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Catalyst-Controlled Torquoselectivity Switch in the 4π Ring-Opening Reaction of 2-Amino-2-azetines Giving β-Substituted α,β-Unsaturated Amidines

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Supporting Information

ABSTRACT: The torquoselectivity of the 4π electrocyclic ring-opening reaction of 2-azetines can be controlled by the Brønsted acidity of the catalyst and the polarity of the solvent. DFT calculations provided insight into the mechanism of this remarkable switch. Anti and syn stereoisomers of α,β-unsaturated amidines were selectively synthesized from ynamides and aldimines in the presence of Tf_2NH and CSA, respectively.

4π Electrocyclic ring-opening reactions of cyclobutene analogues to give 1,3-dienyl compounds have attracted the attention of many synthetic and theoretical chemists.[1] The stereochemical process by which geometrical isomers are formed in these reactions is referred to as "torquoselectivity".[1a] The thermal conrotatory 4π ring-opening allows two senses of rotation of the terminal substituents of the double bonds of the product (inward versus outward rotation). Both steric and electronic factors affect torquoselectivity (Figure 1). Using ab initio calculations, Houk and co-workers showed that electronic effects dominantly control the torquoselectively and an electron-donating substituent at the C-4 position tends to rotate outward, whereas an electron-accepting substituent rotates inward (mode a).[1a] This theoretical prediction successfully explains many experimental results.[2] Steric effects can influence on the torquoselectivity of the 4π ring-opening when the electronic properties of the substituents are not significantly different. When the C-3 substituent is sterically smaller than the forming C(=X)R moiety, the bulky C-4 substituent tends to undergo an outward rotation (mode b). When the C-3 substituent is sterically bulky, an inward rotation of the larger C-4 substituent is preferred (mode c).[3] We have recently reported a selective synthesis of α,β-unsaturated amidines bearing a TIPS group at the α-position from ynesultams and aldimines by a domino [2 + 2] cycloaddition—4π ring-opening in which the torquoselectivity was determined by the steric bulk of the C-3 substituent (mode c).[3]

In most reported cases of 4π ring-opening, including our earlier effort, the torquoselectivity of the electrocyclic reaction is critically dependent on the properties of the substrates; a stereoselective synthesis of both geometrical isomers of the 1,3-dienyl compound from the same substrate is difficult.[4] We now disclose a catalyst-controlled synthesis of α,β-unsaturated amidines in which the rotation modes of the torquoselective electrocyclic ring-opening step can be switched by the properties of the acid catalysts.

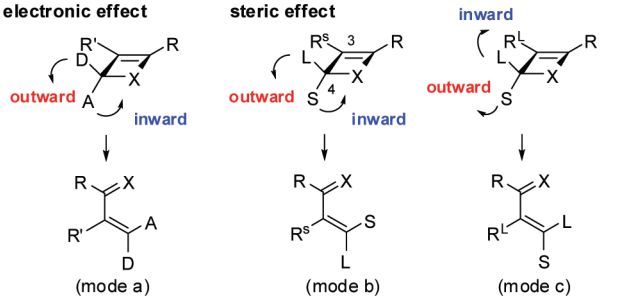
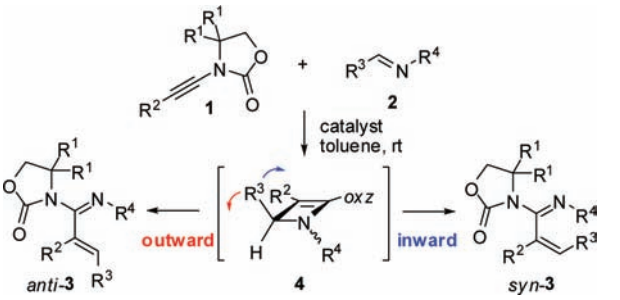


Figure 1. Modes of torquoselectivity in the 4π ring-opening reaction. Substituents, D, A, S, and L, signify electronically donating, electronically accepting, sterically small, and sterically large groups, respectively.

Scheme 1. Catalytic Reaction of Ynecarbamate 1 with Aldimine 2 Giving α,β-Unsaturated Amidine 3



During the course of our efforts to synthesize a variety of α,β-unsaturated amidines, we observed reverse stereoselectivity in the reaction of ynecarbamate **1**[4] with aldimines **2** (Scheme 1). When the reaction of **1a** (R^1 = Me, R^2 = TMS) with **2a** ($R^3 = R^4$ = *p*-$CF_3C_6H_4$) in toluene was carried out with triflic imide (Tf_2NH) as a catalyst, a mixture of two geometrical isomers, *anti*- and *syn*-**3aa**, was obtained in 95% yield (*anti*:*syn* = 92:8) (Table 1, entry 1). Using triflic acid (TfOH) and anhydrous tetrafluoroboric acid as catalysts also gave **3aa** in similar yields and selectivities (entries 2 and 3). Surprisingly, the stereoselectivity of **3aa** was inverted (*anti*:*syn* = ~15:~85) when methanesulfonic acid (MsOH) and 10-camphorsulfonic acid (CSA) were

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employed as catalysts (entries 5 and 6). Using *p*-toluenesulfonic acid (TsOH) resulted in a low yield of **3aa** with low selectivity (entry 4). These results suggested that the acidity of the catalysts affected selectivity; strong Brønsted acids (the pK_a of TfOH in CH_3CN is 2.6)[5] primarily produced the *anti*-product, whereas weaker acids (the pK_a of MsOH in CH_3CN is 10)[6] selectively furnished the *syn*-adduct. We have confirmed that isomerization between *anti*- and *syn*-**3aa** does not occur under the reaction conditions.

It has been shown that the stereochemistry of **3** is kinetically determined during the conrotatory ring-opening of 2-azetine **4**.[7,8] The possibility of acid-catalyzed *anti*/*syn* isomerization of **3** was ruled out; no isomerization of *anti*-**3aa** and *syn*-**3aa** was observed after 24 h in the presence of Tf_2NH and CSA. As previously reported by Houk et al., 4π electrocyclic ring-opening of 2-azetines may proceed exothermically without the assistance of catalysts.[7a] However, our data clearly demonstrate that the torquoselectivity of **4** can be switched by the properties of the acid catalysts. To the best of our knowledge, these are the first observations of a significant influence on the torquoselectivity of the 4π ring-opening reaction by a catalyst.[9]

To clarify the origins of catalyst-induced reverse torquoselectivity, the transition states for the 4π electrocyclic ring-opening of the simplified model compound **4ab** (R^1 = Me, R^2 = TMS, R^3 = Ph, R^4 = *p*-$CF_3C_6H_4$) were calculated using density functional theory (DFT) at the B3LYP/6-31(d) level.[10] The energy difference (ΔG^o) between the diastereomeric ammonium salts *cis*- and *trans*-[**4ab**·H]$^+$ is small, and the diastereomers rapidly equilibrate via deprotonation, inversion of a nitrogen atom, and reprotonation under the reaction conditions. Following the Curtin−Hammett principle,[11] we considered four possible transition states: inward (**TS**s **A** and **B**) and outward (**TS**s **C** and **D**) rotations of the R^3 substituent and *cis* (**TS**s **A** and **C**) and *trans* (**TS**s **B** and **D**) relationships between the R^4 and R^3 substituents (Figure 2). The *E*/*Z* stereochemistry of the C=N moiety of **3** (oxazolidinone vs R^4) readily epimerizes,[12] and the *E* geometry is much more stable than the *Z* geometry. Therefore, only the geometry of the C=C bond reports the torquoselectivity of the ring-opening reaction.

Table 2 summarizes the relative Gibbs free energy ($\Delta\Delta G^{\ddagger}$ of the **TS**s **A**−**D** under three sets of conditions: (1) in the presence of proton (a naked ammonium cation), (2) in the presence of TfOH (an intimate ion pair), and (3) in the presence of MsOH (an intimate ion pair). Under each set of conditions for the reaction of 2-azetinium salt [**4**·H]$^+$, **TS**s **A** and **D** were more stable than **TS**s **B** and **C** and were the structures that produced *syn*- and *anti*-**3**, respectively. These results indicated that the

Table 1. Effect of a Catalyst on *anti*/*syn* Selectivity of 3aa[a]

entry	catalyst	% yield of **3aa**	*anti*/*syn*[c]
1[b]	Tf_2NH	95	92:8
2	TfOH	93	95:5
3[b]	HBF_4·OMe_2	97	94:6
4	TsOH·H_2O	5	55:45
5	MsOH	40	17:83
6	CSA	79	15:85

[a] Conditions: **1a** (R^1 = Me, R^2 = TMS), **2a** (R^3 = R^4 = ^{p}$CF_3C_6H_4$) (1.2 equiv), catalyst (20 mol %), solvent (0.3 M), rt, 24 h. [b] Catalyst (10 mol %), 30 min. [c] Ratios were determined by ^{1}H NMR.

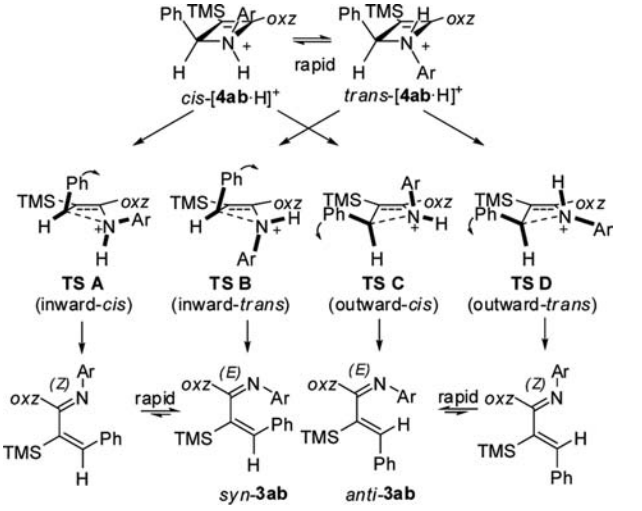

Figure 2. Four possible transition states **TS**s **A**−**D** for conrotatory ring-opening of **4ab**. *oxz* = dimethyloxazolydinoyl, Ar = *p*-$CF_3C_6H_4$.

Table 2. Calculated Ring-Opening Free Energy for Protonated 4ab with/without a Counteranion

entry	azetine[a]	transition structure	$\Delta G^{\ddagger}$ (kcal/mol)[b]	$\Delta\Delta G^{\ddagger}$ (kcal/mol)	final product
1.1	*cis*-[**4ab**·H]$^+$	**TS A**^{1}	6.5	+1.4	*syn*-**3ab**
1.2	*trans*-[**4ab**·H]$^+$	**TS B**^{1}	9.0	+3.9	
1.3	*cis*-[**4ab**·H]$^+$	**TS C**^{1}	8.6	+3.5	*anti*-**3ab**
1.4	*trans*-[**4ab**·H]$^+$	**TS D**^{1}	5.1	**0**	
2.1	*cis*-**4ab**·TfOH	**TS A**^{2}	8.8	**0**	*syn*-**3ab**
2.2	*trans*-**4ab**·TfOH	**TS B**^{2}	22.0	+13.2	
2.3	*cis*-**4ab**·TfOH	**TS C**^{2}	15.4	+6.6	*anti*-**3ab**
2.4	*trans*-**4ab**·TfOH	**TS D**^{2}	9.9	+1.1	
3.1	*cis*-**4ab**·MsOH	**TS A**^{3}	8.9	**0**	*syn*-**3ab**
3.2	*trans*-**4ab**·MsOH	**TS B**^{3}	23.2	+14.3	
3.3	*cis*-**4ab**·MsOH	**TS C**^{3}	15.2	+6.3	*anti*-**3ab**
3.4	*trans*-**4ab**·MsOH	**TS D**^{3}	10.2	+1.3	

[a] $\Delta G^o_{(cis-trans)}$ = +3.1 kcal/mol for [**4ab**·H]$^+$, $\Delta G^o_{(cis-trans)}$ = +1.8 kcal/mol for **4ab**·TfOH, $\Delta G^o_{(cis-trans)}$ = +1.8 kcal/mol for **4ab**·MsOH. [b] $\Delta G^{\ddagger}$ values were calculated based on the more stable *trans*-substrate.

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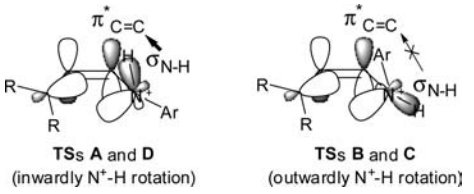


Figure 3. Orbital interactions in the transition states for the ring-opening of $[4\cdot H]^+$. TMS and oxazolidinone moieties are omitted for clarity.

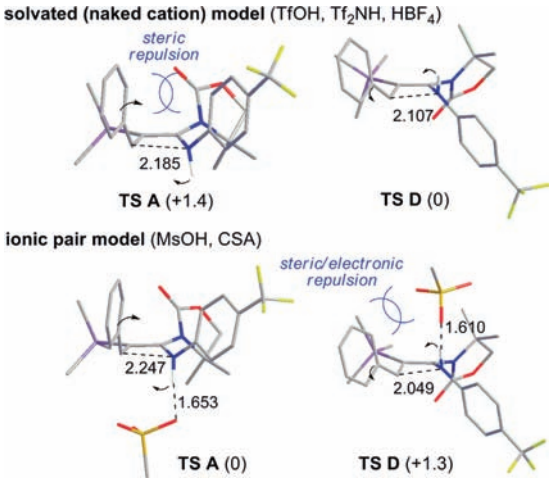


Figure 4. The most stable transition states leading to *anti*- and *syn*-**3ab** in the presence of TfOH and MsOH, respectively. Selected distances in Å. $\Delta\Delta G^{\ddagger}$ (kcal/mol) between **TS A** and **TS D** are shown in parentheses.

torquoselectivity is predominantly determined by the substituents on the ammonium nitrogen. We propose that the key interaction is a hyperconjugation between the ammonium proton (N^+-H) and the π system of the 4-membered ring. Stabilization resulting from alignment of the filled σ_{N-H} orbital with the unfilled $\pi^*_{C=C}$ orbital of the alkene might be expected in **TS**s **A** and **D** (Figure 3). In contrast, the stabilizing contribution of the interaction between the σ_{N-Ar} orbital and the $\pi^*_{C=C}$ orbital in **TS**s **B** and **C** would be smaller, and an interaction between σ_{N-H} and $\pi^*_{C=C}$ is unavailable.[13] A related interaction was proposed to explain torquoselectivity in the ring-opening of 2-azetine (a neutral amine). Houk et al. suggested that one of the lone pairs on the nitrogen atom controls the torquoselectivity by aligning with the π^* orbital of the alkene.[7a]

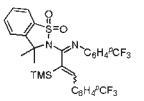
In the absence of a counteranion (Table 2, entries 1.1−1.4), **TS D** giving *anti*-**3ab** was calculated to be the most stable transition state, which is consistent with the experimental results using TfOH. When a sulfonate anion was present, **TS A** giving *syn*-**3ab** was calculated to be the most stable transition state (entries 2.1−2.4 and 3.1−3.4). These computational results agree with the MsOH-catalyzed reaction but are inconsistent with TfOH-catalyzed one. Thus, the results indicate that the ring-opening reaction of azetine **3** with strong Brønsted acid catalysts such as TfOH and Tf_2NH might be preferably promoted by a solvated model. The experiment using an HBF_4 catalyst, which would produce a naked ammonium cation with a coordinate saturated anion (BF_4^-), strongly supports this mechanism. However, weaker sulfonic acids such as MsOH might be favored by an ionic pair model, in which the cationic N−H moiety

Table 3. Solvent Effect on *anti/syn* Selectivity of 3aa[a]

entry	catalyst	solvent	% yield of **3aa**	*anti/syn*[c]
1[b]	Tf_2NH	CH_3CN	86	95: 5
2	Tf_2NH	DMF	0	—
3	CSA	CH_3CN	50	33: 67
4	CSA	$ClCH_2CH_2Cl$	45	25: 75
5	CSA	$CF_3C_6H_5$	77	13: 87

[a] Conditions: **1a**, **2a** (1.2 equiv), catalyst (20 mol %), solvent (0.3 M), rt, 24 h. [b] Catalyst (10 mol %), 30 min. [c] Ratios were determined by ^{1}H NMR.

Table 4. Stereoselective Synthesis of α,β-Unsaturated Amidines Catalyzed by Tf_2NH or CSA[a]

entry	**3** (R^1, R^2, R^3, [R^4 = ^{p}$CF_3C_6H_4$])	Method[b]	%yield (*anti/syn*)[c]
1	**3ab** (Me, TMS, C_6H_5)	A	82 (>99 : 1)
2	**3ab**	B	70 (16 : 84)
3	**3ac** (Me, TMS, 1-naphthyl)	A	62 (>99 : 1)
4[d]	**3ac**	B	88 (16 : 84)
5	**3ba** (Me, TBS, ^{p}$CF_3C_6H_4$)	A	98 (76 : 24)
6	**3ba**	B	57 (7 : 93)
7	**3ca** (-$(CH_2)_4$-, TMS, ^{p}$CF_3C_6H_4$)	A	79 (94 : 6)
8[d]	**3ca**	B	72 (11 : 89)
9	**3da** 	A	62 (47 : 53)
10		B	64 (2 : 98)

[a] Conditions: **1**, **2** (1.2 equiv), rt. [b] Method A: Tf_2NH (20 mol %), MeCN (0.3 M), 1−6 h. Method B: CSA (20 mol %), TFT (0.3 M), 24−48 h. [c] The ratios were determined by ^{1}H NMR. [d] Reactions were carried out at 60 °C.

intimately interacts with a counteranion. For the solvated-ion model, preference for **TS D** giving *anti*-**3** over **TS A** giving *syn*-**3** (+1.4 kcal/mol)[14] might be explained by the steric effect. In the *cis*-orientation, the steric repulsion of the two aromatic rings would somewhat destabilize **TS A**. For the ionic pair model, the calculated structure of **TS D** indicated steric and/or electronic repulsion between the aromatic ring on C-4 and the sulfonate anion (details for the important atomic distances of TSs **A** and **D** in the Supporting Information [SI]). Consequently, the ring-opening reaction would proceed preferably via **TS A** in the presence of MsOH or CSA (Figure 4).

To further clarify the proposed mechanisms and improve selectivity, we next examined the effect of solvents on *anti/syn* selectivity in the reaction of **1a** with **2a** (Table 3). When the reaction was carried out in a polar solvent (CH_3CN) in the presence of Tf_2NH, the *anti*-selectivity of **3aa** was slightly increased relative to toluene (Table 3, entry 1 vs Table 1, entry 1). Unfortunately, the reaction did not proceed in more polar DMF (Table 3, entry 2). A considerable solvent effect was observed in the reaction with CSA. The proportion of *anti*-**3aa** versus *syn*-**3aa** increased in polar solvents such as CH_3CN (entry 3), whereas nonpolar solvents, such as toluene and trifluorotoluene (TFT), led to preferable formation of *syn*-**3aa** (entries 4 and 5). The experimentally observed solvent effect supports the hypothesis that the Tf_2NH- and CSA-catalyzed reactions proceed preferably via the naked cation model and the intimate ionic-pair model, respectively. Thus, the reaction using Tf_2NH in a polar solvent would be optimal for selective synthesis of the *anti*-adduct, whereas the *syn*-adduct would be selectively produced by using

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CSA in a nonpolar solvent (details for the computational study in the SI).

Having determined the optimal conditions for selective synthesis of both isomers, we then examined the scope of the reaction using several ynecarbamates and aldimines as substrates. As shown in Table 4, *anti*- and *syn*-**3** were obtained in good to excellent yield and selectivity in reactions with Tf_2NH and CSA, respectively. The stereoselectivity change was also observed in the reaction of ynesultam **1d** (entries 9 and 10), although no anti selectivity was observed in the reaction with Tf_2NH.

In conclusion, we have shown that external factors, such as the Brønsted acidity of the catalyst and the polarity of the solvent, affect the torquoselectivity of 4π ring-opening of 2-azetine compounds. The inward/outward torquoselectivity may be inverted by the use of Tf_2NH or CSA. This is the first successful example of a catalyst-controlled selectivity switch in electrocyclic ring-opening reactions.

■ ASSOCIATED CONTENT

Supporting Information. Details of the computational study, experimental methods, spectral data for all new compounds, and X-ray crystallographic data of *anti*-**3ac**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) The electronic effect of the *N*-Ar of **4** on the torquoselectivity was also evaluated. See SI.

(14) The *anti*/*syn* selectivities based on the calculated $\Delta\Delta G^{\ddagger}$ are estimated to be 91: 9 and 11: 89 in the solvated and ionic pair models, respectively, at 25 °C.