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A Formal [3 + 3] Cycloaddition Reaction. 5. An Enantioselective Intramolecular Formal Aza-[3 + 3] Cycloaddition Reaction Promoted by Chiral Amine Salts

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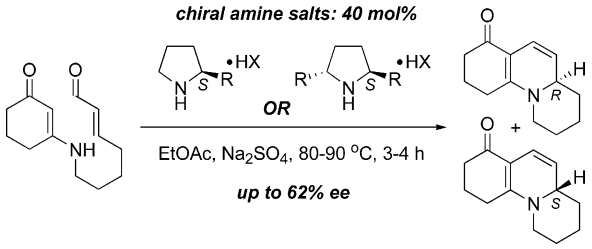

A detailed account on chiral secondary amine salt promoted enantioselective intramolecular formal aza-[3 + 3] cycloadditions is described here for the first time. The dependence of enantioselectivity on the structural feature of these chiral amines is thoroughly investigated. This study also reveals a very interesting reversal of the stereochemistry in the respective cycloadducts obtained using C_1- and C_2-symmetric amine salts. In addition, the influence of solvents, counteranions, and temperatures on the enantioselectivity is described, and a unified mechanistic model based on experimental results as well as semiempirical calculations is proposed.

Introduction

Over the past several years we have been developing an annulation reaction using vinylogous amides and α,β-unsaturated iminium salts.[1,2] Specifically, this annulation provides a powerful synthetic access to nitrogen heterocycles such as dihydropyridines **3** and quinolizidines **7** in intermolecular and intramolecular manifolds, respectively [Figure 1].[3−7] It represents a formal aza-[3 + 3] cycloaddition[8,9] with two of the five carbons along with the nitrogen atom coming from the vinylogous amide [see **1** or **4**] and the remaining three carbons coming from the α,β-unsaturated iminium salt [see **2** or **5**]. The net result is the formation of two σ-bonds and a new stereocenter adjacent to the nitrogen atom.

While both reaction manifolds provide a unique and novel approach to the synthesis of alkaloids,[7,10,11] they proceed through very different mechanistic courses.[5,6] The intermolecular formal aza-[3 + 3] cycloaddition reaction [**1** + **2** → **3**] mechanistically constitutes a tandem Knoevenagel condensation-6π-electron electrocyclic ring-closure involving a 1-azatriene intermediate.[12−14] The latter part of this tandem sequence, the pericyclic ring-

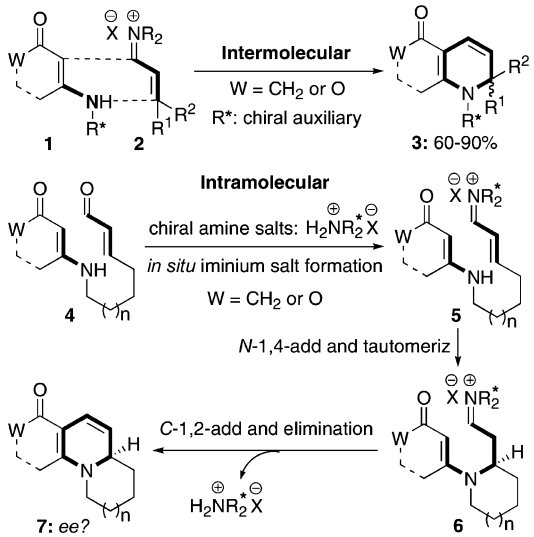

FIGURE 1. A formal aza-[3 + 3] cycloaddition.

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closure, can be rendered highly stereoselective when driven by a chiral auxiliary.[5b,c,7b] On the other hand, the intramolecular process [**4** → **7**] proceeds through a tandem sequence that features an *N*-1,4-addition via the in situ generated α,*β*-unsaturated iminium salt **5**, and a *C*-1,2-addition through the iminium intermediate **6** [Figure 1].[5b,6] Because it is possible to regenerate the amine salt during the *C*-1,2-addition and subsequent elimination, only a sub-stoichiometric amount of secondary amine salts was needed to afford **7**.[6]

Consequently, this difference in mechanism allowed us to envision the possibility of an asymmetric intramolecular formal aza-[3 + 3] cycloaddition using a catalytic amount of chiral amine salt [Figure 1]. Given that organocatalysis has attracted much attention recently,[15−19] investigations here should represent a unique opportunity to explore organocatalysis in a tandem process. In the current paper, we reveal details on chiral amine salt-promoted enantioselective intramolecular formal aza-[3 + 3] cycloadditions.

Results and Discussions

1. Feasibility and Absolute Stereochemistry. 1.1. Synthetic Feasibility. To explore the feasibility of an enantioselective formal aza-[3 + 3] cycloaddition, vinylogous amide **8** was synthesized[20] and its reaction was examined using a series of L-proline based amine salts **9a**−**e**, which are C_1-symmetric, and various pyrrolidine-based amine salts **10a**−**c**, which are C_2-symmetric. These results are summarized in Table 1.

It can be seen that in all cases the reaction proceeded well to give the formal cycloadduct **11** in moderate to good yields. The use of 30−40 mol % of the chiral catalyst was sufficient to promote the cycloaddition [entries 1, 2, 6, 8, and 10], while increasing the amount of the catalyst did not necessarily lead to an improved enantioselectivity [entries 3−5, 7, and 9].

More importantly, three features of the cycloaddition captured our attention. First, C_2-symmetric pyrrolidine-

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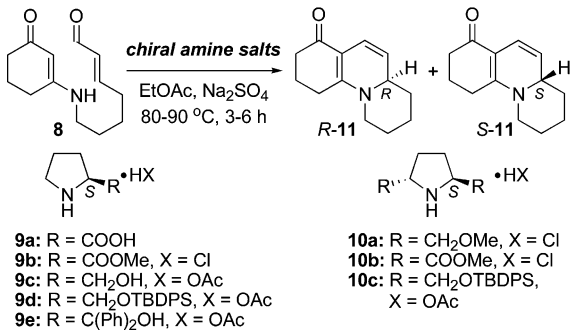
(20) See the Supporting Information for details of all preparations, characterizations, and relevant Spartan'02 models.

TABLE 1. Chiral Pyrrolidine-Catalyzed Cycloaddition



entry	catalyst	mol %	yield[a] (%)	er (*R*:*S*)[b]
1	**9a**[c]	40	26	56:44
2	**9b**[c]	30	68	52:48
3	**9b**	100	68	52:48
4	**9c**[c,d]	100	52	50:50
5	**9d**[d]	100	56	55:45
6	**9e**[e]	40	60	81:19
7	**9e**	100	63	80:20
8	**10a**[f]	40	57	50:50
9	*ent*-**10b**[g]	100	67	60:40
10	**10c**[d]	40	46	27:73

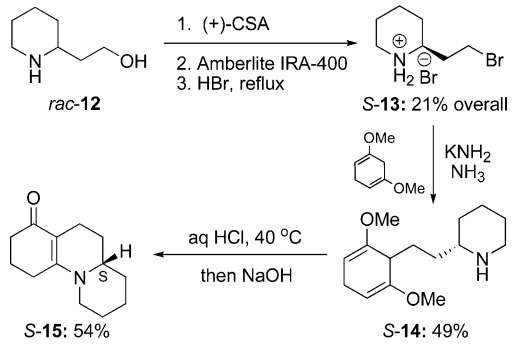
[a] Isolated yields. [b] Determined by CSP-HPLC. [c] Commercially available. [d] The acetate salt was generated in situ by addition of 1.0 equiv of AcOH to the reaction mixture. [e] The acetate salt was synthesized from commercially available free amine (see ref 20). [f] For the synthesis, see ref 21. [g] The 2*R*,5*R*-isomer was used for the reaction.

based catalysts gave higher enantiomeric ratios than those obtained from using L-proline-based derivatives [i.e., entries 2 and 5 versus 9 and 10, respectively]. Second, the enantioselectivity could be modestly enhanced by using sterically more bulky catalysts such as **9e** [entry 6] and **10c** [entry 10] but appears to have reached the maximum. Third, it was found that C_1- and C_2-symmetric catalysts provided cycloadduct **11** with enrichment for the opposite enantiomer [entry 6 versus 10].

1.2. Absolute Configuration Assignment. To assess the origin of observed enantioselectivity, the absolute configuration of the major enantiomer was first determined. After numerous failed attempts to derivatize the cycloadduct **11**,[22] *S*-**15** was synthesized independently as shown in Scheme 1,[23] featuring a resolution of racemic piperidine **12** with (+)-CSA using a procedure developed by Toy.[24]

The absolute configuration was determined based on CSP-HPLC comparison between the scalemic **15** obtained via hydrogenation of the formal cycloadduct **11** and the

SCHEME 1. Independent Synthesis of *S*-15



enantiomerically pure *S*-**15** [Figure 2]. Interestingly, when the *S*-enantiomer of C_1-symmetric catalyst such as **9e** was used, the cycloaddition favored the *R*-enantiomer, while the 2*S*,5*S*-enantiomer of C_2-symmetric catalyst **10c** gave predominantly *S*-enantiomer.

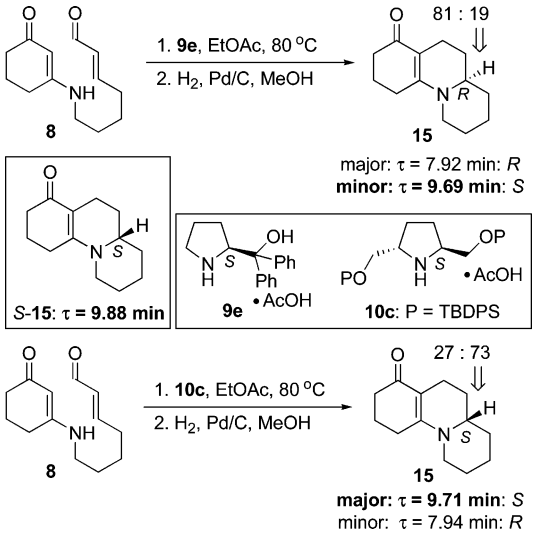


FIGURE 2. Determination of absolute configuration.

2. Catalyst Screening and Synthetic Scope. 2.1. Catalyst Screening. In the search for an amine catalyst that can provide improved asymmetric induction, chiral piperidines **16a**−**f** were screened [Table 2]. The first observation was that the nature of the counteranion in the catalyst did not appear to have any impact on the enantioselectivity. For instance, using the L-tartrate salt of pipecolic acid (**16b**) did not lead to any improvement in the enantiomeric ratio when compared to the acetate salt **16a** [entry 2 versus 1]. Most disappointingly, none of the chiral piperidines provided any meaningful enantioselectivity.

Moreover, treatment of vinylogous amide **8** with the amine salt **16e** bearing a diphenylhydroxymethyl substituent did not lead to the desired dihydropyridine **11** under standard reaction conditions [entry 5]. Instead, the reaction had to be heated at an elevated temperature (130 °C) for 14 h in a sealed tube in which severe decomposition occurred with only ca. 50% conversion. Although we were able to isolate some **11**, it was racemic. The reaction temperature could be lowered to 80 °C when using the more active trifluoroacetate salt **16f** [see Section 3 below for more details]. In this case, the

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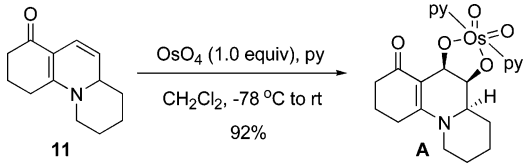

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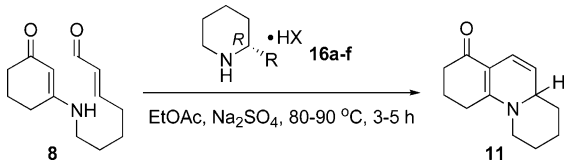
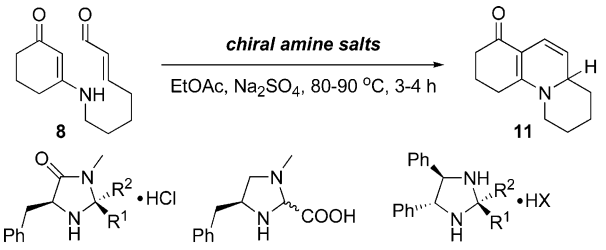
TABLE 2. Chiral Piperidines as Catalysts



entry	piperidine catalyst		mol %	yield[a] (%)	er (*R*:*S*)[b]
1	**16a**[c,d]	R = COOH X = OAc	40	45	48:52
2	**16b**[c]	R = COOH X = L-tartrate	40	53	47:53
3	**16c**[e]	R = COOMe X = Cl	50	65	48:52
4	**16d**[d]	R = $CH_2OTBDPS$ X = OAc	100	42	47:53
5	**16e**[e]	R = $C(Ph)_2OH$ X = Cl	40	~15[f]	49:51
6	**16f**	R = $C(Ph)_2OH$ X = O_2CCF_3	40	62	48:52

[a] Isolated yields. [b] Determined by CSP HPLC. [c] For its synthesis, see ref 25a. [d] The acetate salt was generated in situ via addition of 1.0 equiv of AcOH to the reaction mixture. [e] See ref 25a,b. [f] The reaction was carried out at 130 °C for 14 h. The product **11** was isolated at ca. 50% conversion.

TABLE 3. MacMillan's and Jørgensen's Amine Salts



17a: $R^1 = R^2$ = Me
17b: R^1 = *t*-Bu, R^2 = H
17c: R^1 = H, R^2 = *t*-Bu

19a: R^1 = COOH, R^2 = H
19b: $R^1 = R^2 = CH_3$, X = OAc
19c: R^1 = Ph, R^2 = H, X = OAc

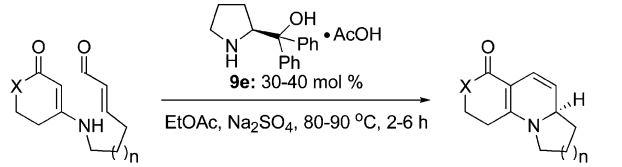
entry	catalyst	mol %	yield[a] (%)	er (*R*:*S*)[b]
1	**17a**[c,d]	50	16[e]	50:50
2	**17b**[f]	50	27	50:50
3	**17c**[f]	50	22	58:42
4	**18**[g]	100	57	60:40
5	**19a**[g]	100	53	63:37
6	**19b**[g,h]	100	48	62:38
7	**19c**[g,h]	100	63	50:50

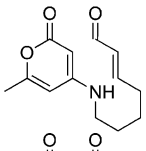
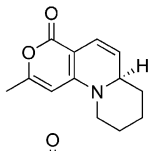
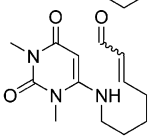
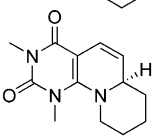
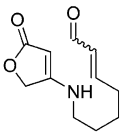
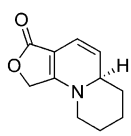
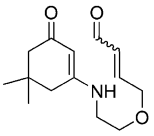
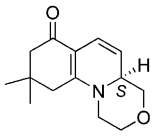
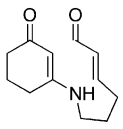
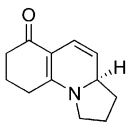
[a] Isolated yields. [b] Determined by CSP-HPLC. [c] For its synthesis, see ref 16i. [f] The reaction was carried out at room temperature for 30 h. [e] Significant decomposition observed. [f] See ref 16d. [g] See ref 18g. [h] The acetate salt was generated in situ by addition of 1.0 equiv of AcOH to the reaction mixture.

cycloaddition of **8** went to completion in 2 h and **11** was isolated in good yield [entry 6]. However, the product remained racemic. These results suggest that chiral piperidines are even less useful as chiral catalysts than chiral pyrrolidines for this particular reaction.

To continue our efforts, we turned to MacMillan's chiral amine salts **17a**−**c**[16d,i] [Table 3] as well as those developed by Jørgensen [**18** and **19a**−**c**].[18g] These amines are known to catalyze a variety of organic transformations in a highly enantioselective manner.[15−19] As summarized in Table 3, the desired cycloadduct **11** was isolated in all cases, but the highest enantiomeric ratio was only 63:37 when using C_2-symmetric catalyst **19a**

TABLE 4. Synthetic Scope



entry	starting amide		cycloadduct		yield[a] (%)	*er* (*R* : *S*)[b]
1		**20**		**25**	56	75 : 25
2		**21**		**26**	65[c]	80 : 20
3		**22**		**27**	41[c]	74 : 26[d]
4		**23**		**28**	61[c]	27 : 73
5		**24**		**29**	44	60 : 40

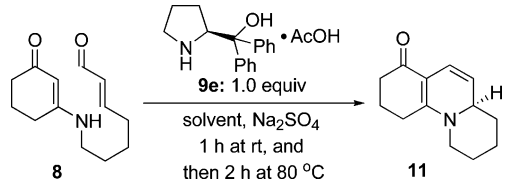
[a] Isolated yields. [b] Determined by CSP-HPLC. [c] *E*/Z mixtures were used. [d] Determined by LC/MS (see ref 20).

[entry 5]. In addition, for reactions catalyzed with **17a**−**c**, a significant amount of decomposition occurred, thereby leading to lower yields [entries 1−3].

2.2. Synthetic Scope. On the basis of these results, the acetate salt of α,α-diphenyl-2-pyrrolidinemethanol **9e** appears to be the most efficient catalyst to promote a modestly enantioselective intramolecular formal aza-[3 + 3] cycloaddition reaction of vinylogous amide **8**. Thus, various other vinylogous amides **20**−**24** were prepared and employed in the formal aza-[3 + 3] cycloaddition catalyzed by **9e**. As illustrated in Table 4, all reactions proceeded to give the respective cycloadducts **25**−**29** in modest to good yields and comparable enantioselectivity with the exception of vinylogous amide **24**, bearing a 3-carbon tether, which gave only 20% ee [entry 5].

3. Solvent, Counteranion, and Temperature Effects. 3.1. Solvent Effect. We subsequently pursued a series of studies to investigate what other factors could effect or improve the enantioselectivity of this formal cycloaddition. Toward this goal, the reaction of vinylogous amide **8** was carried out in different solvents in the presence of 1.0 equiv of the amine salt **9e** [Table 5]. The reaction was kept at room temperature for 1 h, and was then heated to 80 °C for 2 h. At this point complete consumption of **8** was observed by TLC. Only in the case of acetic acid [entry 6], no formation of the desired cycloadduct **11** was detected besides decomposition of starting material. Under these conditions, there appears to be no significant dependence of the enantioselectivity

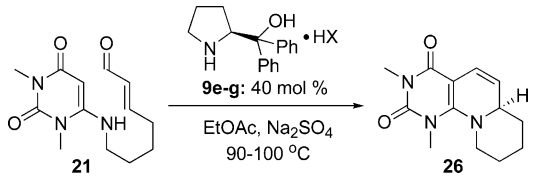
TABLE 5. Solvent Effect



entry	solvent	yield[a] (%)	er (*R*:*S*)[b]
1	EtOAc	60	81:19
2	$CHCl_3$	57	76:24
3	EtOH	42	81:19
4	acetone	53	84:16
5	THF	48	83:17
6	AcOH	NA	decomp

[a] Based on ^{1}H NMR. [b] Determined by CSP-HPLC.

TABLE 6. Counteranion Effect



entry	catalyst	time (h)	yield[a] (%)	er (*R*:*S*)[b]
1	**9e**: X = OAc	1.5	61	80:20
2	**9f**: X = O_2CCF_3	1	58	79:21
3	**9g**: X = Cl[c]	12	66	76:24

[a] Isolated yield only. [b] Determined by CSP-HPLC. [c] For its synthesis, see ref 26.

on solvent. The observed enantiomeric ratio stayed at about 80:20, which was initially found for reactions carried out in EtOAc [see also entry 1]. Only a slight increase in selectivity was detected when acetone was used [entry 4].

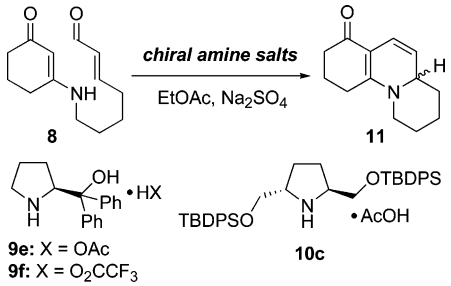
3.2. Counteranion Effect. We then examined the possibility of a counteranion effect in the case of the most effective amine, α,α-diphenyl-2-pyrrolidinemethanol. Toward that goal, vinylogous amide **21** was allowed to react with three different amine salts **9e**−**g** under standard reaction conditions [Table 6].

In all cases, the desired cycloadduct **26** was isolated in good yield, but there was again no significant dependence on the nature of the counteranion. However, there was a noticeable difference in reaction rate between the three catalysts. It turned out that the trifluoroacetate salt **9f** was the most active with complete conversion of **21** to **26** in 1 h [entry 2]. The reaction with the acetate salt **9e** took a longer time to complete [entry 1], while the chloride salt **9g** was found to be the least active [entry 3].

The observed difference in reactivity can be rationalized in two possibilities. First, the chloride salt **9g** is not as soluble in EtOAc as the acetate salt **9e** or the trifluoroacetate salt **9f**. Second, a more important possibility would be that the difference in reactivity is related to the dissociation capacity of the respective amine salts.

Since both "free amine" and "free acid" are needed in a synergistic manner to generate the α,*β*-unsaturated iminium salt from the corresponding aldehyde, the ability

TABLE 7. Temperature Effect



entry	cat. (mol %)	temp (°C)	time (h)	yield[a] (%)	er (*R*:*S*)[b]
1	**9f** (40)	rt	10	43	75:25
2	**9e** (50)	80	6	60	81:19
3	**10c** (40)	rt	14	16	23:77
4	**10c** (40)	80	3	46	27:73

[a] Isolated yields. [b] Determined by CSP-HPLC.

of the amine salt to dissociate to its "free amine" and "free acid" can exert an impact on the rate of the iminium salt formation. The low reactivity of the chloride salt **9g** can be attributed to its higher resistance toward dissociation, or **9g** is simply a tighter ion-pair compared to the acetate salt **9e** and the trifluoroacetate **9f**. At the same time, the formation of α,*β*-unsaturated iminium salt from the aldehyde and the "free amine" is also promoted by protonation of the carbonyl group via the "free acid". Consequently, increased reactivity of the trifluoroacetate salt **9f** from the acetate salt **9e** can be attributed to a higher acidity of trifluoroacetic acid.

3.3. Temperature Effect. Finally, we examined the temperature effect as shown in Table 7. Vinylogous amide **8** was reacted with chiral amine salt **10c** and reactive trifluoroacetate **9f** at room temperature, and the resulting enantiomeric ratios were compared with reactions carried out at 80 °C. The reaction took much longer at room temperature and led to lower yields of **11** [entries 1 and 3], and no significant increase in enantioselectivity was observed in either case.

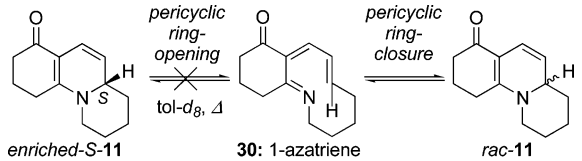
4. A Proposed Mechanistic Model. 4.1. Racemization Possibility and Enal Geometry. As indicated in the Introduction, the intermolecular aza-[3 + 3] cycloaddition undergoes a pericyclic ring-closure of 1-azatriene intermediates en route to the formation of 1,2-dihydropyridines.[5b] Although intramolecular reactions proceed through a different mechanism altogether,[5b,6] we still questioned if the modest enantioselectivity obtained from these chiral amine catalyzed cycloadditions could be a result of racemization of the final cycloadduct via the same 6*π*-electron electrocyclic ring-opening and ring-closure through the 1-azatriene intermediate **30** [Table 8].

To test this possibility, an enantiomerically enriched sample of cycloadduct **11** was heated in toluene-d_8. After 3 h at 85 °C, no loss of ee was detected [entry 2]. More significantly, even after **11** was heated at 130 °C for 12 h, no racemization had occurred [entry 3]. Ab initio calculations[27] indicate 1-azatriene **30** to be destabilized

(25) (a) Shiraiwa, T.; Shinjo, K.; Kurokawa, H. *Bull. Chem. Soc. Jpn.* **1991**, *64*, 3251. (b) Portoghese, P. S.; Pazdernik, T. I.; Kuhn, W. L.; Hite, G.; Shaf'ee, A. *J. Med. Chem.* **1968**, *11*, 12.

(26) Aggarwal, V. K.; Lopin, C.; Sandrinelli, F. *J. Am. Chem. Soc.* **2003**, *125*, 7596.

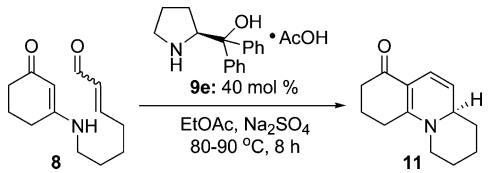
TABLE 8. Racemization via Pericyclic Ring-Opening



entry	time (h)	temp (°C)	er (R:S)[b]
1	0	rt	27:73
2	3	85	26:74
3	12	130	27:73

[a] Determined by CSP-HPLC.

TABLE 9. Impact of Enal Geometry



entry	E:Z	yield[a] (%)	er (R:S)[b]
1	100:0	60	81:19
2	27:73	58	77:23

[a] Isolated yields. [b] Determined by CSP-HPLC.

relative to **11** by ~31 kcal/mol. Since the activation barrier would be even higher, we believe that the 6π-electrocyclic ring-opening process is not thermally accessible under our standard reaction conditions.

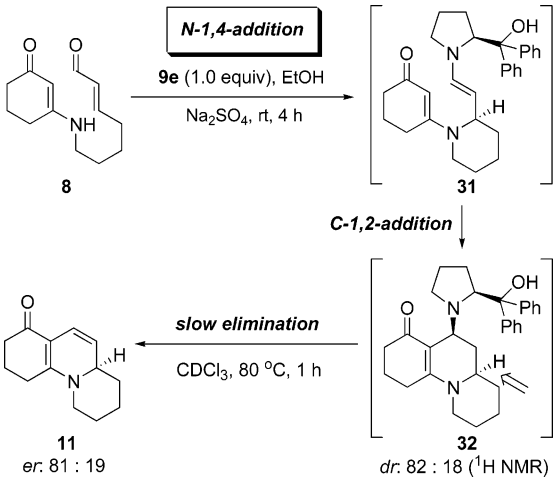
To examine the influence of the enal geometry on enantioselectivity, a mixture of *E*/*Z*-isomers of vinylogous amide **8** was submitted to standard reaction conditions using **9e** [Table 9]. The product **11** was isolated in comparable yield and its enantiomeric purity [entry 2] was virtually the same as in the reaction of pure trans-isomer [entry 1]. We believe that a facile isomerization of *Z*-enal to the more stable *E*-isomer takes place under the reaction conditions, thereby rendering the enal geometry irrelevant to the asymmetric induction.

4.2. Detection of the Key Intermediate. When vinylogous amide **8** was reacted with 1.0 equiv of the amine salt **9e** at room temperature in EtOH, the formation of the intermediate **32** was detected by ^{1}H NMR and mass spectroscopy [Scheme 2]. Interestingly, only two of the four possible diastereomers were seen with a ratio of 82:18, and heating of the intermediate **32** at 80 °C led to the formation of **11** with an enantiomeric ratio of 81:19. This experimental outcome suggests that the stereochemical induction likely occurs during the *N*-1,4-addition step.

4.3. A Proposed Mechanism. With all of the above experimental findings, we propose the following mechanism for our enantioselective intramolecular aza-[3 + 3] cycloaddition reaction [Figure 3]. The initial chiral iminium salt **33** can undergo *N*-1,4-addition in either a *Re*- or *Si*-facial approach toward the β-carbon, leading to two diastereomeric enamines *R*-**34a** and *S*-**34a**. At this stage,

(27) Calculations were carried out in Spartan′02 software on a Dell Precision 650 Dual Xeon (2.00 GHz) workstation.

SCHEME 2. Detection of the Key Intermediate



the enantiomeric induction is already determined. Protonation of these two enamines should give the respective iminium salts *R*-**34b** and *S*-**34b**, and a subsequent *C*-1,2-addition should furnish the second bond in this formal cycloaddition sequence, leading to tricyclic intermediates *R*-**35** and *S*-**35**.

Finally, given the fact that we were able to detect the diastereomeric mixture [see **32** in Scheme 2] related to *R*-**35** and *S*-**35**, regeneration of the chiral amine via elimination is likely to be slow. This makes intuitive sense, as generation of vinyl iminium salts *R*-**36** and *S*-**36** could be uphill energetically. Subsequent tautomerization of *R*-**36** and *S*-**36** should lead to the enantiomeric 1,2-dihydropyridines *R*-**11** and *S*-**11** concomitant with the chiral amine salt turning over.

4.4. Computational Study. To further probe the origin of the observed enantioselectivity as well as the difference in the stereochemical outcomes from cycloaddition reactions carried out with C_1- and C_2-symmetric amine salts, computational studies were performed. Foremost, when an iminium salt such as **33** [see Figure 3] is generated with a C_1-symmetric catalyst such as **9e**, two geometric isomers can be formed. Ab initio calculations[27] with a simplified model system (crotonaldehyde) suggest that the formation of "cis"-isomer **37** is disfavored by 3.5 kcal/mol relative to "trans"-isomer **38**, presumably due to allylic strain present in **37** [Figure 4]. Therefore, to simplify the computational analysis, we assumed the exclusive formation of the "trans"-isomer of the iminium salt.

To understand the preferred formation of the *R*-enantiomer of **11** when using the *S*-isomer of C_1-symmetric amine salt **9e**, we calculated the stabilities of the two diastereomeric enamines **39** and **40** [Figure 5], which are products after the initial *N*-1,4-addition step [see Figure 3]. Using a Monte Carlo simulation in the Spartan′02 program,[28] we found that enamine **39**, which

(28) *Spartan′02*, PC version; Wavefunction, Inc.: 18401 Von Karman Avenue, Suite 370, Irvine, CA 92612; 2002.

(29) Klumpp, D. A.; Aguirre, S. L.; Sanchez, G. V.; de Leon, S. J. *Org. Lett.* **2001**, *3I*, 2781.

(30) Aggarwal, V. K.; Sandrinelli, F.; Charmant, J. P. H. *Tetrahedron*: *Asymmetry* **2002**, *13*, 87.

(31) Willems, J. G. H.; Hersmis, M. C.; de Gelder, R.; Smits, J. M. M.; Hammink, J. B.; Dommerholt, F. J.; Thijs, L.; Zwanenburg, B. *J. Chem. Soc.*, *Perkin Trans. 1* **1997**, 963.

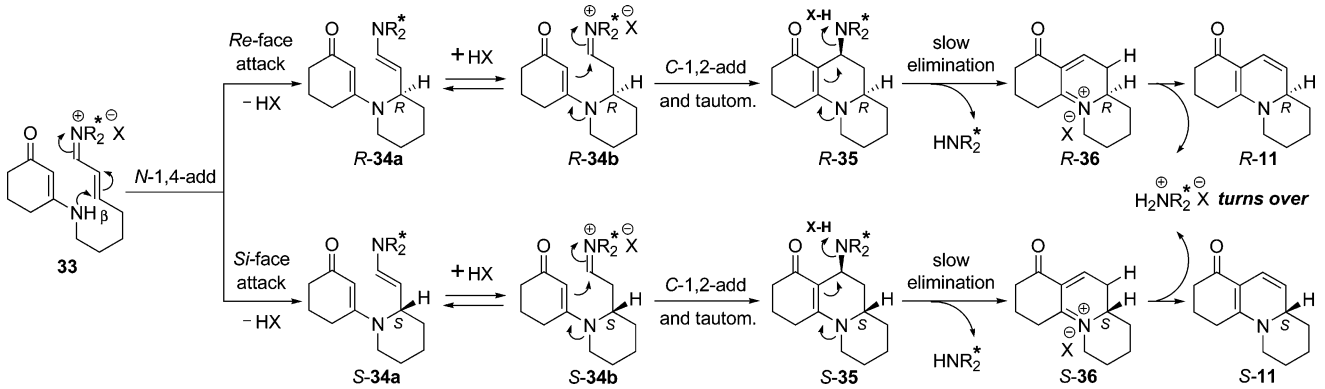


FIGURE 3. A proposed mechanism for the enantioselective formal aza-[3 + 3] cycloaddition.

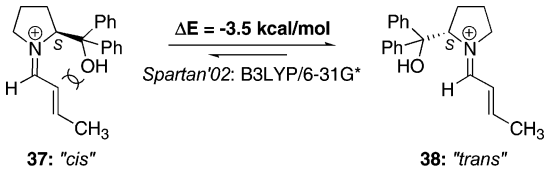


FIGURE 4. Iminium salt stereoisomers.

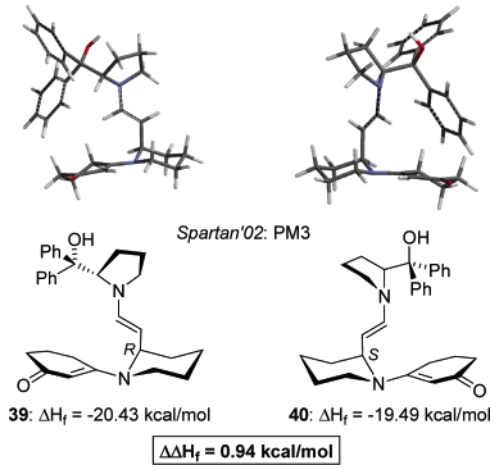


FIGURE 5. C_1-symmetric amine salts: enamine stability and conformation.

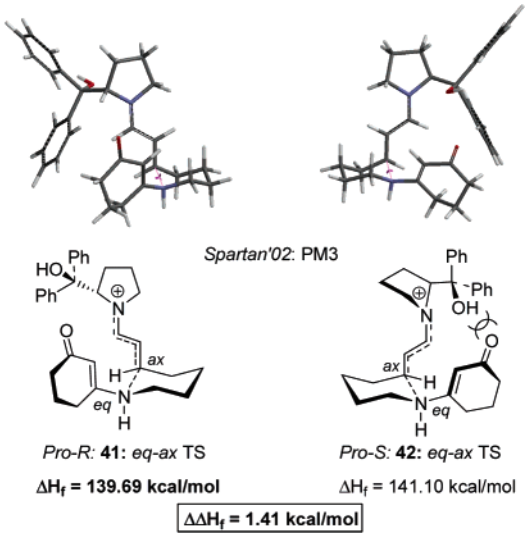


FIGURE 6. C_1-symmetric amine salts: relevant transition states.

would give *R*-**11**, is ∼1 kcal/mol more stable than the corresponding diastereomer **40** leading to the *S*-enantiomer.

Based on this product stability analysis and the preferred conformations shown for **39** and **40**, the corresponding transition states [TS‡] **41** and **42** for the *N*-1,4-addition step of the reaction were identified. It is noteworthy that the localization of the transition state structures was proven by the presence of one negative eigenvalue and the corresponding imaginary frequency, which reflect formation of the N−C bond. Models and their respective energies are shown in Figure 6.

Both transition state structures represent a *chair* form with the nitrogen substituent being *equatorial* and the enal moiety being *axial*. Calculations indicate that *Pro-R* TS‡-**41** is more stable relative to the corresponding diastereomeric *Pro-S* TS‡-**42** by ∼1.41 kcal/mol. This is consistent with calculations obtained for the respective enamines **39** and **40**. This energy difference can be rationalized by the steric interaction between the bulky diphenylhydroxymethyl substituent on the pyrrolidine ring and the cyclohexenone moiety in *Pro-S* TS‡-**42** [Figure 6].

To be cautious, we looked at all six other possible *chair* transition states that differ in the relative localized positions of the nitrogen substituent and the enal functionality. Structures for four pairs of diastereomeric TS‡-[**41**−**48**] along with their energies are shown in Figure 7. None of the other transition states are lower in energy than *Pro-R* TS‡-**41**. In particular, TS‡-**43** and TS‡-**44** having the nitrogen substituent *axial* are destabilized in comparison with *Pro-R* TS‡-**41** due to more severe 1,3-diaxial interactions. A similar interpretation can be made in the case of TS‡-**45** and TS‡-**46** where both side chains are *axial*. Finally, placing both substituents *equatorial* as shown in TS‡-**47** and TS‡-**48** leads to destabilization of the transition state structures due to the gauche interaction. On the basis of these computational results, it can be postulated that the asymmetric intramolecular formal aza-[3 + 3] cycloadditions promoted with C_1-symmetrical catalysts such as **9e** proceed predominantly through *Pro-R* TS‡-**41** giving rise to *R*-**11** as the major enantiomer.

A similar approach was used to rationalize the observed formation of *S*-enantiomer of **11** when C_2-symmetric amine salts are employed. To reduce the compu-

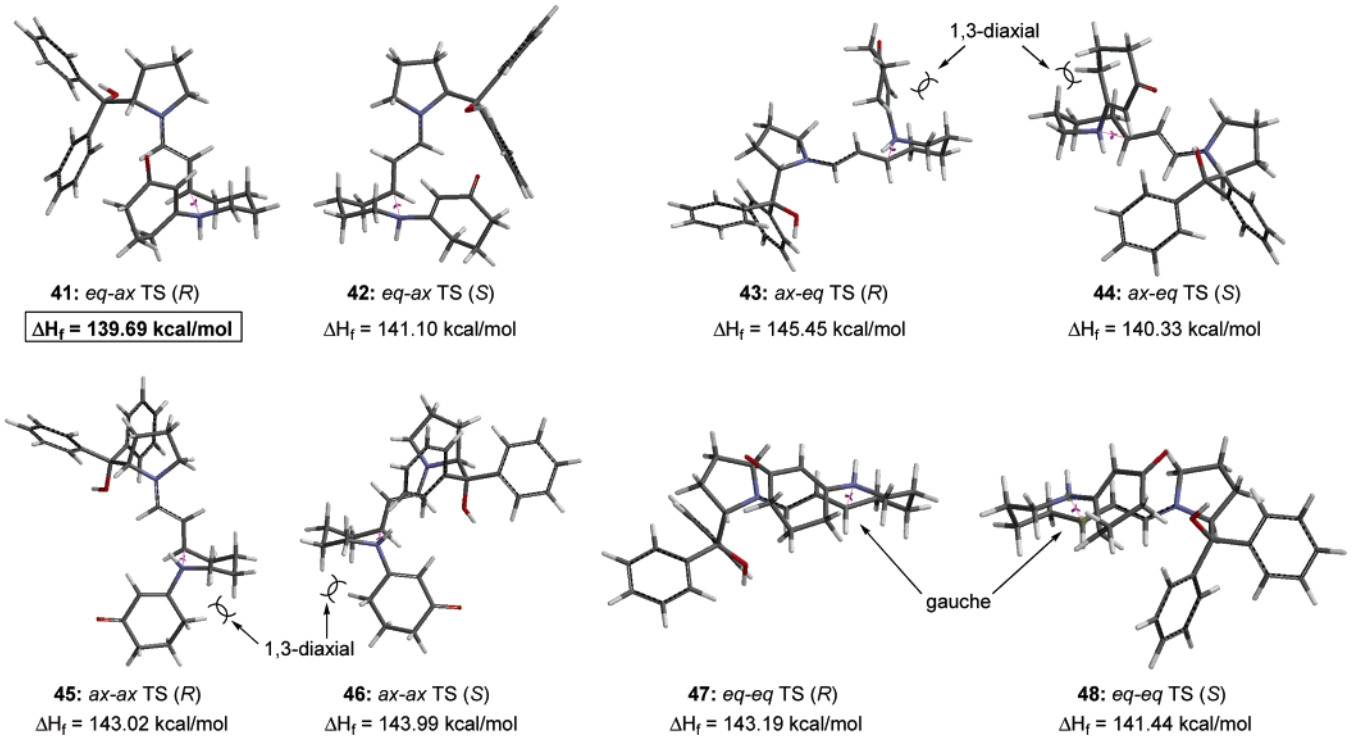


FIGURE 7. C_1-symmetrical amine salts: all possible transition states.

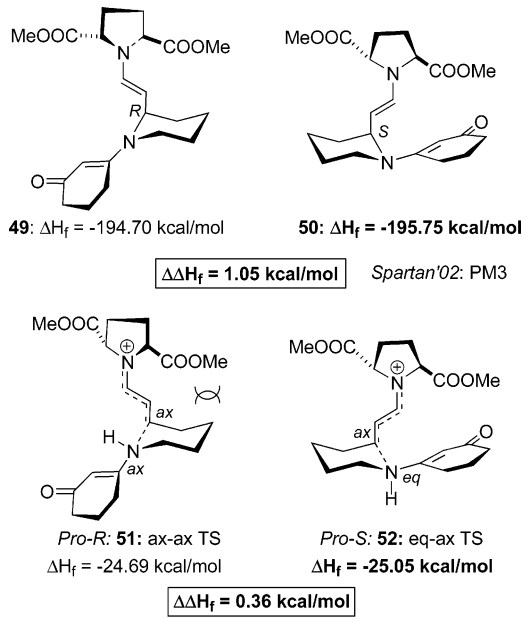
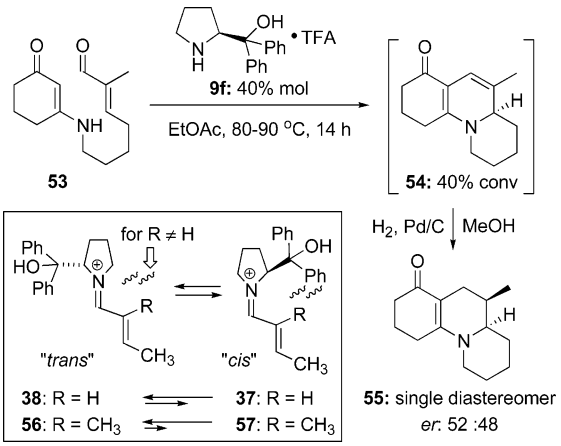


FIGURE 8. C_2-symmetrical amine salts: enamine stability and relevant transition states.

tational time, all calculations were performed with **10b** bearing two methyl ester substituents. It should be noted that in this case only one geometric isomer of the iminium salt exists due to the C_2-symmetric nature of **10b**. Stabilities and conformations for the two diastereomeric enamines **49** and **50** were again found through Monte Carlo simulation in Spartan′02 [Figure 8].[20] The relative stability of conformers is now reversed compared to the C_1-symmetric case. Specifically, enamine **50**, which would yield the *S*-**11**, is ∼1 kcal/mol more stable than **49**, which would lead to the *R*-enantiomer.

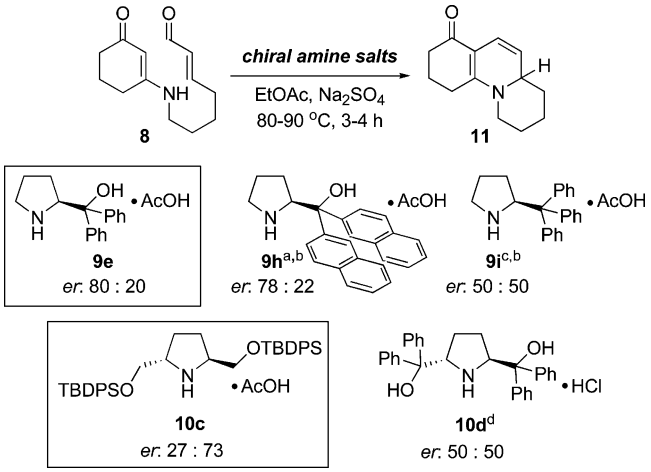
SCHEME 3. The Effect of the α-Methyl Substituent



When the corresponding TS‡-**51** and TS‡-**52** were localized, the same trend in relative stabilities was observed. *Pro-S* TS‡-**52**, which has the nitrogen substituent *equatorial* and the enal functionality *axial*, is lower in energy than *Pro-R* TS‡-**51** where now both side chains are *axial* [Figure 8]. Six other chairlike transition states were also modeled but none of them show greater stability than *Pro-S* TS‡-**52**.

Most likely the steric interaction between one of the ester groups on **10b** and the piperidine ring is responsible for destabilization of *Pro-R* TS‡-**51** in comparison with *Pro-S* TS‡-**52** [Figure 8]. An increase in the substituent size as shown in the amine salt **10c** would further disfavor *Pro-R* TS‡-**51**, thereby leading to enhanced enantioselectivity in favor of *S*-**11**. It can be suggested that this particular steric interaction, which does not exist in C_1-symmetric amine salts, is responsible for the opposite stereochemical outcome.

SCHEME 4. Tuning of the Amine Salts



[a] Commercially available. [b] The acetate salt was generated in situ by addition of 1.0 equiv of AcOH to the reaction mixture. [c] For its synthesis see ref 29. [d] See ref 30.

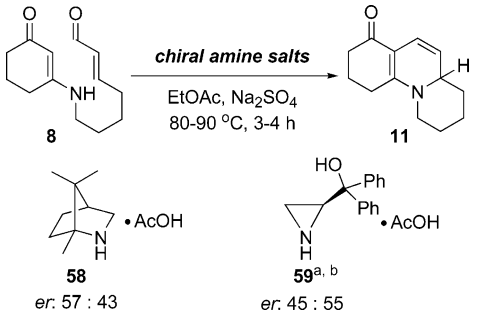
5. Final Attempts. One of the key assumptions in our mechanistic model is the exclusive formation of the "trans"-isomer of the iminium salt **38** [see the box in Scheme 3] for the case of C_1-symmetric amine salts. To validate this assumption, vinylogous amide **53** containing a methyl substituent at the α-position was synthesized [Scheme 3]. Since the formation of the "cis"-isomer of iminium salt **57** [see the box] intuitively should be further disfavored in this case compared to **37**, the enantioselectivity of the cycloaddition should stay the same if not improve.

It was found that vinylogous amide **53** would undergo formal cycloaddition only if the most active trifluoroacetate salt **9f** was used [Scheme 3]. No product formation was detected after running the reaction overnight with chloride salt **9g** or acetate salt **9e**. In the case of **9f**, only 40% conversion was observed after 14 h at 80 °C, and after hydrogenation of initial cycloadduct **54**, quinolizidine **55** was isolated as a single isomer. Relative "trans"-stereochemistry was assigned based on the coupling constants analysis as well as nOe data. But to our surprise, CSP-HPLC revealed that quinolizidine **55** was nearly racemic.

Due to the low-yielding and sluggish nature of this reaction, it is not clear what caused the drop in the enantioselectivity and we did not follow up in this pursuit. It could be that the background reaction gained momentum given that formation of the iminium salt is now more difficult with severe allylic strain present in both **56** and **57**.

We also attempted to modify the structures of the most efficient catalysts **9e** and **10c** in a rational manner to increase the enantioselectivity of the cycloaddition reaction. As shown in Scheme 4, the use of the amine salt **9h**, which has more extensive naphthyl-substituents relative to **9e**, did not lead to any improvement in the enantioselectivity. To ensure that the presence of the tertiary hydroxyl group did not impede our efforts, the amine salt **9i** was employed but it also led to the racemic **11**.

SCHEME 5. "Rigid" Amine Salts



[a] For the synthesis see ref 31. [b] The acetate salt was generated in situ by addition of 1.0 equiv of AcOH.

We then examined the C_2-symmetric **10d** amine salt bearing two bulky diphenylhydroxymethyl substituents, but again, the desired cycloadduct **11** was isolated as a racemate. These experimental results intuitively suggest that more bulky catalysts could simply impede the formation of the α,β-unsaturated iminium salt and increase the opportunity for background reactions.

Finally, we tried to use more rigid chiral amine salts, presuming that the conformational flexibility of pyrrolidine-based amine salts might have compromised the enantioselectivity. To that end, amine salts **58** and **59** were tested in the cycloaddition of **8** but neither was useful [Scheme 5]. It is nonetheless noteworthy that both amine salts were efficient in promoting the reaction.

Conclusion

We have described here a detailed study using chiral secondary amine salts to promote enantioselective intramolecular formal aza-[3 + 3] cycloaddition. The dependence of enantioselectivity on the structural feature of these chiral amines has been thoroughly investigated, and we found a very interesting reversal of the stereochemistry in the respective formal cycloadducts obtained using C_1- and C_2-symmetric amine salts. Effects of solvents, counteranions, and temperatures on the enantioselectivity were also investigated and appear to have no real impact. On the basis of these experimental results and some semiempirical calculations, a unified mechanistic model is proposed.

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Supporting Information Available: Experimental procedures, characterization data for all new compounds, ^{1}H NMR spectra, nOe data, and HPLC traces. This material is available free of charge via the Internet at http://pubs.acs.org.

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