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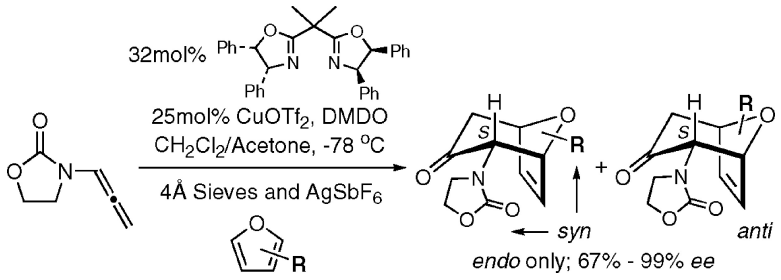

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Chiral Lewis Acid-Catalyzed Highly Enantioselective [4 + 3] Cycloaddition Reactions of Nitrogen-Stabilized Oxyallyl Cations Derived from Allenamides

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We have been actively developing synthetic methods employing allenamides.[1−3] Specifically, we demonstrated that nitrogen-stabilized chiral oxyallyl cations **2b**, generated in situ via epoxidations of allenamides **1**, can undergo highly diastereoselective inter-[4] and intramolecular[5] [4 + 3] cycloadditions with dienes [Scheme 1]. While oxygen-,[6a−c] sulfur-,[6d] and chlorine-substituted[6e] oxyallyl cations are well-known,[7−9] nitrogen-substituted oxyallyl cations only emerged recently to offer a unique opportunity to achieve highly stereoselective [4 + 3] cycloadditions.[10−13]

In our studies,[4] we had rationalized that the diene would approach favorably from the more accessible *endo*-1 face in model **4** and that $ZnCl_2$ could lock up the oxyallyl cation to provide a greater π-facial differentiation and selectivity. This analysis implies that a catalytic asymmetric [4 + 3] cycloaddition[11] could be realized [see model **5**] by employing a chiral Lewis acid along with the oxazolidinone group serving as an achiral template.[14] We report here a catalytic asymmetric [4 + 3] cycloaddition of nitrogen-stabilized oxyallyl cations.

Although the model provides a distinct goal, it was not readily clear how we could establish the feasibility of this asymmetric cycloaddition. Thus, we screened a variety of Lewis acids and chiral ligands [**9**−**16**][15] while using allenamide **7** as the model example. These efforts are summarized in Table 1. In short, C_2-symmetric bisoxazolines are the most suitable chiral ligands along with $CuOTf_2$ being the best Lewis acid [entries 9−17], and a syringe pump was used to add DMDO.

Specifically, we were able to start reaching ees in the 80−90% range for the *endo* cycloadduct **8**-*S* [see Table 1 for definition],[16a] although not always in good yields using **15a** and **15b** [entries 14−16]. In addition, it is noteworthy that these reactions are again exclusively *endo*-selective and could be carried out at temperatures as low as −78 °C, while reaction is very slow at −78 °C without any catalysts.[3d,4]

Having established a suitable protocol, we explored the scope and found two more critical factors that could enhance the asymmetric induction. As shown in Table 2, the use of molecular sieves allowed us to improve the yield without lowering the ee [entry 1], and second, with $[SbF_6]^-$ as the counteranion, it allowed us to improve the ee in a similar manner as illustrated by Evans[17] [entry 2].

Entry 3 demonstrates that the use of *ent*-**15b** provides the desired antipode **8**-*R* as expected.[16] Substituting furan with cyclopentadiene led to a decreased ee [entry 4], presumably due to a more reactive cyclopentadiene that contributes to a great amount of background reactions. In addition, allenamides **17** and **20** substituted with γ-lactam and δ-lactam, respectfully, gave inferior yields and ees compared to **7** substituted with oxazolidinone [entries 5 and 6].

We next turned to substituted furans, which were completely unsuccessful in our previous efforts involving diastereoselective intermolecular reactions.[4] Although ees were modest [entries 8 and 10], we were pleased to find that employing both 2-methyl-furan

Scheme 1

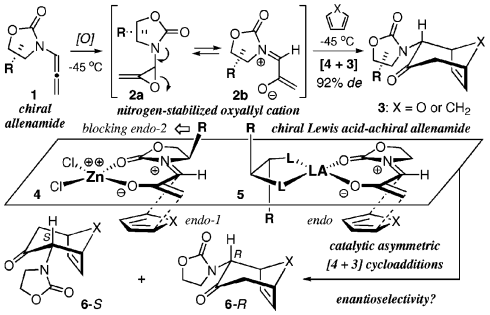
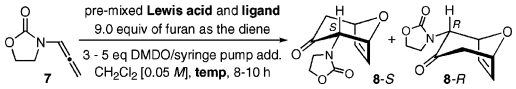
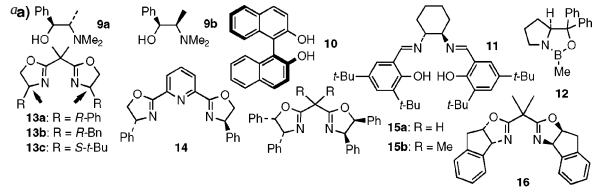


Table 1



entry	Lewis acids	equiv	ligands[a]	L [equiv]	temp	yield[b] (%)	ee[c] (%)
1	$ZnOTf_2$	1.1	**9a**	1.3	−55 °C	48	8[*R*]
2		1.1	**9b**	1.3	−55	58	2[*R*]
3		1.1	**10**	1.3	−55	70	21[*R*]
4	$Co(OAc)_2{\cdot}4H_2O$	1.1	**11**	1.0	−55	0	nd
5		0.25	**11**	1.0	−55	46	1[*R*]
6	no metal		**12**	0.25	−78[d,e]	40	3[*R*]
7	$SnOTf_2$	1.1	**13a**	1.3	−55	48	5[*R*]
8	MgI_2	0.25	**13a**	0.32	−78	46	3[*R*]
9	$CuOTf_2$	0.85	**13a**	1.1	−55 °C	62	78[*S*]
10		0.25	**13a**	0.32	−78[d,f]	46	74[*S*]
11		1.1	**13b**	1.2	−55	53	22[*S*]
12		0.25	**13c**	0.32	−78[d,e]	46	10[*R*]
13		0.25	**14**	0.32	−78[d,e]	54	61[*S*]
14		0.25	**15a**	0.32	−78[d,e]	46	82[*S*]
15		0.25	**15b**	0.32	−78[d,e]	46	90[*S*]
16		0.10	**15b**	0.12	−78[d,f]	76	59[*S*]
17		0.25	**16**	0.32	−78[d,e]	84	2[*R*]



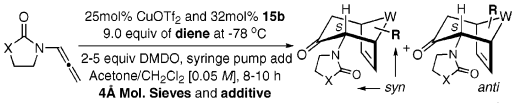
[b] Isolated yields. [c] HPLC determination for ee's. [d] Concn = 0.01 M. [e] In 3:1 acetone/CH_2Cl_2. [f] In acetone.

and methyl furylcarboxylic ester was feasible and provided excellent regioselectivity in favor of the syn isomer [see Table 2 for definition].[18] The peculiarity of such regioselectivity has been documented.[19] More importantly, we found that this catalytic protocol clearly promotes the cycloaddition, for the reaction took place very sluggishly in the absence of any catalysts [entries 7 and 9].

In contrast to Harmata's work involving 2,5-disubstituted furans,[11] 2,5-dimethyl furan provided low ee values and could not be optimized with $[SbF_6]^-$ [entry 11]. On the other hand, reactions of 3-substituted furans were successful, leading to cycloadducts

10.1021/ja044760b CCC: $30.25

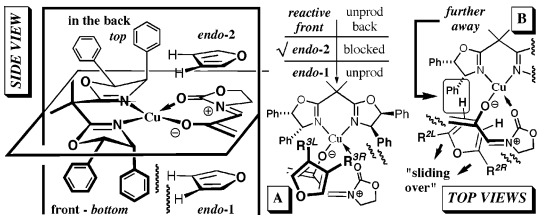
Table 2



entry	dienes	allenes X	W	R =	additive	product	yield[a]	ee[b]
1		**7** O	O	-	-	**8**-*S*	90%	92%
2		**7** O	O	-	$AgSbF_6$	**8**-*S*	91	99
3		**7** O	O	-	-	**8**-*R*	87	82[c]
4		**7** O	CH_2	-	$AgSbF_6$	**18**-*S*	90	43[d]
5		**17** CH_2	O	-	-	**19**-*S*	60	58
6		**20** $(CH_2)_2$	O	-	-	**21**-*S*	47	14
7		**7** O	-	Me	-	**22**-*S* [4 : 1][e]	37%[f]	-
8		**7** O	-	Me	$AgSbF_6$	**22**-*S* [• 20 : 1]	88	71[g]
9		**7** O	-	CO_2Me	-	**23**-*S* [*syn* only]	33[f]	-
10		**7** O	-	CO_2Me	$AgSbF_6$	**23**-*S* [*syn* only]	61	67[g]
11		**7** O	-	-	-	**24**-*S*	81	36
12		**7** O	-	Me	$AgSbF_6$	**25**-*S* [*anti only*]	91	99[h]
13		**7** O	-	Br	$AgSbF_6$	**26**-*S* [1 : 14]	58	84[h]
14		**7** O	-	CH_2OTPS	$AgSbF_6$	**27**-*S* [1 : 2.3]	66	92[h,i]

[a] Isolated yields. [b]HPLC determination for ees. [c]*ent*-**15b** was used with the ee not optimized. [d]Ee was 24% without $AgSbF_6$. [e]Syn:anti ratios are in brackets and were determined by ^1H and/or ^{13}C NMR. [f]No Lewis acid was used. [g]Ees for syn regioisomers without $AgSbF_6$ [entries 8 and 10] are 67 and 64%, respectively. [h]Ees for anti regioisomers without $AgSbF_6$ [entries 12−14] are 70, 80, and 63%, respectively. [i]Ee for the syn regioisomers was not determined.

Scheme 2



25−**27** with high ees but in favor the anti regioisomers instead of syn regioisomers [entries 12−14]. Finally, we note that the oxazolidinone ring could be cleaved using SmI_2.[16b,20]

A working model can be proposed on the basis of a known mechanistic analysis for asymmetric catalysis employing chiral C_2-symmetric ligands [Scheme 2].[21] Use of this model allows the observed enantioselectivity to be readily rationalized. Out of the two productive front quadrants, the bottom *endo*-1 approach would be sterically unfavorable due to the interaction between the furan-H and bottom Ph ring, while the top *endo*-2 approach would predominate leading to the *S*-enantiomers [side view and top view-A].

This model provides a rationale for C3-substituted furans in which anti isomers were found [top view-A]. To approach from the favored *endo*-2 face, the substituent at C3 would prefer to be on the left side [see R^{3L}], for being on the right side [see R^{3R}] would lead to steric interaction with the top Ph ring. The ees of the anti regioisomer should also be high, for the bottom *endo*-1 approach would experience additional steric interaction between the R^{3L} and the bottom Ph ring.

Reactions of 2-substituted furans and 2,5-dimethyl furan led to a reduced ee from that of the parent furan. This is likely due to an enhanced steric interaction between the C2-substituent(s) [R^{2L} and/or R^{2R}: top view-B] and the oxyallyl cation moiety. To alleviate this interaction, 2-substituted furans and 2,5-dimethyl furan would have to "slide over," thereby diminishing the critical interaction between the furan-H and bottom Ph ring [see the boxed area], especially for 2,5-dimethyl furan.

We have described here chiral Lewis acid-catalyzed highly enantioselective [4 + 3] cycloadditions using nitrogen-stabilized chiral oxyallyl cations derived from allenamides. Efforts in applications in natural product syntheses and further mechanistic exploration are underway.

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Supporting Information Available: Experimental procedures, as well as $^1H/^{13}C$ NMR spectra and characterization data for all new compounds (CIF, PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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