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SYNTHESIS OF AZAHETEROCYCLES AND RELATED MOLECULES BY Tf_2NH -CATALYZED CYCLOADDITIONS

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Abstract – Acid-catalyzed cycloadditions utilizing nitrogen-containing building blocks are powerful tools for the synthesis of azaheterocyclic molecules. This review summarizes Tf_2NH -catalyzed cycloadditions of imines and other related building blocks with electron-rich alkenes, alkynes, and 1,3-dienes, giving a various type of azaheterocycles and related nitrogen-containing compounds.

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1. INTRODUCTION

Azaheterocycles are found in a myriad of biologically active natural products and pharmaceuticals, thus the development of methodologies for their efficient construction continues to be of particular importance in synthetic organic chemistry. Cycloaddition reactions employing nitrogen-containing building blocks are ideal approaches toward azaheterocycles: the reactions provide fast access to structurally diverse products from two (or sometimes three) simple substrates while realizing high atom economy¹ in case that the reaction is facilitated catalytically. Imines are one of the most versatile building blocks for the synthesis of azaheterocycles by cycloaddition reactions because they can act as both nitrogen-containing dienophiles and azadienes (Figure 1).² In most cases, imines can easily be prepared from the corresponding carbonyl compounds and amines by dehydrative condensation. Application to multicomponent reactions in which imines are formed *in situ* is possible, as the condensation of typical aldehydes with aliphatic amines or anilines proceeds readily without a catalyst.

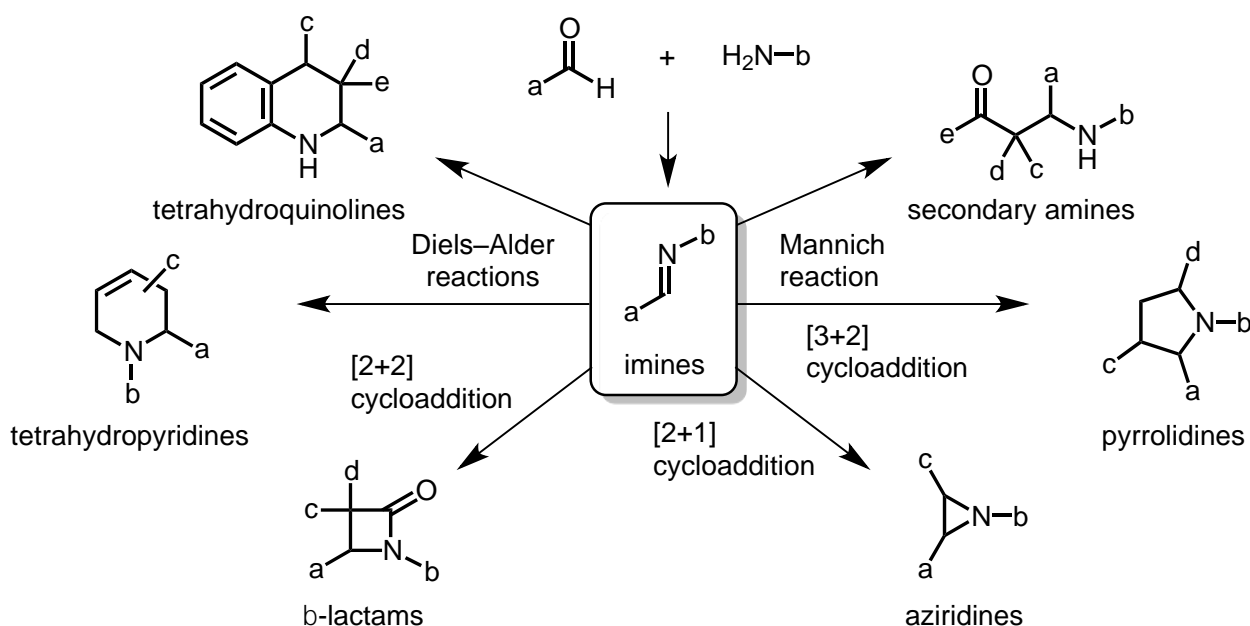
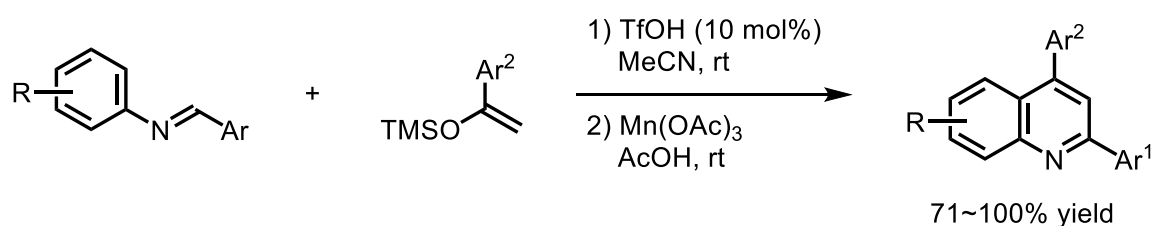


Figure 1. The Utility of Imines in the Synthesis of Azaheterocycles

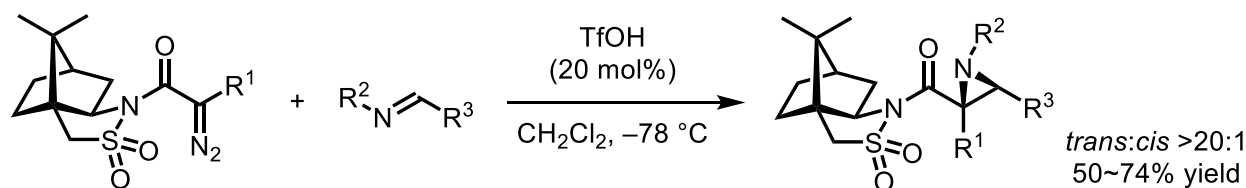
Brønsted or Lewis acids enhance the electrophilic reactivity of imines. However, due to the Lewis basicity of the imine nitrogen atom, catalytic activation of imines was usually considered difficult in comparison with the corresponding carbonyl compounds. While Lewis acids such as triflate salts of groups III (Sc, lanthanides, etc.) or IV metals (Zr, Hf, etc.) were shown to be able to catalytically activate imines in a variety of C–C bond forming reactions,³ activation of imines by Brønsted acid usually

required a stoichiometric amount of the acid owing to low catalyst turnover. Meanwhile, in 1999, Akiyama reported that a catalytic amount of strong Brønsted acid, HBF_4 , facilitated Mannich reaction of imines with silyl enol ethers⁴ and aza Diels–Alder reaction of imines with Danishefsky's diene.⁵ Since then, a range of C–C bond forming reactions utilizing Brønsted acids for catalytic activation of imines has been reported.⁶ Brønsted acid catalysts employ a proton, existing universally on the earth, as the active center. In contrast to typical Lewis acids, organic Brønsted acids are in general chemically stable, easy to handle, and environment-friendly. In particular, super Brønsted acids, which exhibit stronger acidity than concentrated sulfuric acid, have been proven highly effective for catalytic activation of imines. Trifluoromethanesulfonic acid (TfOH; triflic acid) is received as a representative organic super Brønsted acid: It has been employed in various C–C bond forming reactions utilizing imines such as Mannich reactions,⁷ aza Diels–Alder reactions,⁸ Darzens-type imine aziridinations with α -diazo esters,⁹ and Friedel–Crafts-type reactions with indoles.¹⁰

Aza Diels–Alder reaction (ref. 8)



Imine aziridination/[2 + 1] Cycloaddition (ref. 9)



Scheme 1. TfOH-Catalyzed Cycloadditions Giving Azaheterocycles

Trifluoromethanesulfonimide (Tf_2NH ; triflic imide, triflimide)¹¹ is also categorized to be an organic super Brønsted acid, of which proton on the nitrogen atom shows higher acidity than that of TfOH (relative $\text{p}K_a$ in 1,2-dichloroethane to picric acid: $\text{H}_2\text{SO}_4 = -2.5$; TfOH = -11.4 ; $\text{Tf}_2\text{NH} = -11.9$).¹² Both Tf_2NH and TfOH possess desirable properties as an acid catalyst: They show not only good stability against moisture and oxygen in the atmosphere, but also high solubility in nonpolar solvents. Along with C–C bond forming reactions like Mukaiyama aldol and Michael reactions,^{13,14} Tf_2NH has been utilized as a Brønsted acid catalyst in a variety of cycloadditions giving carbocycles. The author's group reported Tf_2NH -catalyzed [2 + 2] cycloadditions of silyl enol ethers or allylsilanes with acrylates,^{15,16} a [3 + 2]

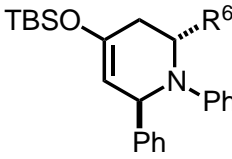
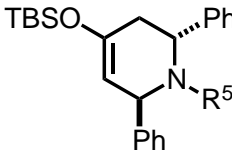
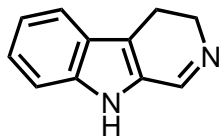
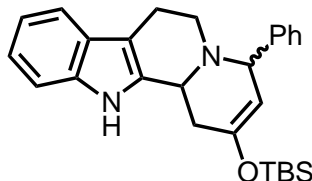
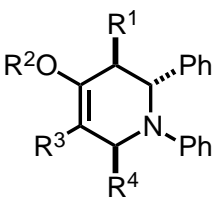
cycloaddition of silyl enol ethers with activated cyclopropanes,¹⁷ a formal [3 + 3] cycloaddition of silyl enol ethers with acrylates,¹⁸ and a three-component cascade [4 + 2]–[2 + 2] cycloaddition of 2-siloxy-1,3-dienes with acrylates.¹⁹ It should be noted that R₃SiNTf₂, formed *in situ* from Tf₂NH and silyl enol ethers or allylsilanes, works as the actual catalyst in these reactions. In contrast, almost no application of Tf₂NH to catalytic cycloadditions giving azaheterocycles was reported before 2006. Over the last decade, we and other groups revealed that Tf₂NH works as a highly active catalyst in various types of cycloadditions for azaheterocycle synthesis. In this paper, we will review Tf₂NH-catalyzed cycloadditions affording azaheterocycles, reported from 2006 to 2017.

2. REACTIONS OF 2-SILOXY-1,3-DIENES WITH ALDIMINES

The imino Diels–Alder reaction, where imines act as the nitrogen-containing dienophile, is one of the most powerful and useful tools to construct a piperidine skeleton. Danishefsky's diene (1-alkoxy-3-siloxy-1,3-butadiene) has frequently been utilized as the electron-rich, highly reactive diene in imino Diels–Alder reactions to give 2,3-dehydropiperidin-4-ones. A large number of Lewis or Brønsted acid-catalyzed imino Diels–Alder reactions employing Danishefsky's diene, including enantioselective ones, have appeared in the literature.²⁰ In contrast, less reactive 2-siloxy-1,3-butadienes have rarely been utilized in imino Diels–Alder reactions. In addition to several precedent examples of Lewis acid-catalyzed reactions,²¹ we reported the first Brønsted acid-catalyzed imino Diels–Alder reaction between 2-siloxy-1,3-dienes (**1**) and aldimines (**2**) to afford multi-substituted 4-siloxy-3,4-dehydropiperidines (**3**) (Table 1).²² The reaction of **1a** and **2a** proceeded smoothly at ambient temperature in the presence of 2 mol% of Tf₂NH, giving a diastereomeric mixture of **3aa** in high yield. The stereochemistry of the major diastereomer was confirmed to be *trans* configuration of 2,6-substituents by X-ray crystallography of the desilylated piperidin-4-one (**4aa**). Reducing the catalyst loading to 0.1 mol% afforded **3aa** without significant loss of the yield, proving high catalytic activity of Tf₂NH in this reaction. Imines with a broad range of substituents including heterocycles afforded the desired piperidine derivatives. However, activated imine **2h** with the electron-withdrawing Ts group on the nitrogen atom gave substantial amounts of by-products, resulting in low yield. As for the 1,3-dienes, various substituent patterns gave the desired products. Interestingly, 5,6-*trans*-substituted piperidine (**3ca**) was obtained as the sole diastereomer from a geometrical mixture of 1-methyl-1,3-diene (**1c**). The highly reactive Danishefsky-type diene (**1e**) only resulted in decomposition of the diene in this reaction system. Remarkably, 2-methoxy-1,3-diene (**1f**) also gave the product (**3fa**) in moderate yield. This result indicated that Tf₂NH works as a Brønsted acid catalyst as it is, in contrast to aforementioned Tf₂NH-catalyzed cycloadditions giving carbocycles where R₃SiNTf₂ formed *in situ* acts as the actual catalyst.¹⁵⁻¹⁹ The

application of the reaction to a three-component reaction where imine (**2a**) was formed *in situ* from benzaldehyde and aniline was also successful.

Table 1. Tf₂NH-Catalyzed Imino Diels–Alder reaction of 2-Siloxy-1,3-dienes (**1**) and Aldimines (**2**)

Diene 1 (R ¹ , R ² , R ³ , R ⁴)	Aldimine 2 (R ⁵ , R ⁶)	Product	% Yield ^a (<i>trans</i> : <i>cis</i>) ^b
1a (H, TBS, H, Ph)	2a (Ph, Ph)	3aa	85 (80:20)
1a	2b (Ph, <i>p</i> -NO ₂ C ₆ H ₄)	3ab	85 (75:25)
1a	2c (Ph, <i>p</i> -MeOC ₆ H ₄)		3ac 67 (77:23)
1a	2d (Ph, 1-naphthyl)	3ad	73 (84:16)
1a	2e (Ph, 3-pyridyl)	3ae	61 (73:27)
1a	2f (Ph, 3-indolyl)	3af	35 (81:19)
1a	2g (Bn, Ph)		3ag 89 (85:15)
1a	2h (Ts, Ph)	3ah	32 (89:11)
1a	2i 		3ai 60 (60:40)
1b (H, TBS, Me, H)	2a	3ba	86
1c (Me, TBS, H, H)	2a	3ca	69
1d (H, TBS, H, H)	2a	3da	69
1e (H, TBS, H, OMe)	2a	3ea	0
1f (H, Me, H, H)	2a		3fa 48 (79:21)

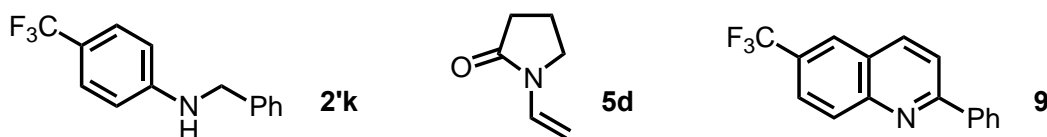
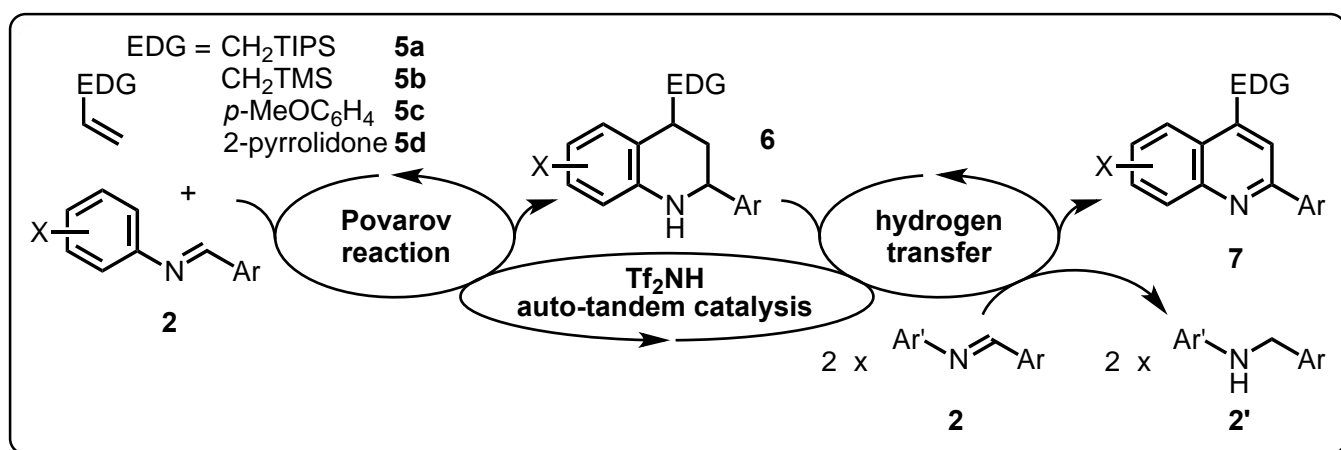
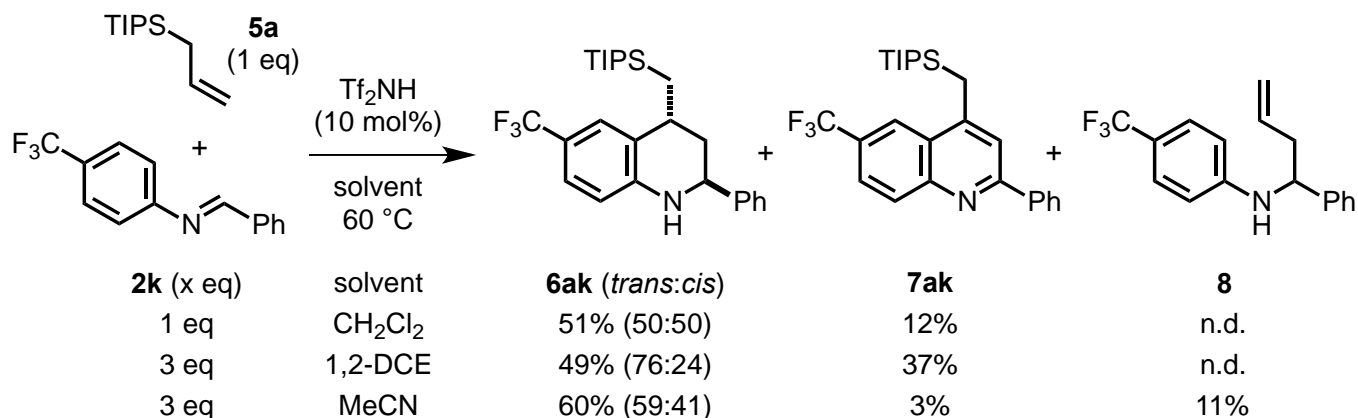
^aIsolated yields. ^bDetermined by ¹H NMR

3. REACTIONS OF ELECTRON-RICH ALKENES WITH *N*-ARYLALDIMINES

3-1. Cascade Povarov–Hydrogen-Transfer Reaction

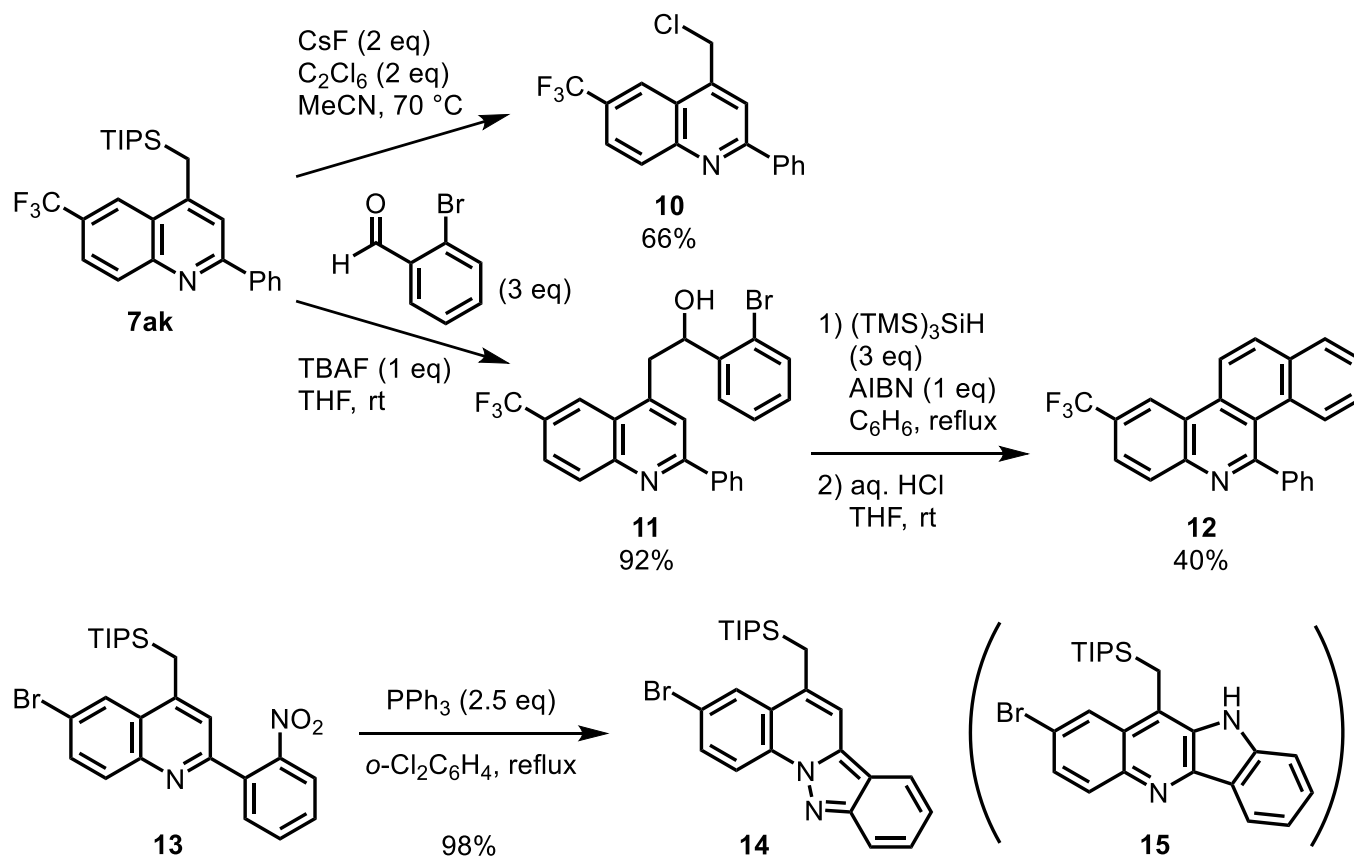
N-Arylimines act not only as nitrogen-containing dienophiles but also as azadienes. The inverse electron-demand Diels–Alder reaction between *N*-arylimines with electron-rich alkenes, named Povarov reaction, affords 1,2,3,4-tetrahydroquinoline derivatives. Electron-rich alkenes such as vinyl ethers, *N*-vinylamides, and styrenes have widely been used in the Povarov reaction.²³ On the other hand, allylsilanes have scarcely employed in the Povarov reaction: only one example utilizing a stoichiometric amount of SnCl₄ as the Lewis acid was reported before 2006.²⁴ Allylsilanes are stable, easy-to-handle allyl metal equivalents whose silyl group can be used for further chemical transformations. Accordingly, we have developed the Tf₂NH-catalyzed Povarov reaction utilizing *N*-arylaldimines and allylsilanes (Scheme 2).²⁵ In the presence of 10 mol% Tf₂NH at 60 °C, equimolar amounts of *N*-arylaldimine (**2k**) and allylsilane (**5a**) in CH₂Cl₂ gave tetrahydroquinoline (**6ak**) as a diastereomeric mixture in moderate yield. In addition to **6ak**, minor amounts of quinoline (**7ak**) and benzylamine (**2'k**) were also isolated. This observation indicated that **6ak** was oxidized to **7ak** by hydrogen transfer to imine (**2k**). Although hydrogen transfer between 3,4-dihydroquinolines and imines are reported,²⁶ oxidation of 1,2,3,4-tetrahydroquinolines by hydrogen transfer usually requires a strong hydride acceptor such as 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ). Further experiments revealed that Tf₂NH promotes not only the Povarov reaction but also the hydrogen transfer reaction. Namely, in this reaction system, Tf₂NH worked as the catalyst for both cycloaddition and oxidation. A reaction system in which a single catalyst promotes two or more mechanistically distinct reactions is called auto-tandem catalysis.²⁷ It attracts much attention in current organic chemistry since it enables complex molecular transformation with a simple experimental operation. By using an excess amount of imine (**2k**) and 1,2-dichloroethane (1,2-DCE) as the solvent, a mixture of tetrahydroquinoline (**6ak**) and quinoline (**7ak**) were obtained in good yields. The *trans*-isomer of **6ak** was obtained in a diastereomeric ratio of 76:24, implying a faster reaction rate for *cis*-**6ak** in the hydrogen transfer reaction with the imine. In polar solvents (MeCN, THF, AcOEt), homoallylamine (**8**) was produced as a by-product. The formation of **8** indicates a non-concerted, stepwise mechanism of the cycloaddition process. In polar solvents, the β-silyl cation intermediate formed by Hosomi–Sakurai-type addition of the allylsilanes to the imines would be stabilized and would result in the formation of **8** by elimination of the silyl group. Formation of **8** was also observed when allyl-TMS (**5b**) was used instead of bulky allyl-TIPS (**5a**) in non-polar solvents. In this case, the cation intermediate would be unstable because of sterically less hindered silyl group and lead to fast desilylation from the intermediate. Electron-rich alkenes other than allylsilanes such as styrenes and *N*-vinyl-2-pyrrolidone also furnished tetrahydroquinolines and/or quinolines by the Tf₂NH-catalyzed cascade Povarov–hydrogen transfer reaction. In the case of *N*-vinylpyrrolidone (**5d**), however,

4-unsubstituted quinoline (**9**) was obtained instead of the expected nitrogen-substituted quinoline by the elimination of pyrrolidone before the hydrogen transfer.



Scheme 2. Tf₂NH-Catalyzed Cascade Povarov–Hydrogen Transfer Reaction

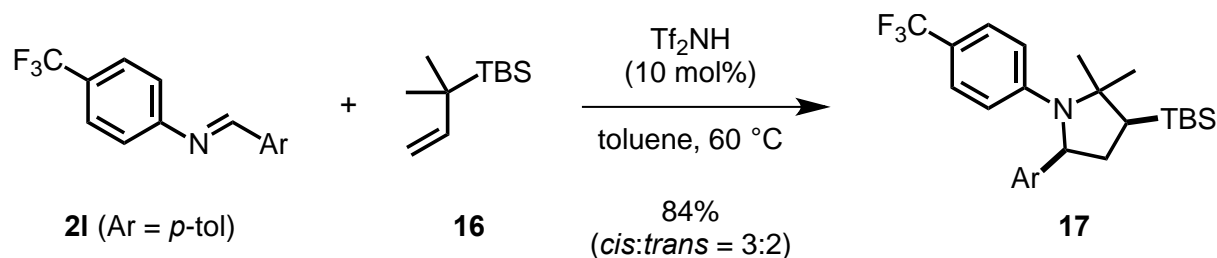
The synthetic utility of the obtained quinolines was also demonstrated (Scheme 3). Desilylation of the TIPS group with CsF in the presence of C₂Cl₆ as the electrophile afforded **10**, of which chloromethyl group would be a hurdle for further chemical transformations.²⁸ Moreover, desilylation with TBAF in the presence of an aldehyde furnished alcohol (**11**) with a new C–C bond formation in good yield. **11** could further be transformed into tetracyclic azaheterocycle (**12**) by radical cyclization–dehydration. In analogy to Cadogan's carbazole synthesis,²⁹ quinoline (**13**) having an *ortho*-nitrophenyl group was heated in the presence of PPh₃. In this case, indazolo[2,3-*a*]quinoline (**14**) with a new N–N bond was exclusively obtained via the formation of a nitrene. No formation of δ -carboline (**15**) with a new C–N bond was observed. The bulkiness of the TIPSCH₂ group would cause the chemoselectivity.



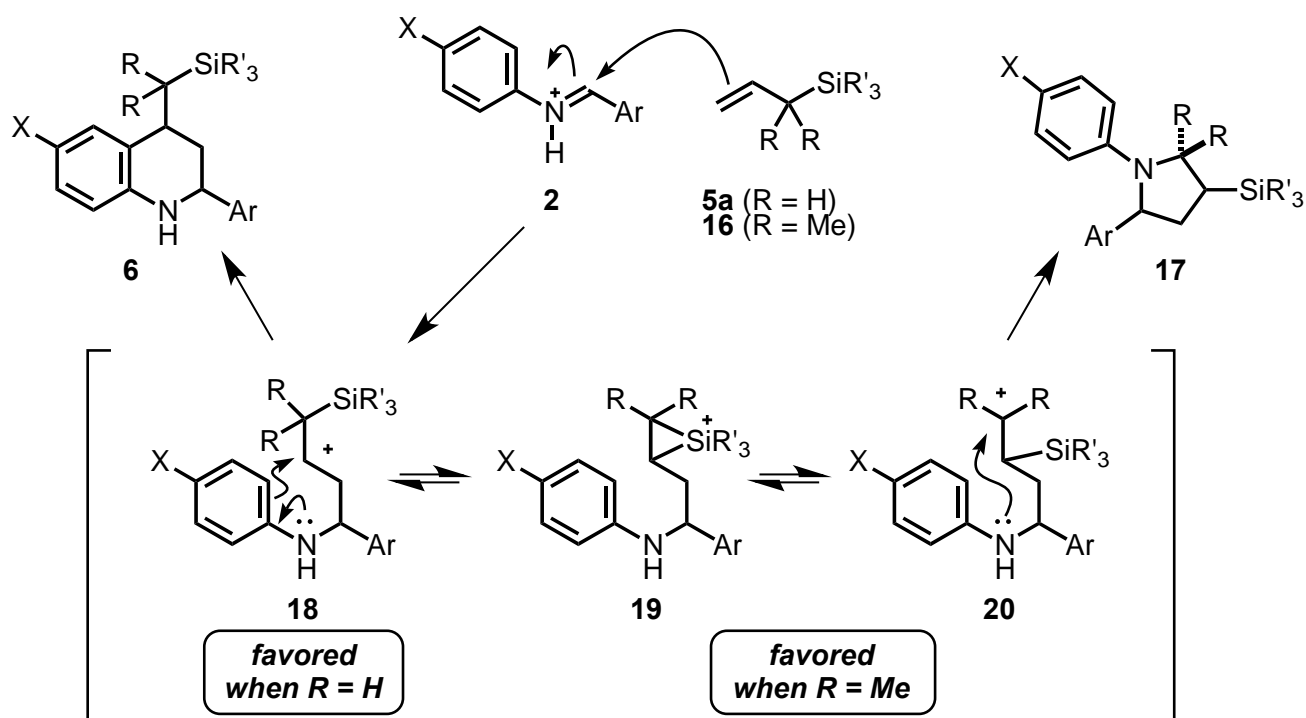
Scheme 3. Transformations of Quinolines (7)

3-2. [3 + 2] Cycloaddition with α,α -Dimethylallylsilane

We unexpectedly found that when α,α -dimethylallylsilane (**16**) and aldimine (**21**) were subjected to the same reaction conditions as above, substituted pyrrolidines (**17**) were obtained by a Tf₂NH-catalyzed [3 + 2] cycloaddition instead of the Povarov reaction (Scheme 4).³⁰ The structure and the stereochemistry of **17** was established by X-ray crystallography. A plausible mechanism for the Tf₂NH-catalyzed reactions of allylsilanes (**5a**) or (**16**) with imines (**2**) is as follows: Initially, the addition of the allylsilane to the imine carbon would give the β -silyl cation intermediate (**18**). In Povarov reaction, the aromatic carbon would attack the cation to form a six-membered ring. In contrast, in the reaction with α,α -dimethylallylsilane (**16**), the intermediate (**18**) would transform into more stable non-classical siliranium cation (**19**) or β -silyl cation (**20**) by silacyclopropanation or 1,2-silyl shift, respectively. Finally, the intramolecular attack of the nitrogen atom in the intermediate (**19**) or (**20**) would afford the [3 + 2] cycloadduct. Thus, the mode of cyclization could be altered by the α -substituents of the allylsilanes.



A plausible mechanism for Povarov reaction and [3 + 2] cycloaddition

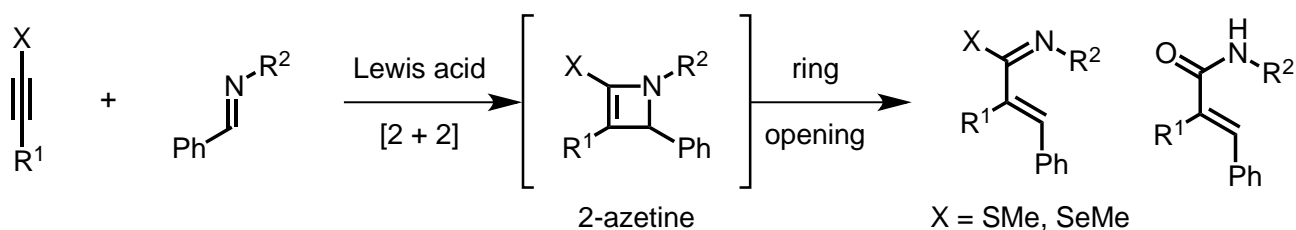


Scheme 4. Tf_2NH -Catalyzed [3 + 2] Cycloaddition of α,α -Dimethylallylsilane (**16**) with Imines

4. REACTIONS OF YNAMIDES WITH ALDIMINES

4-1. Cascade [2 + 2] Cycloaddition– 4π Cycloreversion

Two modes are known for the cycloadditions of imines with electron-rich alkynes. Several alkynes with a carbon substituent are reported to give quinolines by the Povarov reaction with *N*-arylimines in the presence of Brønsted or Lewis acid.³¹ On the other hand, alkynes directly attached to a hetero atom tend to undergo [2 + 2] cycloaddition with imines (Scheme 5). In most cases, the four-membered cycloadduct (2-azetine) immediately undergoes electrocyclic ring opening reaction (cycloreversion) to afford α,β -unsaturated amide derivatives. Alkynyl sulfides,³² alkynyl selenides,³³ and silyl ynol ethers³⁴ are reported to participate in a Lewis acid-catalyzed [2 + 2] cycloaddition– 4π ring opening reaction with imines to afford α,β -unsaturated thioimidates, selenoimidates, and amides, respectively. The cascade process corresponds to a formal aza-ene metathesis.

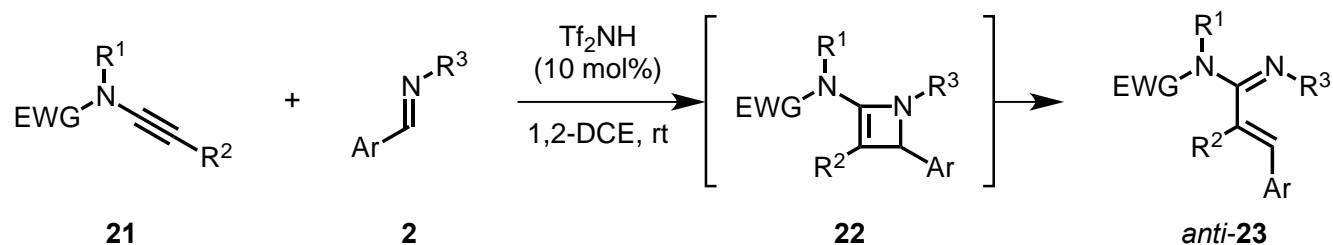


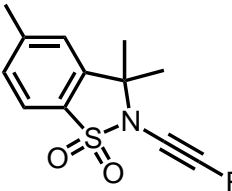
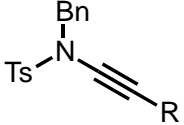
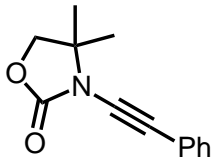
Scheme 5. Lewis Acid-Catalyzed Formal Aza Enyne Metathesis of Electron-Rich Alkynes with Imines

We reported a Tf_2NH -catalyzed cascade $[2 + 2]$ cycloaddition– 4π cycloreversion of ynamides with aldimines to afford highly substituted α,β -unsaturated amidines (Table 2).³⁵ Although a related BF_3 -catalyzed synthesis of α,β -unsaturated amidines from nitrogen-substituted alkynes and imines was reported in 1985, the reaction employed highly reactive and unstable ynamines.³⁶ In contrast, ynamides are stabilized by an electron-withdrawing group on the nitrogen atom. They show an excellent balance between stability and reactivity, and are recognized as useful synthetic building blocks in modern organic chemistry.³⁷⁻³⁹ In the presence of 10 mol% Tf_2NH , the reaction of ynamide (**21a**) bearing cyclic sulfonyl moiety and aldimine (**2l**) proceeded rapidly at room temperature to give highly substituted α,β -unsaturated amidine (**23al**) as a single diastereomer in 93% yield. X-Ray crystallography revealed *E* geometry for both the alkene and the amidine moieties of **23al**. Various *N,C*-diaryldimines and *N*-alkyl-*C*-aryldimines afforded the desired α,β -unsaturated amidines in high yields. Aryl-, alkyl-substituted, and terminal ynamides exclusively gave *anti*-**23** where the Ar group and the amidine moiety are placed on the opposite sides of the alkene. The configuration of the alkene moiety of the α,β -unsaturated amidines is determined by the direction in which the σ -orbital of the central bond rotates in the thermal, conrotatory cycloreversion of the four-membered ring intermediate. This stereoselectivity, termed torquoselectivity, has been well studied both experimentally and theoretically for the related thermal cycloreversion of cyclobutenes to give 1,3-butadienes.⁴⁰ In the cycloreversion of the 2-amino-2-azetines (**22**) generated from ynamides and aldimines, the C(3) substituent derived from the alkyne terminus could be a determining factor for the torquoselectivity (Scheme 6). That is, when the R^2 group at the C(3) position is comparatively small, an outward rotation of C(4) Ar group would prefer *anti* geometry to avoid a steric repulsion between the C(4) Ar substituent and the forming amidine moiety. This explains the exclusive formation of the *anti* isomers from ynamides described above ($\text{R}^2 = \text{aryl, alkyl, and H}$). By contrast, when the R^2 group is sufficiently large, the steric repulsion between the R^2 and the C(4) Ar substituents would result in an inward rotation to afford *syn* geometry. In fact, ynamide (**21g**) with highly bulky TIPS group at the alkyne terminus selectively produced *syn*-**23**. Interestingly, the ^1H NMR spectra of the *syn*-**23** indicated the existence of atropisomers at room temperature, whereas *anti*-**23** showed no evidence of atropisomerism even at -90°C . The atropisomers of α,β -unsaturated amide

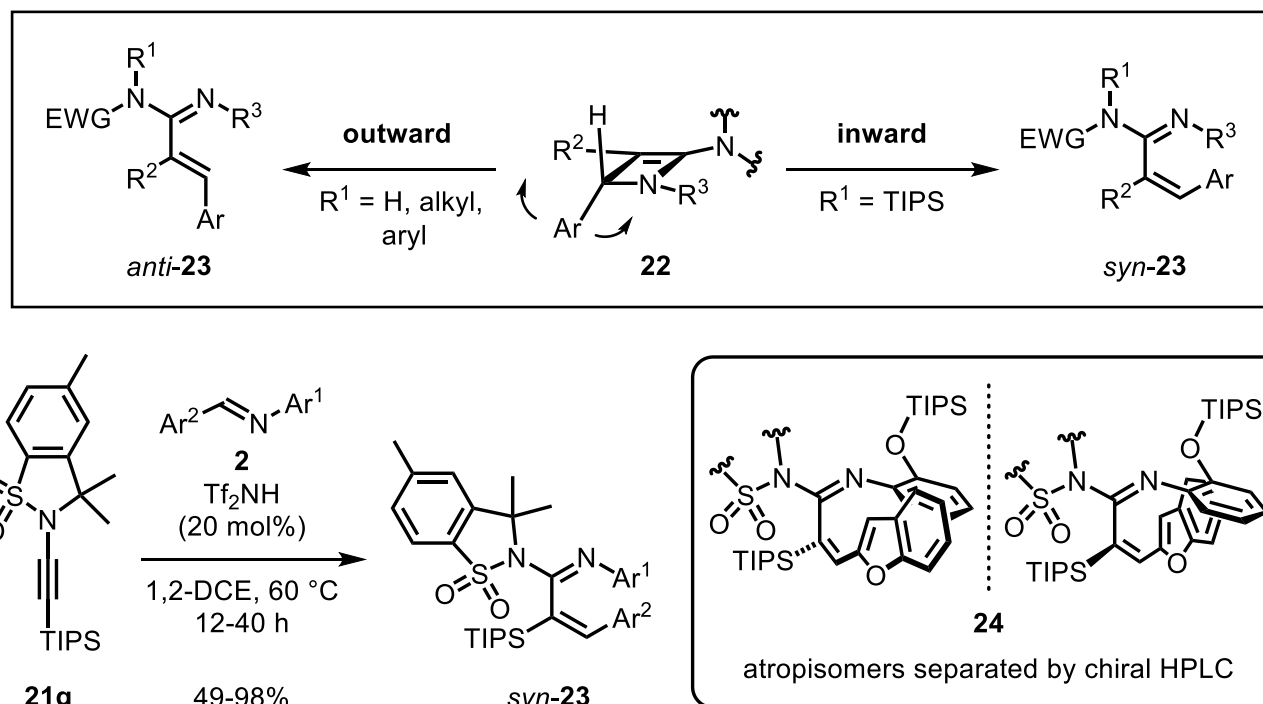
derivatives are generally unstable and prone to racemization since the alkene is relatively flexible compared to the well-known atropisomeric biaryl compounds. Nevertheless, we successfully separated each enantiomer of **24** using preparative chiral HPLC at 10 °C.

Table 2. Tf₂NH-Catalyzed Cascade [2 + 2] Cycloaddition–4π Cycloreversion to Afford *anti*-**23**



Ynamide 21	Aldimine 2 (R ³ , Ar)	time (h)	Product	% Yield ^a	
	21a (R = Ph)	2l (<i>p</i> -CF ₃ C ₆ H ₄ , <i>p</i> -tol)	0.25	23al	93
	21b (R = H)	2l	0.25	23bl	78
	21c (R = CH ₂ OTBS)	2l	0.25	23cl	92
	21d (R = Ph)	2l	0.5	23dl	76
	21e (R = H)	2l	0.25	23el	81
	21f	2l	0.25	23fl	80
21a	2m (<i>p</i> -NO ₂ C ₆ H ₄ , Ph)	0.25	23am	68	
21a	2n (<i>p</i> -BrC ₆ H ₄ , Ph)	0.25	23an	72	
21a	2o (<i>o</i> -BrC ₆ H ₄ , Ph)	0.25	23ao	73	
21a	2p (<i>o</i> -IC ₆ H ₄ , <i>p</i> -tol)	0.25	23ap	88	
21a	2a (Ph, Ph)	1.5	23aa	67 ^b	
21a	2q (<i>p</i> -MeOC ₆ H ₄ , Ph)	17	23aq	64 ^c	
21a	2g (Bn, Ph)	24	23ag	94 ^d	
21a	2r (allyl, Ph)	24	23ar	90 ^d	

^aIsolated yields. ^b15 mol% Tf₂NH. ^c20 mol% Tf₂NH. ^d20 mol% Tf₂NH at 60 °C



Scheme 6. Stereoselective Synthesis of *syn*-**23** from TIPS-Substituted Ynamide (**21g**)

4-2. Catalyst-Controlled Torquoselectivity Switch in the 4π Cycloreversion

As stated above, the torquoselectivity in the 4π electrocyclic cycloreversion of the four-membered intermediate determines the stereochemistry of the alkene moiety of the α,β -unsaturated amidines. Both steric and stereoelectronic factors affect torquoselectivity (Figure 2). Using *ab initio* calculations, Houk and co-workers showed that stereoelectronic effects dominantly control the torquoselectivity in the 4π cycloreversion of cyclobutenes and their analogs.⁴⁰ The interaction between the orbital of the C(4) substituent and the σ -orbital of the breaking C(4)–X bond is maximized in the inward transition state. Since the breaking central σ -bond is electron-rich, an electron-donating substituent at the C(4) position would favor outward rotation in order to avoid the electronic repulsion. Conversely, an electron-accepting substituent (eg. BH_2 , CHO) would prefer inward rotation, as the interaction between the substituent and the breaking σ -bond would stabilize the transition state (mode A). As explained earlier, steric effects can also determine the torquoselectivity in case that the electronic properties of the C(4) substituents are not significantly different. When the C(4) substituent is sterically smaller than the forming C(=X)R group, the bulky C(4) substituent would undergo an outward rotation (mode B). When the C(3) substituent is sterically bulky, an inward rotation of the larger C(4) substituent would be favorable (mode C). In any case, the torquoselectivity critically depends on the nature of the substrate, and hardly be altered by the reaction conditions such as solvents and additives.⁴¹ A stereoselective synthesis of both geometrical isomers of the 1,3-dienyl compound from the same substrate is generally difficult.

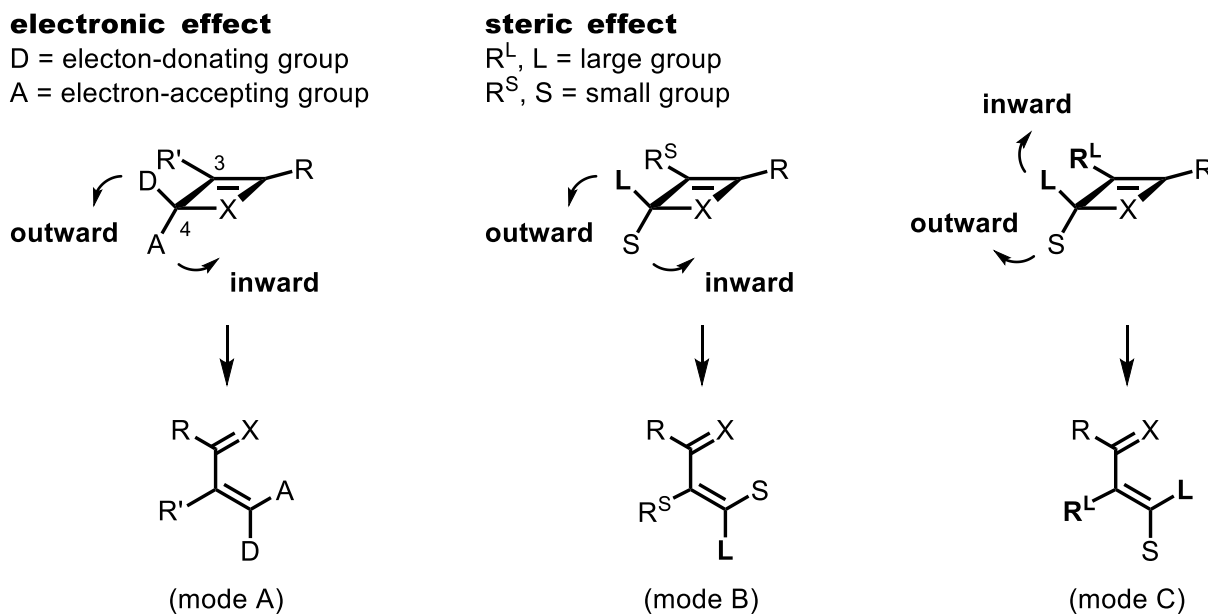
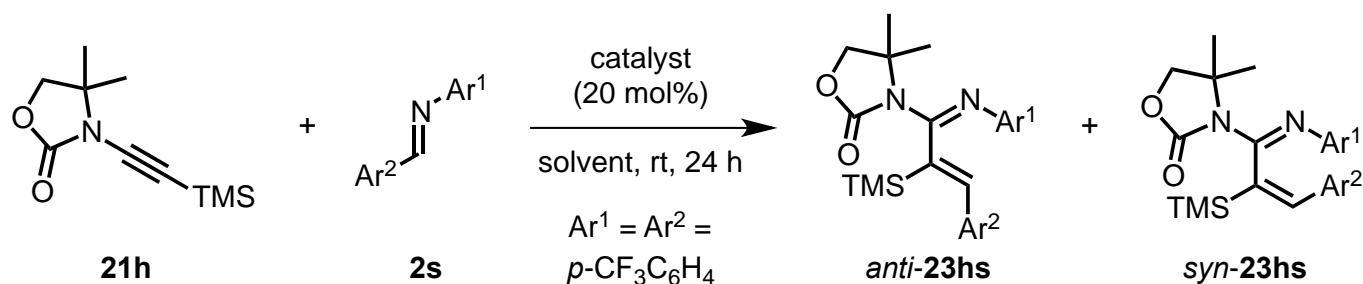


Figure 2. Modes of Torquoselectivity in the 4π -Cycloreversion of Cyclobutadiene Analogs
 ($X = CR_2, O, NR$)

In contrast, we reported a catalyst-controlled torquoselectivity switch in the 4π cycloreversion of the 2-amino-2-azetidine **22** generated from the TMS-substituted yne-oxazolidinone (**21h**) and *N,C*-diarylaldimines (**2s**) (Table 3).⁴² The acidity of the Brønsted acid catalyst displayed a striking effect on the *anti/syn* diastereomeric ratio of the product. In the presence of a catalytic amount of super strong Brønsted acids such as Tf₂NH and TfOH, the reaction of **21h** and **2s** in toluene afforded *anti*-**23hs** in high stereoselectivity. When less acidic sulfonic acids were employed as the catalyst, the ratio of the *syn*-**23hs** increased as the acidity of the catalyst decreased (pK_a in acetonitrile: TfOH = 2.6, MsOH = 10).^{43,44} In particular, CSA (10-camphorsulfonic acid) produced *syn*-**23hs** in good yield and selectivity. On the other hand, the cation center of the acid catalyst showed little influence on the torquoselectivity. All Lewis acids tested (BF₃•OEt₂, Sc(OTf)₃, TiCl₄, PtCl₄, In(OTf)₃, Yb(OTf)₃, etc.) preferentially gave *anti*-amidine in a similar diastereomeric ratio. The reaction solvent affected the torquoselectivity: Acetonitrile, a polar solvent, increased *anti*-selectivity under both Tf₂NH and CSA catalysis, while non-polar solvents such as aromatic solvents and 1,2-DCE preferred the formation of the *syn*-isomer. The optimal reaction conditions found to be Tf₂NH in acetonitrile for *anti*-**23hs**, and CSA in α,α,α -trifluorotoluene (TFT) for *syn*-**23hs**. Since no isomerization of *anti*- and *syn*-**23hs** was observed after 24 h in the presence of Tf₂NH or CSA, it has been confirmed that the stereochemistry of **23hs** is kinetically determined during the conrotatory ring opening of the 2-azetidine. Thus, the choice of an appropriate combination of the Brønsted acid and the reaction solvent enabled stereoselective synthesis of both geometrical isomers of **23hs** from the same set of the substrates by the catalyst-controlled torquoselectivity switch.

Table 3. Effect of the Catalyst and the Solvent on the Torquoselectivity in the Reaction of **21h** and **2s**

Catalyst	Solvent	% Yield ^a	<i>anti/syn</i> ^b
Tf ₂ NH ^c	toluene	95	92:8
TfOH	toluene	93	95:5
<i>p</i> -TsOH	toluene	5	55:45
MsOH	toluene	40	17:83
CSA	toluene	79	15:85
Tf ₂ NH ^c	MeCN	86	95:5
Tf ₂ NH ^c	1,2-DCE	74	76:24
CSA	CH ₂ Cl ₂	87	18:82
CSA	1,2-DCE	45	25:75
CSA	MeCN	50	33:67
CSA	benzene	70	14:86
CSA	chlorobenzene	76	14:86
CSA	TFT	77	10:90

^aIsolated yields. ^bDetermined by ¹H NMR. ^c15 mol% Tf₂NH, 15 min

DFT calculations were performed at B3LYP/6-31(d) level to explain the mechanism of the torquoselectivity switch. There are four possible transition states for the ring opening of protonated 2-azetinium cation [**25**•H]⁺ depending on the direction of the C(4) phenyl group rotation (inward vs outward) and the relative configuration of the two aryl groups at the C(4) and the N(1) positions (*cis* vs *trans*) (Figure 3). The energy difference between *cis*- and *trans*-[**25**•H]⁺ is small, and the diastereomers rapidly equilibrate under the reaction condition through deprotonation of the nitrogen atom, nitrogen inversion, and re-protonation. As the *E/Z* stereochemistry of the C=N bond of **23hk** readily epimerizes, only the geometry of the C=C bond reports the torquoselectivity. The activation energies of TSs **A** (inward-*cis*) and **D** (outward-*trans*) in which the N(1) aryl group undergoes an outward rotation were found to be lower than that of the other two TSs. Thus, the *anti/syn* ratio of the final product (**23hk**) would reflect the

relative Gibbs free energy ($\Delta\Delta G^\ddagger$) of the TSs **A** and **D**, which produce *syn*-**23hk** and *anti*-**23hk**, respectively. In the naked cation model where the counter anion is solvated and not present in the vicinity of the azetinium [**25**•H]⁺, TS **D** leading to the formation of *anti*-**23hk** was calculated to be more stable compared to TS **A** by 1.4 kcal/mol (Figure 4). By contrast, when a sulfonate anion was included in the transition state structures (ionic pair model), TS **A** giving *syn*-**23hk** became more stable than TS **D** by 1.3 kcal/mol. The steric effect would explain the reversal of the stability of TSs **A** and **D**. In the naked cation model, the steric repulsion between the C(4) phenyl group and the forming amidine moiety and/or N(1) aryl group would destabilize TS **A**. On the other hand, in the ionic pair model, TS **D** would be destabilized by the steric and electronic repulsion between the C(4) phenyl group and the sulfonate anion. These computational results provide a reasonable explanation for the mechanism of the catalyst-controlled torquoselectivity switch: In a super strong acid (Tf₂NH, TfOH) catalysis, the counter anion is likely to be solvated and the 2-azetine cycloreversion would preferably proceed through the naked cation model which leads to a selective formation of the *anti*-isomer, whereas a weaker sulfonic acid (MsOH, CSA) would preferentially provide the *syn*-isomer via the ionic pair model. The experimentally observed solvent effect on the *anti*/*syn* selectivity also agrees with this mechanism.

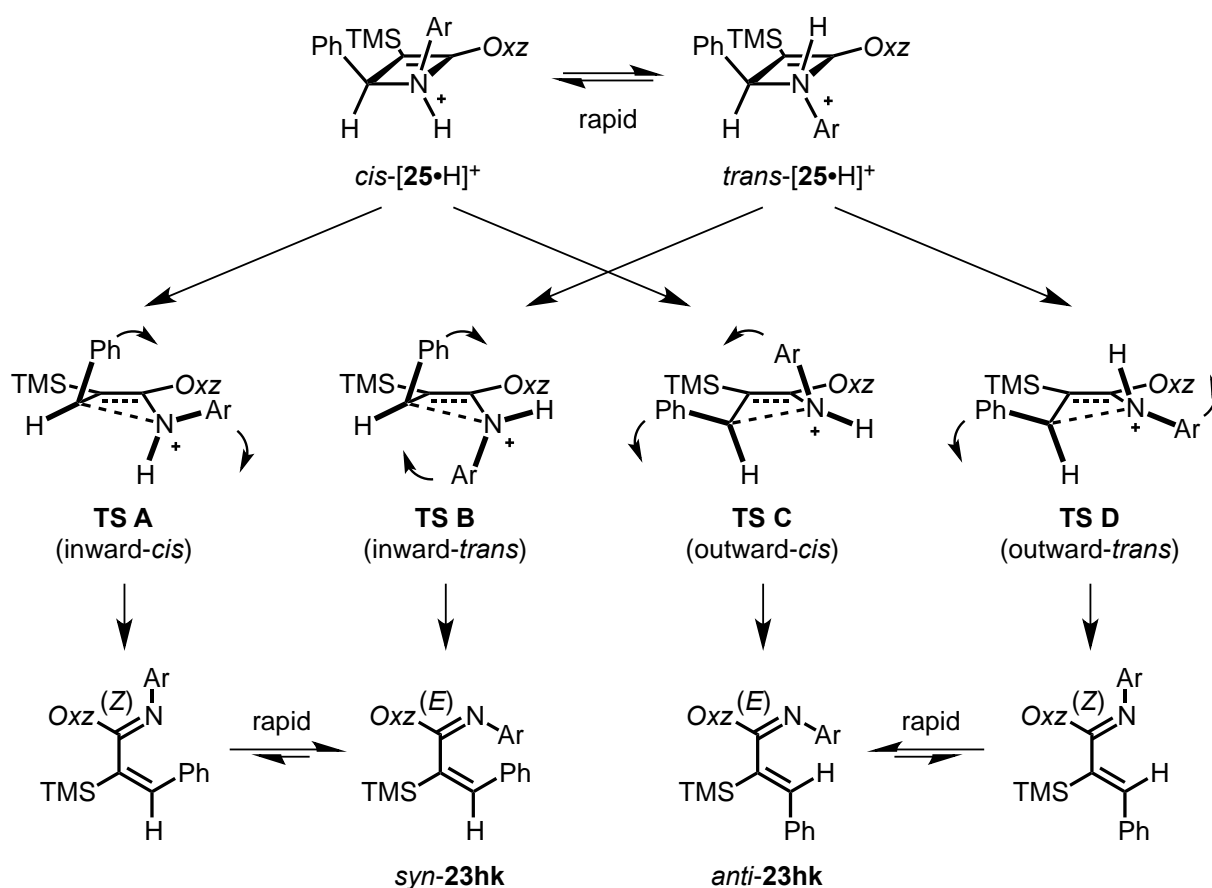
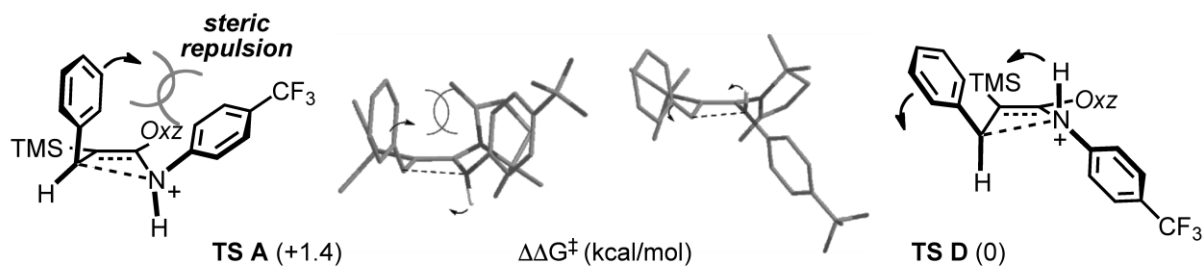


Figure 3. Possible Transition States **TS A–D** for the 4 π -Cycloreversion of [**25**•H]⁺ (Ar = *p*-CF₃C₆H₄)

solvated (naked cation) model (Tf₂NH, TfOH)



ionic pair model (MsOH, CSA)

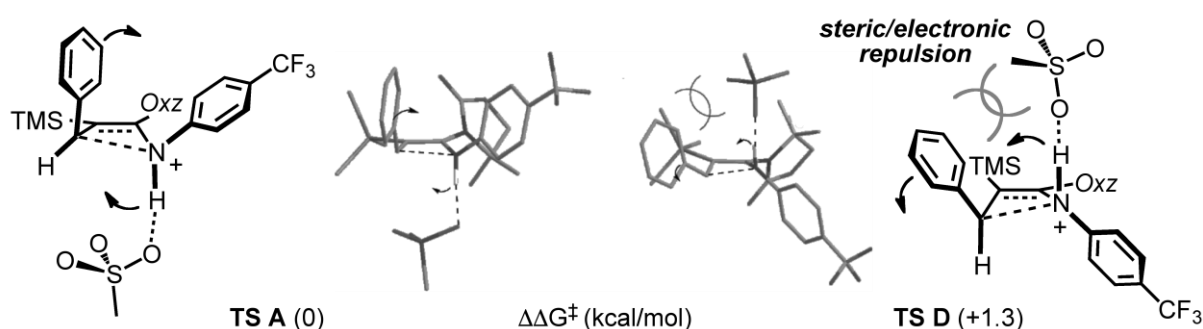
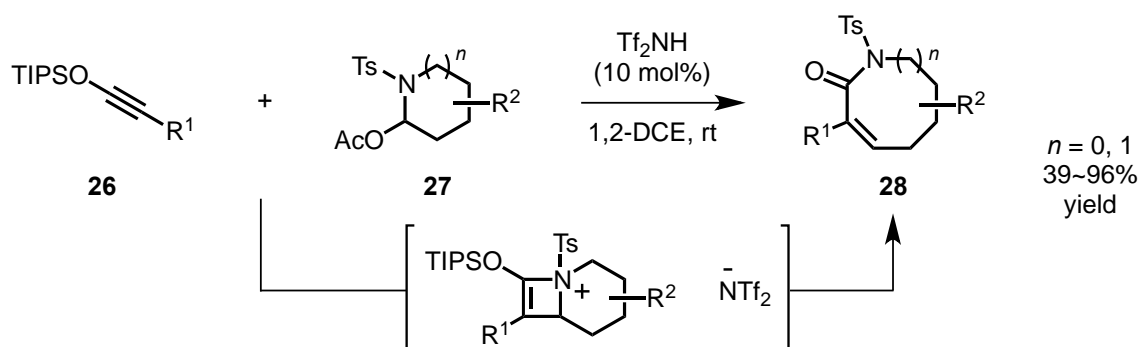


Figure 4. Solvated and Ionic Pair Models of the Most Stable Transition States for the 4 π -Cycloreversion

4-3. Catalytic Ring Expansion of Cyclic Hemiaminals with Silyl Ynol Ethers

Sun and Li utilized the acid-catalyzed cascade [2 + 2] cycloaddition–4 π cycloreversion strategy to a catalytic ring expansion of *N*-sulfonyliminiums generated *in situ* from cyclic hemiaminals (Scheme 7).⁴⁵ They employed silyl ynol ethers instead of ynamides as the electron-rich alkyne. In the presence of 10 mol% Tf₂NH, the reaction of silyl ynol ethers (**26**) and cyclic hemiaminals (**27**) proceeded smoothly at room temperature to afford seven- and eight-membered ring lactams (**28**) in good yields. The use of Ts group as the nitrogen-protecting group seemed essential to selectively promote the desired reaction. Only Tf₂NH was able to catalytically facilitate the reaction in good yields.

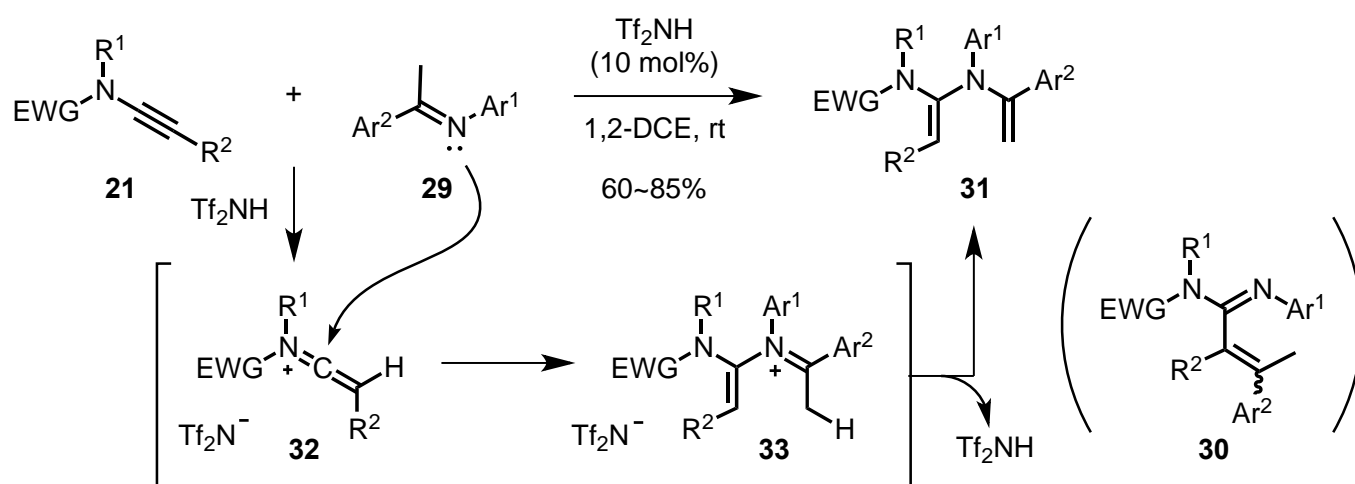


Scheme 7. Tf₂NH-Catalyzed Ring Expansion of Cyclic Hemiaminals (**27**)

5. REACTIONS OF YNAMIDES WITH KETIMINES

5-1. Reaction with *N*-Aryl Acetophenone Imines

During the course of the study to apply the above Tf₂NH-catalyzed formal aza-enyne metathesis to the stereoselective synthesis of tetra-substituted alkenes, we came across an unprecedented synthesis of *N,N*-divinylamines from ynamides and acetophenone imines (Scheme 8).⁴⁶ The Tf₂NH-catalyzed reaction of ynamide (**21**) and *N*-aryl acetophenone imine (**29**) proceeded smoothly at room temperature in spite of the low electrophilicity of the imine carbon of **29** compared to aldimines. However, the product was not the expected α,β -unsaturated amidine (**30**) bearing a tetra-substituted alkene moiety, but 3-azapentadiene (**31**) whose structure was unambiguously confirmed by X-ray crystallography. Although the diaminoalkene and divinylamine moieties of **31** seemed highly reactive, **31** was stable to be isolated and handled under both the solution and solid states. A plausible reaction mechanism of the formation of **31** is as follows: Due to the low electrophilicity of **29**, a nucleophilic attack of ynamide to the imine carbon did not occur under the reaction condition. Instead, ynamide (**21**) was protonated by Tf₂NH to form the keteneiminium cation (**32**), followed by addition of the imine nitrogen of **29** at the sp carbon to generate the iminium intermediate (**33**). The imine attack would preferentially take place from the opposite side of the R² substituent to avoid the steric hindrance. Finally, deprotonation of the methyl group of **33** afforded the final product (**31**) and regenerated Tf₂NH.

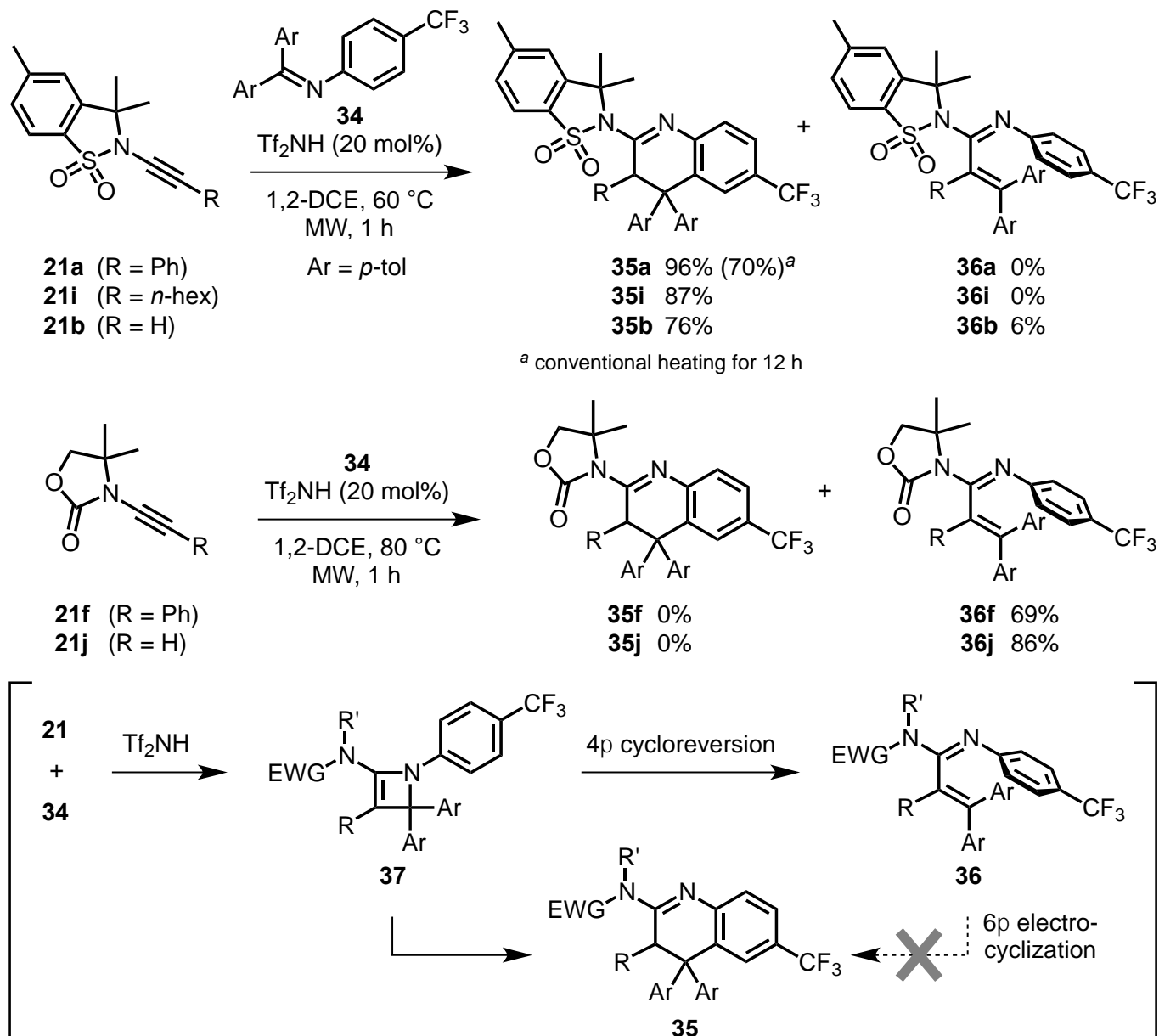


Scheme 8. Tf₂NH-Catalyzed Synthesis of *N,N*-Divinylamines (**31**) from Ynamide (**21**) and Imine (**29**)

5-2. Reaction with *N*-Aryl Benzophenone Imines

We also reported the Tf₂NH-catalyzed reaction of ynamides with benzophenone imines.⁴⁷ In this case, the product was either 2-amino-3,4-dihydroquinoline or α,β -unsaturated amidine depending on the electron-withdrawing group of the ynamide (Scheme 9). When yne-benzosultam (**21a**) and *N*-aryl

benzophenone imine (**34**) were treated with a catalytic amount of Tf₂NH (20 mol%) at 60 °C in 1,2-DCE, dihydroquinoline (**35a**) was obtained as the sole product. X-Ray crystallography confirmed the structure of **35a**. Microwave irradiation (120 W) greatly improved the yield of **35a**.



Scheme 9. Tf₂NH-Catalyzed Reaction of Ynamides (**21**) and Benzophenone Imines (**34**)

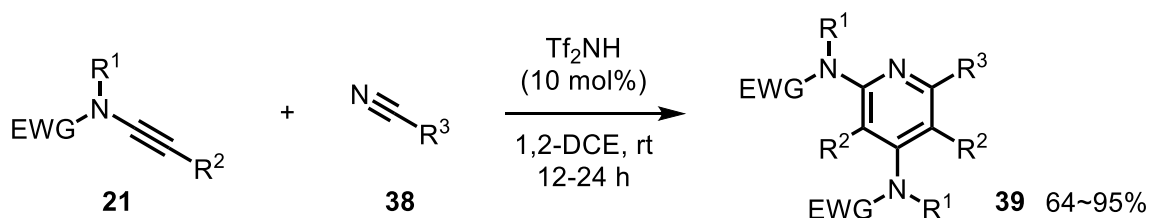
Alkyl-substituted and terminal yne-benzosultam (**21i**) and (**21b**) also afforded the corresponding dihydroquinolines (**35**) in good yields. Interestingly, terminal ynamide **21b** produced a minor amount of α,β -unsaturated amidine (**36b**) as a side product, whereas no formation of amidine was observed in the reaction of aryl- or alkyl-substituted yne-benzosultams. Surprisingly, yne-oxazolidinones (**21f**) and (**21j**) exclusively afforded amidines (**36**) in good to excellent yields. No formation of dihydroquinolines (**35**)

was detected even on reaction at higher temperatures for longer periods under microwave irradiation. Thus, the electron-withdrawing group of the ynamide displayed a remarkable influence on the reaction course with benzophenone imines. Like the reaction with aldimines, α,β -unsaturated amidines (**36**) would be produced through the cascade [2 + 2] cycloaddition– 4π cycloreversion via the intermediacy of 2-azetine (**37**). Dihydroquinolines (**35**) could be generated by a cycloisomerization of amidine (**36**) via an intramolecular Friedel–Crafts-type reaction or a thermal 6π -electrocyclic pathway. However, attempts on the transformation of isolated amidine (**36b**) into dihydroquinoline (**35b**) were unsuccessful even under harsher conditions (higher temperature, longer reaction time, a stoichiometric amount of Tf_2NH). The detailed mechanism is yet to be elucidated, dihydroquinoline (**35**) might be formed directly from 2-azetine (**37**) before the formation of amidine (**36**).

6. REACTIONS OF YNAMIDES WITH OTHER NITROGEN COMPOUNDS

6-1. Cyclotrimerization with Nitriles

Tf_2NH has also been utilized in several cycloadditions of ynamides with nitrogen-containing building blocks other than imines. Sun reported a Tf_2NH -catalyzed [2 + 2 + 2] cycloaddition (cyclotrimerization) of ynamides (**21**) with nitriles (**38**) (Scheme 10).⁴⁸ A gold-catalyzed version of the cyclotrimerization was previously reported to give pyrimidine derivatives from one ynamide molecule and two nitrile molecules.⁴⁹ By contrast, Tf_2NH catalysis altered the reaction chemoselectivity: The reaction employs two ynamide molecules and one nitrile molecule to afford fully substituted pyridines (**39**) in highly chemo- and regioselective manner. The reaction is supposed to proceed via initial protonation of ynamides with Tf_2NH to form the keteneiminium cation. DFT calculations suggested that another ynamide molecule attacks the α -carbon of the keteneiminium, followed by nitrile addition and intramolecular cyclization to afford the final product.

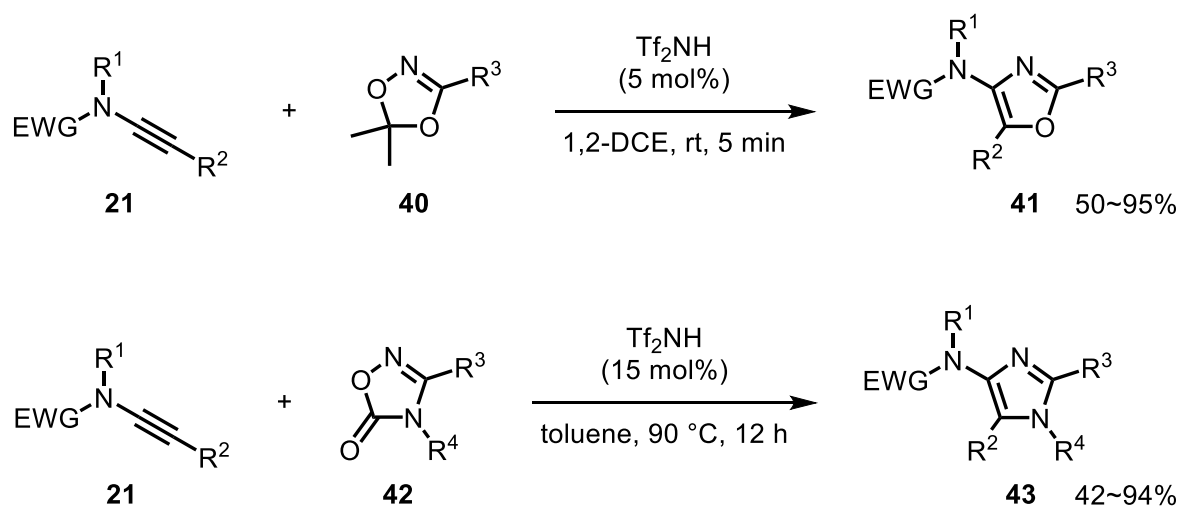


Scheme 10. A Tf_2NH -Catalyzed Cyclotrimerization of Ynamides (**21**) with Nitriles (**38**)

6-2. [3 + 2] Cycloadditions with Three-Atom Building Blocks

Cycloadditions of ynamides with nitrogen-containing three-atom building blocks afford five-membered azaheterocycles (Scheme 11). Wan and Li employed dioxazoles (**40**) as the building block in a [3 + 2]

cycloaddition with ynamides.⁵⁰ The reaction readily proceeded at room temperature in the presence of 5 mol% Tf_2NH , affording polysubstituted 4-aminoisoxazoles (**41**). The same authors also reported a [3 + 2] cycloaddition giving aminoimidazoles (**43**) utilizing oxadiazolones (1,2,4-oxadiazol-5(4*H*)-one) (**42**) as the three-atom unit.⁵¹ In this case, heating to 90 °C and 15 mol% catalyst loading were required. Likewise the cyclotrimerization with nitriles, these reaction are considered to be initiated by protonation of ynamides with Tf_2NH to form the keteneiminium cation.



Scheme 11. Tf_2NH -Catalyzed Cycloadditions of Ynamides with Nitrogen-Containing Three-Atom Units

7. CONCLUSION

This review showcases the global utility of Tf_2NH -catalyzed cycloadditions in azaheterocycle synthesis. High activity of Tf_2NH enables employment of relatively stable substrates rather than highly reactive but unstable substrates. Moreover, Tf_2NH facilitates cascade processes such as Povarov–hydrogen transfer reaction and [2 + 2] cycloaddition– 4π cycloreversion, allowing complex molecular transformations in a single operational step. Thus, Tf_2NH -catalyzed cycloadditions can be a powerful approach for the synthesis of structurally diverse azaheterocycles and related compounds from readily available materials with a simple experimental operation.

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