10 mol % amount) has been developed leading to substituted piperidin-4-ones. Tf_2NH catalyst is compatible with basic functions, such as pyridine and indole rings in the imino Diels–Alder reaction. Furthermore, X-ray crystallographic analysis indicates that *trans*-2,6-diphenyl-4-piperidinone **4a** obtained by this reaction has a unique conformation in the solid state.

1. Introduction

The piperidine ring system is a ubiquitous structural motif of naturally occurring alkaloids, biologically active synthetic molecules, and organic fine chemicals.[1] The imino Diels–Alder reaction is one of the most powerful and useful tools used to prepare heterocycles containing the piperidine nucleus.[2,3] There have been many studies on the imino Diels–Alder reaction, which is typically classified into two variants. One is the reaction of all-carbon 1,3-dienes (C=C–C=C synthon) with imines (C=N synthon). The other is the cycloaddition of azadienes (C=N–C=C or N=C–C=C synthons) with dienophilic alkenes (C=C synthon). The former strategy has been more extensively studied because a variety of imine dienophiles are readily available by the reaction of corresponding aldehydes or ketones with amines. The literature contains many studies of the imino Diels–Alder reaction of imines with Danishefsky's dienes (1-alkoxy-3-siloxybutadienes)[4] to give 2,3-dehydropiperidin-4-ones. Numerous kinds of Lewis acids,[5] including chiral catalysts and Brønsted acids[6] have been developed in the reaction of Danishefsky's dienes. On the contrary, few studies have focused on the reaction of less active 2-siloxydienes with imines, which affords substituted piperidin-4-ones (Scheme 1).[7,8] Although several Lewis acids have been found to activate the imino Diels–Alder reaction of 2-siloxydienes, to the best of our knowledge, the Brønsted acid-catalyzed reaction has not been reported yet.[9] Substituted piperidin-4-one produced in the above reaction would be useful in medicinal chemistry.[10]



Scheme 1.

We have recently reported that triflic imide (Tf_2NH) works as a good catalyst for (2+2)-cycloaddition of silyl enol ethers with α,β-unsaturated esters even in low catalyst loading (∼1 mol %).[11] Furthermore, we have found that Tf_2NH also catalyzes various cycloaddition reactions, such as (2+2)-cycloaddition of allylsilane with acrylates,[12] and the Diels–Alder reaction of 2-siloxydiene and α,β-unsaturated carbonyl compounds.[13,14] In these contexts, silyl triflic imides (R_3SiNTf_2), which are generated from Tf_2NH and silyl enol ether substances, act as an active catalyst of the above cycloadditions.[10,11,14b] Herein, we report the Tf_2NH-catalyzed imino Diels–Alder reaction of 2-siloxydiene with aldimine to give functionalized piperidin-4-one derivatives and its application to the one-pot synthesis of piperidin-4-ones from 2-siloxydiene, aldehyde, and amine.

Keywords: Imino Diels–Alder reaction; Substituted piperidines; Triflic imide; Three component reaction.
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2. Results and discussion

2.1. Imino Diels–Alder reaction of 2-siloxydienes with aldimines

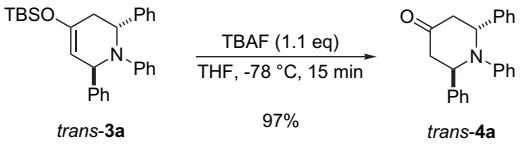
At the outset of this study, the imino Diels–Alder reaction of 2-siloxy-1,3-butadiene **1a** (1.2 equiv) with benzaldimine (**2a**) (1.0 equiv) in the presence of Tf_2NH was examined under various conditions (Scheme 1). With a 2 mol % of Tf_2NH in CH_2Cl_2 at ambient temperature, a diastereomeric mixture of 2,6-diphenyl-4-siloxy-3,4-didehydropiperidine **3a** was obtained in 85% yield, and the diastereomeric ratio was determined to be 4:1 (trans–cis) by ^1H NMR (Table 1, entry 1), whereas no reaction occurred in the absence of the catalyst (entry 2). It is noteworthy that the reaction proceeds smoothly even with 0.1 mol % catalyst loading (entry 3). However, when a stoichiometric amount of Tf_2NH was used, decomposition of siloxydiene owing to its protodesilylation was observed prior to promotion of the desired cycloaddition (entry 4). The Tf_2NH-catalyzed reaction can be successfully performed in various solvents, such as toluene, THF, and acetonitrile (entries 5–7), and the diastereomeric ratio of **3a** was similar within a range of 3:1–4:1 in these solvents. When the reaction of **1a** with **2a** was conducted in CH_3CN, **3a**, which is hardly soluble in the solvent, precipitated. It is noteworthy that **3a** can be isolated with ease only by filtration even in a multi-gram scale (entry 7). The reaction temperature does not affect the diastereomeric ratio, and no desired product was obtained at high temperature (80 °C in a sealed tube) (entries 8 and 9).

The major diastereomer of **3a** was almost quantitatively converted into piperidin-4-one **4a**, which could be crystallized from CH_2Cl_2–hexanes, by treatment with TBAF at −78 °C (Scheme 2). Neither epimerization nor retro-Michael reaction was observed in the process. X-ray crystallographic analysis determined that compound **4a**, derived from the major diastereomer of **3a**, possesses trans-oriented 2,6-substituents (Fig. 1). Fascinatingly, the crystallized form of *trans*-**4a** exists as an unusual conformation. Namely, both phenyl substituents at the C(2) and C(6) positions are oriented axially, and the conformation of the six-membered piperidine ring is a twist-boat form. Three continuous bulky phenyl substituents at N(1), C(2), and C(6) of *trans*-**4a** would prevent the chair-conformation with equatorially oriented bulky substituents at C(2) and C(6).

Table 1. Imino Diels–Alder reaction of **1a** with **2a**

Entry	Cat. (mol %)	Solvent	Temp (°C)	Time (h)	% Yield (trans–cis)[b]
1	Tf_2NH (2.0)	CH_2Cl_2	rt	3	85 (80:20)
2	None	CH_2Cl_2	rt	72	0 (—)
3	Tf_2NH (0.1)	CH_2Cl_2	rt	3	80 (75:25)
4	Tf_2NH (100)	CH_2Cl_2	rt	3	0 (—)
5	Tf_2NH (2.0)	THF	rt	3	69 (63:37)
6	Tf_2NH (2.0)	Toluene	rt	3	82 (67:33)
7	Tf_2NH (2.0)	CH_3CN	rt	0.3	75 (82:18)
8	Tf_2NH (2.0)	CH_2Cl_2	−78	3	61 (79:21)
9[a]	Tf_2NH (2.0)	CH_2Cl_2	80	3	0 (—)

[a] Reaction was carried out in a sealed tube.
[b] Diastereomeric ratios were determined by ^1H NMR.



Scheme 2.

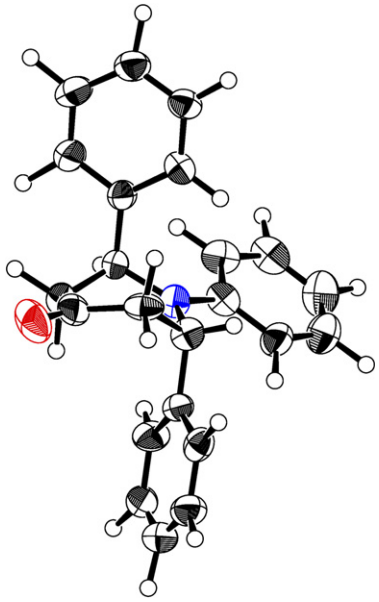
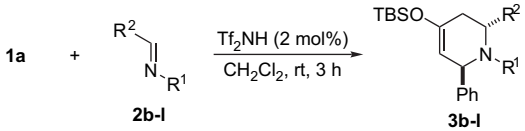


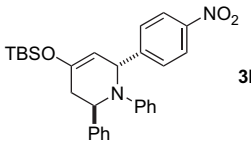
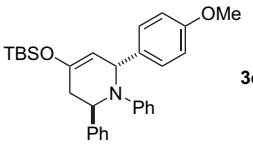
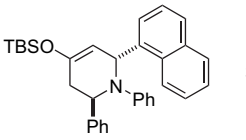
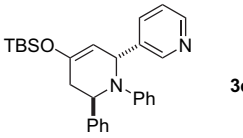
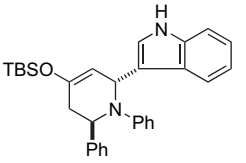
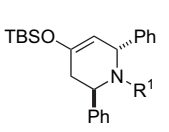
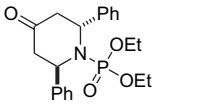
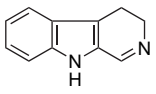
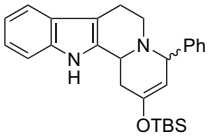
Figure 1. Crystallographic structure of *trans*-**4a** (ORTEP drawing).

Next, the imino Diels–Alder reactions of **1a** with various aldimines **2b**–**2l** under optimal conditions (2 mol % Tf_2NH, CH_2Cl_2, rt) were examined (Scheme 3). Electron-poor (**2b**), electron-rich aromatic (**2c**), and naphthyl substituted (**2d**) aldimines also afforded desired adducts in good yields with a similar stereoselectivity (Table 2, entries 1–3). Substrates with a heterocyclic ring, such as pyridine (**2e**) and indole (**2f** and **2l**), underwent cycloaddition in the presence of Tf_2NH, but their reaction rates were decreased (entries 4, 5, and 11). No protection is necessary for indole N–H in the Tf_2NH-catalyzed reaction (entries 5 and 11). Further studies revealed that aldimines obtained from benzylamine (**2g**) and allylamine (**2h**) afforded the corresponding piperidinone derivatives **3g** and **3h** in good yields, respectively (entries 6 and 7). On the contrary, electrophilic aldimines, which possess an electron-withdrawing function on the nitrogen atom, afforded poor results. Reaction with acyl imine **2i** and sulfonyl imine **2j** resulted in the formation of many side products although trace amounts of cycloadducts **3i** and **3j**, respectively, were produced (entries 8 and 9). The strongly electrophilic imines, such as **2i** and **2j**, may be too reactive to selectively promote the desired cycloaddition in the presence of the Tf_2NH catalyst. Phosphonyl imine **2k** promoted the imino Diels–Alder reaction. However, desilylated piperidinone **4k** was obtained in a moderate yield (entry 10) because of the



Scheme 3.

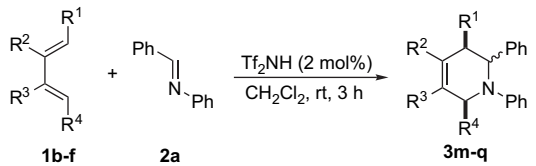
Table 2. Imino Diels–Alder reaction of **1a** with various aldimines

Entry	Imine **2**	Product	% Yield (trans–cis)[e]
1	**2b** (Ph, *p*-$NO_2C_6H_4$)	 **3b**	85 (75:25)
2	**2c** (Ph, *p*-$MeOC_6H_4$)	 **3c**	67 (77:23)
3	**2d** (Ph, 1-naphthyl)	 **3d**	73 (84:16)
4[a]	**2e** (Ph, 3-pyridyl)	 **3e**	61 (73:27)
5[b]	**2f** (Ph, 3-indolyl)	 **3f**	35 (81:19)
6[c]	**2g** (Bn, Ph)	 **3g** (R^1 = Bn)	89 (85:15)
7[c]	**2h** (Allyl, Ph)	**3h** (R^1 = allyl)	88 (80:20)
8	**2i** (CO_2Et, Ph)	**3i** (R^1 = CO_2Et)	Trace (—)
9	**2j** (Ts, Ph)	**3j** (R^1 = Ts)	32 (89:11)
10	**2k** ($PO(OEt)_2$, Ph)	 **4k**	62 (63:37)
11[d]	 **2l**	 **3l**	60 (60:40)[f]

[a] Cat. 5 mol %, 5 h.
[b] Cat. 6 mol %, 24 h.
[c] Cat. 5 mol %
[d] Cat. 10 mol %, CH_3CN, 8 h.
[e] Diastereomeric ratios were determined by ^1H NMR.
[f] Stereochemistry of each diastereomer was not assigned.

poor stability of the corresponding silyl enol ether **3k** (the reason is still unclear).

Results of the imino Diels–Alder reaction of various 2-siloxydienes **1b–1e** and 2-methoxydiene **1f** with aldimine **2a** to give a variety of substituted piperidin-4-ones are summarized in Scheme 4 and Table 3. Whereas 3-methyl-2-siloxydiene **1b** efficiently reacted (86% yield, entry 1), reactions with 1-methyl-2-siloxydiene **1c** and 2-*tert*-butyldimethylsiloxy-1,3-butadiene (**1d**) required 5 mol % of catalyst for complete consumption of aldimine **2a** (entries 2 and 3). Notably, *trans*-**3n** was exclusively obtained as a sole diastereomer in 69% yield, although a mixture of the geometrical isomer (cis–trans=ca. 5:2) of **1c** was conducted in the reaction



Scheme 4.

Table 3. Imino Diels–Alder reaction of **2a** with various dienes

Entry	Diene (R^1, R^2, R^3, R^4)	Cat. (mol %)	Product	% Yield (dr)[a]
1	**1b** (H, OTBS, Me, H)	2	**3m**	86
2	**1c** (Me, OTBS, H, H)	5	**3n**	69 (100:0)[b]
3	**1d** (H, OTBS, H, H)	5	**3o**	69
4	**1e** (H, OTBS, H, OMe)	2	**3p**	0 (—)
5	**1f** (H, OMe, H, Ph)	2	**3q**	48 (79:21)[c]

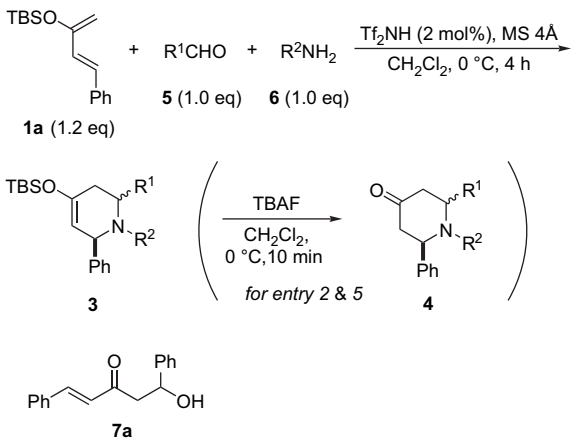
[a] Diastereomeric ratios were determined by ^{1}H NMR.
[b] The relative configuration of the major diastereomer was assigned as *trans*-**3n** because both protons at C(5) and C(6) exist on an equatorial position ($J_{[H(C5)–H(C6)]}$=3.1 Hz in ^{1}H NMR).
[c] The relative configuration of major diastereomer was tentatively assigned as *trans*-**3q** by an analogy to **3a**.

(entry 3). The mechanistic detail including the stereochemical outcome is under investigation. Danishefsky diene **1e** was evaluated as a more electron-rich diene partner, but only decomposition of **1e** by Tf_2NH was observed (entry 4).

We initially considered that the actual catalyst of the imino Diels–Alder reaction would be R_3SiNTf_2, which is formed from Tf_2NH and siloxydiene in situ.[11] However, the reaction of 2-methoxydiene **1f** occurred in the presence of 2 mol % of catalyst to give **3q** in moderate yield (entry 5). This observation indicates that Tf_2NH (pK_a=1.7 in water)[15] directly activates aldimines as a Brønsted acid in the imino Diels–Alder reaction. The action of the Tf_2NH catalyst in the reaction is different from that in the (2+2)-cycloaddition, which was recently established by our group.[11] The following experiment also suggests the catalytic role of Tf_2NH. Thus, when the mixture of **1a** and **2a** was treated with pre-organized $TBSTf_2$ (50 mol %), which was prepared from TBSCl and $AgNTf_2$ in CH_2Cl_2, decomposition of silyl enol ether **1a** quickly occurred prior to imino Diels–Alder reaction with **2a**.

2.2. Application to multicomponent reaction

We have further assessed the one-pot multicomponent reaction (MCR) for the formation of substituted piperidin-4-ones derivatives starting from three components: siloxydiene **1**, aldehyde **5**, and amine **6** (Scheme 5).[16] When a mixture of the whole substrates, **1a**, benzaldehyde (**5a**), and aniline (**6a**) (molar ratio: **1a**:**5a**:**6a**=1.2:1:1), was treated with Tf_2NH (2 mol %), the desired MCR product **3a** was isolated in ca. 20% yield, but the major product was an aldol adduct



Scheme 5.

7a (ca. 60% yield). The result suggests that the undesired reaction of aldehyde **5** with silyl enol ether **1** (Mukaiyama-aldol reaction) competes with imine formation of **5** with amine **6**. On the other hand, sequential addition of the substrates as an alternative protocol was successful (Table 4, entry 1). Namely, after pre-treatment with aldehyde **5a** and amine **6a** in the presence of molecular sieves 4 Å (MS4A) in CH_2Cl_2 for 20 min at ambient temperature, siloxydiene **1a** and Tf_2NH (4 mol %) were added to the resulting mixture at 0 °C to give the desired product **3a** selectively in 78% yield (no formation of **7a** was observed). After completion of the above three component reaction, successive treatment with tetrabutylammonium fluoride (TBAF) in one-pot furnished piperidinone **4b** in a good yield (entry 2). The MCR using aliphatic amine **6b** instead of aromatic amine **6a** also successfully afforded **3g** in good yield (entry 3). On the contrary, the reaction of aliphatic aldehyde **5b** resulted in a poor yield of **3r**[7a] under similar conditions (entries 4 and 5). This is possibly due to the instability of the corresponding imine derived from **5b** and **6b** in the presence of Tf_2NH (Scheme 6).[17]

Table 4. Three component syntheses of **3** and **4**

Entry	Aldehyde	Amine	Product	% Yield (trans–cis)[c]
1	**5a** (PhCHO)	**6a** ($PhNH_2$)	**3a**	78 (80:20)
2[a]	**5a** (PhCHO)	**6a** ($PhNH_2$)	**4a**	72 (82:18)
3	**5a** (PhCHO)	**6b** ($BnNH_2$)	**3g**	74 (80:20)
4[b]	**5b** (^{i}PrCHO)	**6b** ($BnNH_2$)	**3r**	16 (ND[d])
5[a,b]	**5b** (^{i}PrCHO)	**6b** ($BnNH_2$)	**4r**	15 (68:32)

[a] One-pot process involving three component reaction and desilylation was carried out.
[b] Cat. 6 mol %, 24 h.
[c] Diastereomeric ratios were determined by ^{1}H NMR.
[d] ND means 'not determined'.

3. Conclusion

In summary, we have demonstrated that triflic imide (Tf_2NH) works as an effective catalyst for the imino Diels–Alder reaction of 2-siloxydienes and aldimines as well as the three component reaction. Tf_2NH catalyst is compatible for basic functions, such as pyridine and indole rings in the imino Diels–Alder reaction. In the reaction, Tf_2NH would directly activate the imine partner as a Brønsted acid to promote the imino Diels–Alder reaction. It is clearly different from catalytic (2+2)-cycloaddition, in which Lewis acidic silyl triflic imides, generated from Tf_2NH and silylated substrates, act as a real catalyst. Furthermore, X-ray crystallographic analysis indicates that the obtained *trans*-2,6-diphenylpiperidin-4-one **4a** has a unique conformation in the solid state.

4. Experimental

4.1. General

All reactions were carried out under an inert atmosphere. Anhydrous THF and CH_2Cl_2 were purchased from the Kanto Chemical Co., Inc. Unless otherwise described, other materials were obtained from commercial suppliers and used without further purification. Column chromatography was

performed on Merck silica gel 60 N (230–400 mesh), and flash column chromatography was performed on Cica silica gel 60 (spherical/40–100 μm). Reactions and chromatography fractions were analyzed employing precoated silica gel plate (Merck silica gel $60F_{254}$). All melting points were determined on Yanaco micro melting point apparatus and are uncorrected. IR spectra were measured on Shimadzu FTIR-8300 spectrometer. The ^1H and ^{13}C NMR spectra were recorded on JEOL AL 400 (400 and 100 MHz) and Varian Gemini 2000 (300 and 75 MHz), respectively, as $CDCl_3$ solutions, and were reported in parts per million downfield from TMS (δ=0) for the ^1H NMR and relative to the central $CDCl_3$ resonance (δ=77.00) for the ^{13}C NMR. Mass spectra were recorded on JEOL DX-303 or AX-500 spectrometer. Elemental analyses were performed on Yanagimoto MT-3 or YANACO CHN CORDER MT-6, and the results (C, H) were within ±0.4% of theoretical values. X-ray crystallographic analysis was performed on Rigaku R-AXIX RAPID.

4.2. General procedure for imino Diels–Alder reaction in the presence of Tf_2NH

To a solution of 2-siloxydiene **1** (1.2 equiv) and aldimine **2** (1.0 equiv) in CH_2Cl_2 (1.0 M) was added Tf_2NH (0.08 M toluene solution, 2–10 mol %) dropwise at ambient temperature. The reaction mixture was stirred for an appropriate time, and then was quenched with saturated $NaHCO_3$ aq. The mixture was extracted with $CHCl_3$. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel using hexane–AcOEt (including 1% NEt_3) as an eluent to give **3** as a diastereomeric mixture. Several compounds were recrystallized from MeOH to give its *trans*-**3** as a single diastereomer.

4.2.1. *trans*-4-(*tert*-Butyldimethylsiloxy)-1,2,6-triphenyl-3,4-didehydropiperidine (*trans*-3a). Colorless needles. Mp 125–127 °C; IR (KBr) 2930, 1680, 1599, 1502 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.36–7.14 (m, 10H), 6.99 (dd, *J*=8.7, 7.5 Hz, 2H), 6.63 (m, 3H), 5.24 (d, *J*=5.3 Hz, 1H), 5.19 (m, 2H), 3.02 (ddt, *J*=16.2, 5.8, 1.9 Hz, 1H), 2.45 (dd, *J*=16.2, 3.6 Hz, 1H), 0.80 (s, 9H), −0.03 (s, 3H), −0.12 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.8, 147.4, 144.6, 142.8, 128.6, 128.5, 128.2, 127.3, 126.7, 126.6, 126.4, 118.4, 117.8, 106.9, 60.3, 58.0, 37.1, 25.4, 17.8, −4.7, −4.9; LRMS *m*/*z* 441 (M^+); Anal. Calcd for $C_{29}H_{35}NOSi$: C, 78.86; H, 7.99; N, 3.17. Found: C, 78.59; H, 8.00; N, 3.07.

4.2.2. *cis*-4-(*tert*-Butyldimethylsiloxy)-1,2,6-triphenyl-3,4-didehydropiperidine (*cis*-3a). The compound could not be isolated in a pure form. The ^1H NMR spectrum was assigned from a mixture of *trans*-**3a** and *cis*-**3a**. ^1H NMR (400 MHz, $CDCl_3$) δ 7.41–7.02 (m, 10H), 6.89 (t, *J*=8.3 Hz, 2H), 6.76 (d, *J*=8.3 Hz, 2H), 6.72 (d, *J*=8.3 Hz, 1H), 4.98 (t, *J*=1.9 Hz, 1H), 4.71 (d, *J*=1.9 Hz, 1H), 4.66 (dd, *J*=9.8, 3.9 Hz, 1H), 2.71 (ddt, *J*=16.8, 9.8, 1.9 Hz, 1H), 2.40 (ddt, *J*=16.8, 3.9, 1.7 Hz, 1H), 0.91 (s, 9H), −0.15 (s, 6H).

4.2.3. *trans*-4-(*tert*-Butyldimethylsiloxy)-6-(*p*-nitrophenyl)-1,2-diphenyl-3,4-didehydropiperidine (*trans*-3b). Colorless needles. Mp 139–140 °C; IR (KBr) 2955, 1681, 1597, 1518, 1346, 1207 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.09 (d, *J*=8.5 Hz, 2H), 7.35 (d, *J*=8.8 Hz, 2H), 7.29–7.25 (m, 4H), 7.21–7.17 (m, 1H), 7.01 (t, *J*=7.8 Hz, 2H), 6.69 (t, *J*=7.1 Hz, 1H), 6.58 (d, *J*=8.5 Hz, 2H), 5.27–5.22 (m, 2H), 5.18 (dd, *J*=4.9, 1.5 Hz, 1H), 3.06 (dd, *J*=16.1, 5.4 Hz, 1H), 2.43 (dd, *J*=16.6, 4.1 Hz, 1H), 0.81 (s, 9H), 0.00 (s, 3H), −0.07 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.7, 146.8, 143.6, 128.8, 128.7, 128.6, 128.5, 128.2, 128.1, 127.9, 126.8, 126.4, 126.1, 123.5, 119.2, 118.0, 106.7, 60.3, 57.9, 37.0, 25.5, 17.9, −4.4, −4.5; LRMS *m*/*z* 486 (M^+); Anal. Calcd for $C_{29}H_{34}N_2O_3Si$: C, 71.57; H, 7.04; N, 5.76. Found: C, 71.40; H, 7.14; N, 5.59.

4.2.4. *cis*-4-(*tert*-Butyldimethylsiloxy)-6-(*p*-nitrophenyl)-1,2-diphenyl-3,4-didehydropiperidine (*cis*-3b). Pale yellow oil. IR (neat) 2930, 1680, 1597, 1521, 1346, 1207 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.00 (d, *J*=8.7 Hz, 2H), 7.48 (d, *J*=8.7 Hz, 2H), 7.25–7.15 (m, 5H), 6.96 (t, *J*=8.0 Hz, 2H), 6.82 (t, *J*=7.5 Hz, 1H), 6.77 (d, *J*=8.0 Hz, 2H), 5.02 (t, *J*=2.4 Hz, 1H), 4.81 (dd, *J*=9.9, 3.9 Hz, 1H), 4.72 (d, *J*=1.9 Hz, 1H), 2.69 (ddt, *J*=16.4, 9.4, 2.4 Hz, 1H), 2.42 (dd, *J*=16.4, 3.6 Hz, 1H), 0.96 (s, 9H), 0.21 (s, 3H), 0.03 (s, 3H); LRMS *m*/*z* 486 (M^+); HRMS *m*/*z* 486.2316 (calcd for $C_{29}H_{34}N_2O_3Si$: 486.2339).

4.2.5. *trans*-4-(*tert*-Butyldimethylsiloxy)-6-(*p*-methoxyphenyl)-1,2-diphenyl-3,4-didehydropiperidine (*trans*-3c). Colorless oil. IR (neat) 2930, 1681, 1597, 1510, 1250 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.18–7.09 (m, 4H), 7.04–6.99 (m, 3H), 6.92 (d, *J*=8.8 Hz, 2H), 6.84 (t, *J*=8.8 Hz, 2H), 6.60 (d, *J*=8.8 Hz, 2H), 6.48 (t, *J*=6.3 Hz, 1H), 5.02–4.99 (m, 2H), 4.96 (t, *J*=4.6 Hz, 1H), 3.59 (s, 3H), 2.82 (dd, *J*=16.3, 5.6 Hz, 1H), 2.27 (dd, *J*=16.3, 3.9 Hz, 1H), 0.67 (s, 9H), −0.16 (s, 3H), −0.22 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.3, 147.9, 147.5, 144.4, 129.0, 128.5, 128.4, 127.9, 127.8, 126.5, 126.4, 118.6, 113.5, 113.3, 106.9, 60.2, 57.7, 55.2, 37.2, 25.6, 14.7, −4.5; LRMS *m*/*z* 471 (M^+); HRMS *m*/*z* 471.2580 (calcd for $C_{30}H_{37}NO_2Si$: 471.2594).

4.2.6. *trans*-4-(*tert*-Butyldimethylsiloxy)-6-(1-naphthyl)-1,2-diphenyl-3,4-didehydropiperidine (*trans*-3d). Colorless crystals. Mp 159–160 °C; IR (KBr) 2928, 1686, 1597, 1502, 1207 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.94–7.92 (m, 1H), 7.88–7.85 (m, 1H), 7.70 (d, *J*=8.2 Hz, 1H), 7.49–7.45 (m, 2H), 7.42 (d, *J*=7.0 Hz, 2H), 7.36 (t, *J*=7.5 Hz, 2H), 7.30–7.25 (m, 2H), 7.08 (d, *J*=7.0 Hz, 1H), 6.92 (dd, *J*=7.5, 7.2 Hz, 2H), 6.62 (t, *J*=7.2 Hz, 1H), 6.49 (d, *J*=8.0 Hz, 2H), 5.87 (t, *J*=5.1 Hz, 1H), 5.43 (d, *J*=5.8 Hz, 1H), 5.34 (dd, *J*=5.8, 1.9 Hz, 1H), 2.96 (dd, *J*=15.9, 5.8 Hz, 1H), 2.60 (dd, *J*=15.9, 4.3 Hz, 1H), 0.71 (s, 9H), −0.11 (s, 3H), −0.26 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.4, 147.1, 144.5, 137.7, 133.9, 131.0, 129.0, 128.7, 128.3, 127.6, 126.7, 126.5, 126.0, 125.3, 125.2, 122.9, 118.3, 117.3, 105.9, 61.3, 54.0, 35.0, 25.5, 17.8, −4.5, −4.8; LRMS *m*/*z* 491 (M^+); Anal. Calcd for $C_{33}H_{37}NOSi$: C, 80.60; H, 7.58; N, 2.85. Found: C, 80.55; H, 7.62; N, 2.80.

4.2.7. *trans*-4-(*tert*-Butyldimethylsiloxy)-1,2-diphenyl-6-(3-pyridyl)-3,4-didehydropiperidine (*trans*-3e). Colorless crystals. Mp 116–117 °C; IR (KBr) 2945, 1678, 1597, 1504, 1371, 1196 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$)

δ 8.45 (d, J=2.2 Hz, 1H), 8.42 (dd, J=4.6, 1.4 Hz, 1H), 7.46 (dt, J=8.0, 1.9 Hz, 1H), 7.30–7.24 (m, 4H), 7.19–7.12 (m, 2H), 7.00 (dd, J=8.7, 7.2 Hz, 2H), 6.67 (t, J=7.2 Hz, 1H), 6.61 (d, J=8.9 Hz, 2H), 5.20 (dd, J=5.6, 4.1 Hz, 1H), 5.17 (s, 2H), 3.05 (dd, J=16.4, 5.8 Hz, 1H), 2.42 (dd, J=16.4, 3.9 Hz, 1H), 0.81(s, 9H), 0.00 (s, 3H), −0.06 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.0, 148.1, 147.2, 146.9, 143.7, 137.8, 134.9, 128.5, 126.7, 126.4, 123.0, 119.3, 118.5, 106.9, 60.1, 56.4, 36.9, 25.5, 17.9, −4.4, −4.6; LRMS m/z 442 (M^+); HRMS m/z 442.2440 (calcd for $C_{28}H_{34}N_2OSi$: 442.2440).

4.2.8. *trans*-4-(*tert*-Butyldimethylsiloxy)-6-(3-indolyl)-1,2-diphenyl-3,4-didehydropiperidine (*trans*-3f). Colorless crystals. Mp 144–145 °C; IR (KBr) 1684, 1595, 1502, 1373, 1223 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (br s, 1H), 7.33 (d, J=7.1 Hz, 2H), 7.27–7.04 (m, 6H), 6.95–6.87 (m, 4H), 6.67–6.61 (m, 3H), 5.29 (t, J=4.9 Hz, 1H), 5.11 (dd, J=4.1, 1.7 Hz, 1H), 5.02 (d, J=4.1 Hz, 1H), 2.87–2.82 (m, 1H), 2.48 (dd, J=16.6, 4.9 Hz, 1H), 0.77 (s, 9H), −0.03 (s, 3H), −0.09 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.6, 144.4, 136.0, 128.3, 128.1, 127.1, 126.5, 122.5, 121.8, 120.3, 119.6, 119.3, 119.2, 116.7, 110.8, 106.6, 60.0, 51.9, 35.3, 25.6, 18.0, −4.4; LRMS m/z 480 (M^+); Anal. Calcd for $C_{31}H_{36}N_2OSi$: C, 77.45; H, 7.55; N, 5.83. Found: C, 77.64; H, 7.59; N, 5.71.

4.2.9. *trans*-1-Benzyl-4-(*tert*-butyldimethylsiloxy)-2,6-diphenyl-3,4-didehydropiperidine (*trans*-3g). Colorless oil. IR (neat) 2928, 1665, 1371, 1256, 891 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20–6.92 (m, 15H), 4.83 (d, J=3.9 Hz, 1H), 4.02 (d, J=3.9 Hz, 1H), 3.83 (dd, J=8.5, 5.6 Hz, 1H), 3.22 (d, J=13.6 Hz, 1H), 3.11 (d, J=13.6 Hz, 1H), 2.25 (m, 2H), 0.74 (s, 9H), −0.21 (s, 3H), −0.25 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.6, 144.1, 141.5, 140.3, 128.9, 128.7, 128.4, 128.2, 128.0, 127.9, 127.0, 126.8, 104.5, 59.3, 54.8, 50.8, 31.3, 25.9, 25.7, 18.2, −4.0, −4.1; LRMS m/z 379 (M^+); HRMS m/z 455.2656 (calcd for $C_{30}H_{37}NOSi$: 455.2644).

4.2.10. *trans*-1-Allyl-4-(*tert*-butyldimethylsiloxy)-2,6-diphenyl-3,4-didehydropiperidine (*trans*-3h). Colorless oil. IR (neat) 2928, 1666, 1362, 1171 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50–7.20 (m, 10H), 5.90–5.83 (m, 1H), 5.14 (dd, J=17.1, 1.7 Hz, 1H), 5.09 (dd, J=7.5, 1.7 Hz, 1H), 4.39 (br s, 1H), 4.06 (t, J=7.2 Hz, 1H), 2.92 (dd, J=14.0, 7.0 Hz, 1H), 2.84 (dd, J=14.0, 5.3 Hz, 1H), 2.43 (d, J=7.2 Hz, 1H), 1.28–1.26 (m, 2H), 0.98 (s, 9H), 0.23 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.5, 144.1, 141.5, 137.6, 128.5, 128.4, 128.2, 128.0, 127.9, 127.6, 126.7, 126.6, 116.6, 104.4, 59.1, 54.7, 49.8, 31.1, 25.8, −4.3; LRMS m/z 405 (M^+); Anal. Calcd for $C_{26}H_{35}NOSi$: C, 76.98; H, 8.70; N, 3.45. Found: C, 76.78; H, 8.69; N, 3.21.

4.2.11. *trans*-4-(*tert*-Butyldimethylsiloxy)-2,6-diphenyl-1-(*p*-toluenesulfonyl)-3,4-didehydropiperidine (*trans*-3j). Colorless crystals. Mp 124–126 °C; IR (neat) 1346, 1159, 1093 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (d, J=8.1 Hz, 2H), 7.33 (d, J=8.1 Hz, 2H), 7.10 (t, J=3.9 Hz, 2H), 7.00 (dd, J=8.0, 2.2 Hz, 2H), 6.95–6.89 (m, 6H), 5.69 (t, J=2.4 Hz, 1H), 5.31 (d, J=6.8 Hz, 1H), 4.99 (dd, J=4.1, 2.4 Hz, 1H), 2.45 (s, 3H), 2.40 (dd, J=17.4 Hz, 1H), 2.04 (ddt, J=17.4, 7.2, 2.4 Hz, 1H), 0.88 (s, 9H), 0.09 (s, 3H), −0.01 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.4, 143.3, 140.3, 138.4, 138.1, 129.9, 129.8, 128.2, 127.8, 127.5, 127.1, 102.8, 55.2, 52.8, 28.7, 25.7, 25.6, 18.0, −4.6; LRMS m/z 519 (M^+); HRMS m/z 519.2233 (calcd for $C_{30}H_{37}NO_3SSi$: 519.2263).

4.2.12. *trans*-1-(Diethoxyphosphonyl)-2,6-diphenyl-4-piperidone (*trans*-4k). Colorless needles (from hexane–AcOEt). Mp 92–94 °C; IR (neat) 3206, 1686, 1649, 1613, 1227 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51–7.45 (m, 3H), 7.39–7.21 (m, 7H), 6.64 (d, J=16.2 Hz, 1H), 4.79–4.71 (m, 1H), 4.06–3.92 (m, 4H), 3.79–3.70 (m, 2H), 3.27 (ds, J=16.2, 6.0 Hz, 1H), 3.15 (dd, J=16.2, 6.0 Hz, 1H), 1.28 (t, J=7.1 Hz, 3H), 1.11 (t, J=7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.8, 143.4, 142.7, 134.2, 130.7, 128.9, 128.5, 128.3, 127.3, 126.4, 126.1, 62.5, 62.3, 52.5, 48.4, 16.3, 15.9; LRMS m/z 388 (M^++H); Anal. Calcd for $C_{21}H_{26}NO_4P$: C, 65.11; H, 6.76; N, 3.62. Found: C, 65.15; H, 6.64; N, 3.60.

4.2.13. 2-(*tert*-Butyldimethylsiloxy)-4-phenyl-1,4,6,7,12,12b-hexahydroindolo[2,3a]quinolizine (3l). Pale brown solids (major diastereomer). Mp 155–157 °C; IR (neat) 2930, 1674, 1454, 1201, 837 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (br s, 1H), 7.35–7.15 (m, 7H), 7.03–6.94 (m, 2H), 4.91 (d, J=3.4 Hz, 1H), 4.52 (d, J=5.0 Hz, 1H), 4.13 (q, J=5.0 Hz, 1H), 3.06 (m, 1H), 2.83 (m, 1H), 2.59 (d, J=14.5 Hz, 1H), 2.43 (dd, J=16.4, 4.8 Hz, 1H), 2.36–2.24 (m, 2H), 0.85 (s, 9H), 0.10 (s, 3H), 0.08 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.4, 139.9, 136.3, 135.0, 129.9, 128.0, 127.7, 127.5, 121.6, 119.5, 118.2, 110.7, 108.3, 105.2, 63.1, 48.2, 35.5, 25.7, 21.3, 18.0, −4.1, −4.2; LRMS m/z 430 (M^+); HRMS m/z 430.2455 (calcd for $C_{27}H_{34}N_2OSi$: 430.2440).

Colorless oil (minor diastereomer). IR (neat) 3418, 2972, 1672, 1452, 1163, 835 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (br s, 1H), 7.46–7.06 (m, 9H), 4.77 (s, 1H), 4.03 (s, 1H), 3.90 (d, J=10.1 Hz, 1H), 2.97 (dd, J=11.4, 4.8 Hz, 1H), 2.77–2.68 (m, 1H), 2.63–2.46 (m, 3H), 2.37 (td, J=11.4, 3.9 Hz, 1H), 0.92 (s, 9H), 0.11 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.0, 144.4, 136.6, 134.7, 128.7, 128.4, 128.3, 127.7, 127.2, 126.8, 121.5, 119.5, 118.2, 110.7, 109.0, 67.1, 55.7, 48.7, 35.9, 25.6, 21.7, 18.0, −4.2; LRMS m/z 431 (M^++H); HRMS m/z 430.2467 (calcd for $C_{27}H_{34}N_2OSi$: 430.2440).

4.2.14. 4-(*tert*-Butyldimethylsiloxy)-4-methyl-1,2-diphenyl-4,5-didehydropiperidine (3m). Colorless oil. IR (neat) 2928, 1709, 1597, 1504, 1253 (br) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26–7.15 (m, 7H), 6.83 (d, J=7.9 Hz, 2H), 6.74 (t, J=7.2 Hz, 1H), 5.12 (dd, J=6.0, 1.9 Hz, 1H), 3.84 (d, J=15.5 Hz, 1H), 3.55 (d, J=15.0 Hz, 1H), 2.92 (m, 1H), 2.40 (d, J=16.2 Hz, 1H), 1.65 (s, 3H), 0.92 (s, 9H), 0.00 (s, 3H), −0.01 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.0, 142.0, 140.1, 129.0, 128.1, 126.8, 126.7, 117.9, 114.7, 108.5, 60.3, 57.1, 49.3, 35.7, 25.7, 13.8, −3.9, −4.1; LRMS m/z 379 (M^+); Anal. Calcd for $C_{24}H_{33}NOSi \cdot 0.2H_2O$: C, 75.22; H, 8.78; N, 3.66. Found: C, 75.37; H, 8.72; N, 3.56.

4.2.15. *trans*-4-(*tert*-Butyldimethylsiloxy)-3-methyl-1,2-diphenyl-4,5-didehydropiperidine (*trans*-3n). Colorless

oil. IR (neat) 2930, 1668, 1595, 1495, 1254 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.25–7.13 (m, 7H), 6.81 (d, J=8.1 Hz, 2H), 6.70 (t, J=7.1 Hz, 1H), 4.99 (q, J=3.1 Hz, 1H), 4.92 (d, J=5.8 Hz, 1H), 3.93 (dt, J=15.0, 3.1 Hz, 1H), 3.76 (dt, J=15.0, 3.1 Hz, 1H), 3.11–3.04 (m, 1H), 0.91 (s, 9H), 0.88 (d, J=7.3 Hz, 3H), 0.20 (s, 3H), 0.14 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.2, 138.9, 137.3, 129.4, 129.1, 128.9, 128.7, 128.6, 127.9, 127.8, 117.9, 115.0, 99.2, 63.7, 37.6, 25.7, 18.2, 13.9, 11.2, −3.5, −4.3; LRMS m/z 379 (M^+); Anal. Calcd for $C_{24}H_{33}NOSi$: C, 75.93; H, 8.76; N, 3.69. Found: C, 75.92; H, 8.85; N, 3.67.

4.2.16. 4-(*tert*-Butyldimethylsiloxy)-1,2-diphenyl-4,5-didehydropiperidine (3o). Colorless oil. IR (neat) 2856, 1688, 1597, 1201, 876 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.23–7.15 (m, 7H), 6.84 (d, J=8.0 Hz, 2H), 6.75 (t, J=7.4 Hz, 1H), 5.15 (dd, J=6.3, 1.9 Hz, 1H), 4.96 (dd, J=3.3, 1.6 Hz, 1H), 3.96 (dt, J=15.9, 2.7 Hz, 1H), 3.64 (ddd, J=15.7, 3.0, 1.6 Hz, 1H), 2.89 (m, 1H), 2.42 (dd, J=16.5, 1.4 Hz, 1H), 0.88 (s, 9H), 0.09 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.3, 147.6, 141.7, 129.1, 128.1, 126.9, 118.0, 114.9, 100.8, 56.6, 44.1, 35.4, 25.7, 18.0, −4.4, −4.5; LRMS m/z 365 (M^+); Anal. Calcd for $C_{23}H_{31}NOSi\cdot 0.3H_2O$: C, 74.46; H, 8.59; N, 3.78. Found: C, 74.23; H, 8.72; N, 3.73.

4.2.17. *trans*-4-Methoxy-1,2,6-triphenyl-3,4-didehydropiperidine (*trans*-3q). Colorless oil. IR (neat) 1682, 1599, 1502, 1371, 1221 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.34–7.15 (m, 10H), 7.00 (dd, J=8.8, 7.3 Hz, 2H), 6.66–6.59 (m, 3H), 5.29 (d, J=5.1 Hz, 1H), 5.22 (t, J=5.1 Hz, 1H), 4.99 (dd, J=5.1, 1.2 Hz, 1H), 3.44 (s, 3H), 3.08 (dd, J=15.8, 5.1 Hz, 1H), 2.53 (dd, J=15.8, 3.7 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.2, 147.6, 144.8, 128.5, 128.4, 128.0, 127.1, 126.6, 126.5, 126.3, 118.2, 117.6, 97.1, 59.7, 58.1, 54.4, 35.0; LRMS m/z 341 (M^+); HRMS m/z 341.1785 (calcd for $C_{24}H_{23}NO$: 341.1780).

4.3. Typical procedure for desilylation of *trans*-3a into *trans*-4a[19]

To a solution of *trans*-**3a** (0.30 mmol) in dry THF (0.5 M) was added tetra-*n*-butylammonium fluoride (1.0 M in THF, 0.33 mL, 0.33 mmol) dropwise at −78 °C. The reaction mixture was stirred for 15 min at the same temperature, and then diluted with $CHCl_3$. The solution was poured into water, and the mixture was extracted twice with $CHCl_3$. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude product was purified by flash column chromatography on silica gel using hexane–AcOEt (6:1) with 1% NEt_3 as an eluent to afford *trans*-**4a** as white solids. An analytical sample for X-ray crystallography was prepared by recrystallization from dichloromethane–hexane as pillars, mp 206–207 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.35–7.22 (m, 10H), 7.10 (dd, J=8.9, 7.5 Hz, 2H), 6.71 (t, J=7.2 Hz, 1H), 6.50 (d, J=8.0 Hz, 2H), 5.48 (dd, J=6.3, 2.1 Hz, 2H), 3.24 (dd, J=17.5, 6.3 Hz, 2H), 2.99 (dd, J=17.5, 2.1 Hz, 2H).

Crystal data for *trans*-**4a**.[16] $C_{23}H_{21}NO$, monoclinic, space group $P2_1/n$, a=13.21(2) Å, b=8.586(13) Å, c=16.02(3) Å, β=106.91(7)°, V=1738.7(50) $Å^3$, Z=4, D=1.251 g/cm^3, R=0.1635, R_w=0.1035, GOF=1.419.

4.3.1. Typical procedure for three component reaction starting from 1a, 5a, and 6a (Table 4, entry 1). To a schlenk round-bottom flask was introduced molecular sieves (4 Å, crushed), **5a** (0.40 mmol) and **6a** (0.40 mmol). Small amount of CH_2Cl_2 was used to wash the wall. The mixture was stirred for 30 min at room temperature, then cooled to 0 °C in an ice bath. To the solution were added **1a** (0.48 mmol) and Tf_2NH (0.08 M toluene solution, 200 μL, 16 μmol, 4 mol %) dropwise. The reaction mixture was stirred for 4 h, and then was quenched with saturated $NaHCO_3$ aq. The mixture was extracted twice with $CHCl_3$. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel using hexane–AcOEt with 1% NEt_3 to give **3a**.

4.3.2. Typical procedure for three component reaction, starting from 1a, 5a, and 6a followed by desilylation (Table 4, entry 2). To a schlenk round-bottom flask was introduced molecular sieves (4 Å, crushed), **5a** (0.40 mmol) and **6a** (0.40 mmol). Small amount of CH_2Cl_2 was used to wash the wall. The mixture was stirred for 30 min at room temperature, then cooled to 0 °C in an ice bath. To the solution were added **1a** (0.48 mmol) and Tf_2NH (0.08 M toluene solution, 200 μL, 16 μmol, 4 mol %) dropwise. After the reaction mixture was stirred for 4 h, to the resulting solution was added tetra-*n*-butylammonium fluoride (1.0 M in THF, 0.48 mmol) at 0 °C. The reaction mixture was stirred for 10 min at the same temperature, and then was quenched with saturated $NaHCO_3$ aq. Work-up and purification was followed as above.

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References and notes

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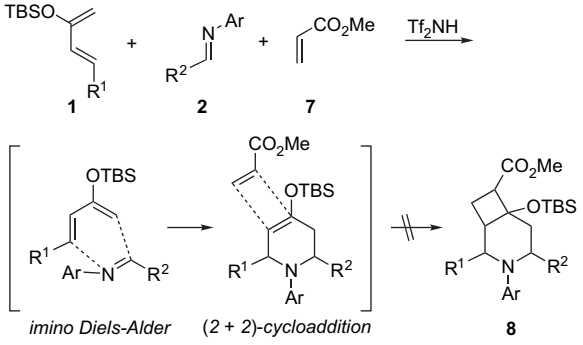
17. Based on our recent finding of the multicomponent (4+2)-(2+2)-cascade cycloaddition of siloxydienes and acrylates,[18] we attempted the imino Diels–Alder variant starting from siloxydienes **1**, imines **2**, and acrylates (Scheme 6). Unfortunately, the desired MCR adduct **8** could not be obtained under various reaction conditions.



Scheme 6.

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