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Lewis Acid Tuned Facial Stereodivergent HDA Reactions Using β-Substituted *N*-Vinyloxazolidinones

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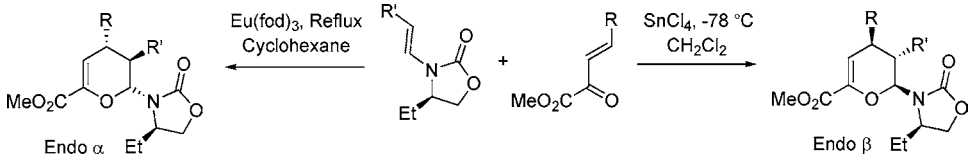
ABSTRACT



The [4 + 2] acido-catalyzed heterocycloaddition between new β-substituted *N*-vinyl-1,3-oxazolidin-2-ones (with R′ = Me, Ar, CH_2 Ar) and β,γ-unsaturated α-ketoesters (R = Ar) afforded heteroadducts with high levels of *endo* and facial selectivities. A complete reversal of facial differentiation was achieved by varying the Lewis acid, leading to the stereoselective formation of either *endo*-α or *endo*-β adducts.

The hetero-Diels−Alder reaction is a common and powerful method to create dihydropyrans[1] combining C−C and O−C bond formations with regio- and diastereoselectivity at several centers. 3,4-Dihydro-2*H*-pyrans, which are important intermediates for the synthesis of natural products, can be obtained by electron inverse-demand cycloaddition between π-electron-deficient heterodienes and electron-rich dienophiles. In this field, aza-substituted dienophiles have been rarely used. Electron-rich enamines[2,3] have aroused more interest than weaker dienophiles like enamides or enecarbamates which are seldom reported. Hsung's group[4] has developed the thermal inverse-electron-demand [4 + 2] heterocycloaddition of chiral allenamides derived from lactams, oxazolidinones, and imidazolidinones. They obtained highly functionnalized pyranyl heterocycles with good stereoselectivities. More recently, we have described the first example of an inverse-electron-demand heterocycloaddition using *N*-vinyl-1,3-oxazolidin-2-one,[5] which proved a valuable dienophile toward β,γ-unsaturated α-ketoesters[6] under appropriate Lewis acid conditions.

The work was extended to chiral *N*-vinyloxazolidinones[7] leading to original heteroadducts with high *endo* and facial selectivities under $Eu(fod)_3$-catalyzed conditions (Scheme 1). *N*-Vinyl-1,3-oxazolidine-2-thiones[8] were also used under these conditions but afforded only moderate facial selectivities. Our interest in this field for developing new stereocon-

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(1) (a) Jorgensen, K. A. *Eur. J. Org. Chem.* **2004**, 2093. (b) Tietze, L. F.; Kettschau, G. *Top. Curr. Chem.* **1997**, *189*, 1 and references therein. (c) Boger, D. L.; Weinreb, S. M. *Hetero-Diels−Alder Methodology in Organic Synthesis*; Wasserman, H., H., Ed.; Academic Press: San Diego, CA, 1987.
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(3) Reviews: (a) Lenz, G. R. *Synthesis* **1978**, 489. (b) Hickmott, P. W. *Tetrahedron* **1982**, *38*, 1975. (c) Hickmott, P. W. *Tetrahedron* **1982**, *38*, 3363. (d) Whitesell, J. K.; Whitesell, M. A. *Synthesis* **1983**, 517. (e) Rappoport, Z. *The Chemistry of Enamines in the Chemistry of Functional Groups*; John Wiley and Sons: New York 1994.
(4) (a) Wei, L.-L.; Xiong, H.; Douglas, C. J.; Hsung, R. P. *Tetrahedron Lett.* **1999**, *40*, 6903. (b) Wei, L.-L.; Hsung, R. P.; Xiong, H.; Mulder, J. A.; Nkanseh, N. T. *Org. Lett.* **1999**, *1*, 2145. (c) Rameshkumar, C.; Hsung, R. P. *Synlett* **2003**, 1241.
(5) Gaulon, C.; Gizecki, P.; Dhal, R.; Dujardin, G. *Synlett* **2002**, 952.
(6) For more recent examples with other activated heterodienes, see: Palasz, A. *Org. Biomol. Chem.* **2005**, *3*, 3207.
(7) Gaulon, C.; Dhal, R.; Chapin, T.; Maisonneuve, V.; Dujardin, G. *J. Org. Chem.* **2004**, *69*, 4192.
(8) Tardy, S.; Tatibouët, A.; Rollin, P.; Dujardin, G. *Synlett* **2006**, 1425.

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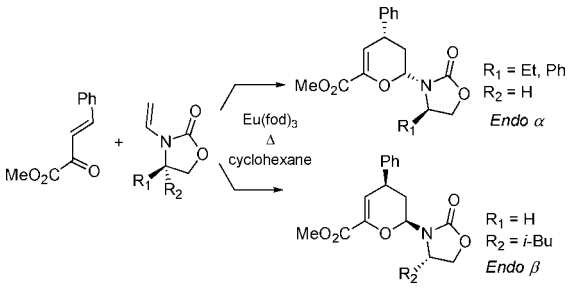
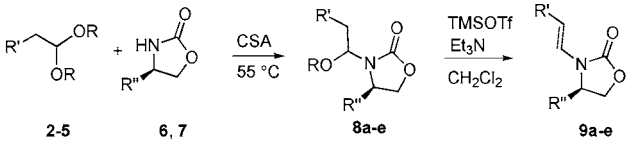
Scheme 1. Heterocycloaddition of *N*-Vinyloxazolidin-2-ones toward β,γ-Unsaturated α-Ketoesters



trolled cycloreactants led us to explore the reactivity of chiral β-substituted *N*-vinyl-1,3-oxazolidin-2-ones in [4 + 2] cycloaddition. This could permit access to adducts possessing three contiguous stereogenic centers, the configuration of which being completely controlled during the cycloaddition process.

Dienophiles were conveniently prepared by a two-step procedure[9] based on the dehydroalkoxylation of *N*,*O*-acetals **8** using TMSOTf/Et_3N (Table 1). Achiral and chiral *N*-

Table 1. Preparation of β-Substituted *N*-Vinyloxazolidin-2-ones



2-5 6, 7 8a-e 9a-e

2 R' = Ph, R = Et **6** R'' = H
3 R' = H,, R = Et **7** R'' = Et
4 R' = Me, R = Et
5 R' = Methylenedioxybenzyl R = Me

entry	R	R'	R''	9	8 (%)	9 (%)[a]
1	Et	Ph	H	**9a**	-	50[b]
2	Et	Ph	Et	**9b**	-	78[b]
3	Et	H	Et	**9c**	quantitative	78
4	Et	Me	Et	**9d**	97	85
5	Me		Et	**9e**	45[c]	37

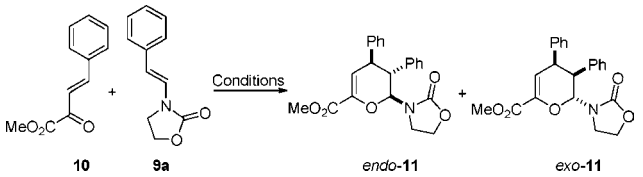
[a] Isolated yield from the second step. [b] Overall yield, **8** has not been isolated. [c] **9** (10%) is also formed at this step.

vinyloxazolidinones **9a**−**e** (Table 1) were generated with a pure (*E*)-geometry in modest to good yields. Styryloxazolidinones **9a** and **9b** were prepared in one pot from **6** and **7**, respectively. In these cases, the elimination of ethanol took place in the first step presumably due to the higher stability of the conjugated styryl structures **9a**,**b**.

We have then embarked on a detailed investigation of the cycloaddition between achiral styryloxazolidinone **9a** and benzylidene pyruvic methyl ester **10** varying the reaction conditions (Table 2). Without any Lewis acid, no reaction

(9) Gaulon, C.; Gizecki, P.; Dhal, R.; Dujardin, G. *Synthesis* **2003**, 2269.

Table 2. Reactions between Achiral Styryl Oxazolidinone **9a** and Oxabutadiene **10** Promoted by Different Lewis Acids



entry	promoter (equiv)	conditions[a]	conv (%)[b] (yield, %)	selectivity *endo*/*exo*[c]
1		5 days reflux		
2	$Eu(fod)_3$ (0.05)	5 days reflux	65 (54)	89/11
3	Et_2AlCl (0.5)	−78 °C to rt overnight		
4	$TiCl_4$ (0.5)	0 °C to rt overnight	<5	
5	$ZnCl_2$ (2)	4 days reflux	66 (34)	91/9
6	$ZnBr_2$ (1)	11 days reflux	100 (48)	90/10
7	$BF_3{\cdot}Et_2O$ (0.5)	−78 °C to −20 °C overnight	100 (72)	88/12
8	TMSOTf (0.5)	−78 to −20 °C overnight	98 (75)	96/4
9	$SnCl_4$ (0.5)	−78 °C, 3 h	100 (81)	>98/2

[a] Reactions were performed in dichloromethane except entries 1 and 2 (cyclohexane). [b] The conversion is based on the remaining diene in the crude reaction mixture analyzed by 400 MHz ^{1}H NMR. [c] Selectivity *endo*/*exo* is determined from the 400 MHz ^{1}H NMR spectrum of the crude reaction mixture.

occurred even after 5 days at 80 °C in cyclohexane (entry 1, Table 2). $Eu(fod)_3$ used as catalyst gave rise to a slow but very clean conversion (no degradation) into major *endo* adduct. Et_2AlCl and $TiCl_4$ proved not efficient to promote the cycloaddition: whereas $TiCl_4$ gave no significant reactivity, we observed with Et_2AlCl the nucleophilic addition of an ethyl substituent on the ketone of the pyruvic benzylidene methyl ester **10**. In contrast, $SnCl_4$ promoted efficiently the cycloaddition between **10** and **9a** (entry 9, Table 2). The *endo*-**11** racemic adduct was obtained without any trace of the *exo*-**11** and with a good yield after purification. Interestingly, $ZnCl_2$, $BF_3{\cdot}Et_2O$, TMSOTf and $Eu(fod)_3$ proved to give less selectively the *endo* product than $SnCl_4$.[10]

The *endo*-selectivity observed with (*E*)-dienophile **9a** and $SnCl_4$ at low temperature (i) contrasts with previous results reported by Tietze's group[11] with the same Lewis acid under similar conditions when starting from a (*Z*)-β-substituted vinyl ether and (ii) is in accordance with those obtained by our group with $SnCl_4$ when using cyclanone enol ethers[12] (of the same *E* geometry). The stereochemical outcome of

(10) In this paper, adducts were designed as "*exo*" and "*endo*" whatever the presumed mechanism, concerted or not.

(11) Tietze, L. F.; Schneider, C. *Synlett* **1992**, 755. A high exo-selectivity (15/1) was reported by these authors when using $SnCl_4$ as Lewis acid promotor at −78 °C.

(12) (a) Dujardin, G.; Martel, A.; Brown, E. *Tetrahedron Lett.* **1998**, *39*, 8647. (b) Martel, A.; Leconte, S.; Dujardin, G.; Brown, Maisonneuve, V.; Retoux, R. *Eur. J. Org. Chem.* **2002**, *3*, 514.

$SnCl_4$-promoted cycloadditions involving these β-substituted dienophiles appears thus as directly dependent on the (*E*/*Z*) geometry of the dienophile: the formation of the adduct featuring a *trans* relationship of substituents on the newly created C−C bond is favored in both cases. This feature also supports the hypothesis of a ionic stepwise[10,13] cycloaddition process (Michael-type addition−cyclization) with $SnCl_4$,[14] in contrast with the asynchronous concerted mechanism generally considered in the reactions involving lanthanide salts as the catalyst.

We have then extended the study, investigating the cycloaddition of chiral styryl oxazolidinones **9b**−**e** toward arylidene pyruvic methyl esters **10** and **12** in the presence of the most efficient Lewis acids (Table 3). The stereochemistry of the obtained cycloadducts was fully elucidated as follows: *endo*/*exo* selectivity was deduced from the observed coupling constants on the 400 MHz ^{1}H NMR spectrum and X-rays of *endo*-α-**13e** and *endo*-β-**13c** allowed to attribute by analogy the absolute configuration of all other heteroadducts. All of the reactions involving β-substituted dienophiles **9b**−**e** proceeded with modest to good yields and with a high level of *endo* selectivity whatever the Lewis acid used.

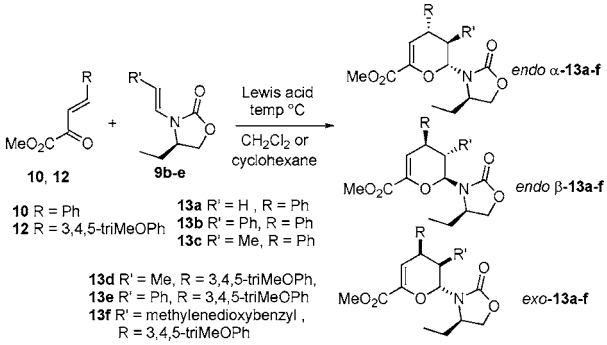
As a surprising and interesting result, $SnCl_4$ and $Eu(fod)_3$ proved to induce a high but opposite facial diastereoselectivity. *Endo*-α-**13b** cycloadduct was obtained with a high stereoselectivity under $Eu(fod)_3$-catalyzed conditions, whereas *endo*-β-**13b** was selectively obtained using $SnCl_4$ as the promotor.

Tietze has already pointed out a facial stereodivergency occurring during the HDA reaction of 1-oxa-1,3-butadienes with an enol ether in the presence of TMSOTf or Me_2AlCl.[15] The reversed facial differenciation was reported to be due to an asymmetric induction under chelation control (with Me_2AlCl) or nonchelation control (with TMSOTf). Moreover, in the course of the cycloaddition of an alkoxydihydropyranone and a diene, Varela et al.[16] have described that a significant change in the facial selectivity could take place using either a chelating Lewis acid ($SnCl_4$, $TiCl_4$) or a monocomplexing one such as $BF_3{\cdot}Et_2O$.

In our case, a high degree of facial selectivity is obtained only with chelating Lewis acids: $Eu(fod)_3$ and $SnCl_4$. Indeed, the use of $BF_3{\cdot}Et_2O$ and TMSOTf (entries 3 and 4, Table 3) resulted in a poorer diastereofacial differenciation, possibly due to the inability of both Lewis acids to form a chelate.[17] A fact that might explain the facial stereodivergency would be that only $SnCl_4$ could chelate both carbonyls of the pyruvic system. In contrast, $Eu(fod)_3$ could act in the concerted transition state by intermolecular chelation involving the oxazolidinone moiety of the dienophile.[18] The facial stereodivergency could thus result from the different conformations adopted by both reactants in the two different modes of chelation (5-membered-ring Sn(IV) chelate vs sandwiched Eu(III) chelate).

Some variations on the dienophile were next studied. Without any β-substituent on the double bond,[19] the cycloaddition took place with high *endo* and facial selectivities under $Eu(fod)_3$ conditions, whereas an assay employing 0.5 equiv of $SnCl_4$ furnished a mixture of all possible four diastereoisomers (entries 1 and 2, Table 3). In contrast, the cycloadduct **13c** possessing a methyl group in C-2 (entries 7 and 8, Table 3) was obtained with very high *endo* and facial selectivities under $SnCl_4$ conditions. The presence of a β-substituent on the dienophile is thus beneficial to the $SnCl_4$-promoted reaction in terms of diastereoselectivities and yields. The cycloaddition was even more successful as compared to the reaction with the dienophile bearing the phenyl group since no *exo* adduct could be detected by ^{1}H

Table 3. Diels−Alder Reactions between Oxazolidinones **9b**−**e** and Oxabutadienes **10** and **12**



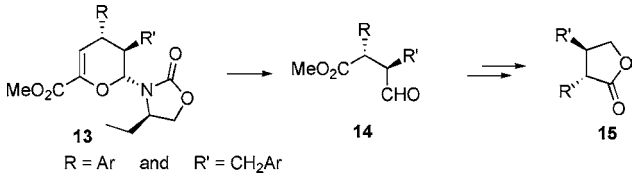
entry	R	R'	lewis acid[a]	**13**	yield (%)[b]	selectivity[c] *endo* /*exo*	selectivity[c] *endo*α /*endo*β
1	Ph	H	$Eu(fod)_3$	**a**	77	98/2	>98/2
2			$SnCl_4$		44[d]	40/60	ND[e]
3	Ph	Ph	$BF_3.Et_2O$	**b**	52	98/2	76/21
4			TMSOTf		61	98/2	83/17
5			$Eu(fod)_3$		57	98/2	96/4
6			$SnCl_4$		72	80/20[f]	<2/98
7	Ph	Me	$Eu(fod)_3$	**c**	62	>98/2	>98/2
8			$SnCl_4$		71	>95/5	<2/98
9		Me	$Eu(fod)_3$	**d**	64	>98/2	>98/2
10			$SnCl_4$		67	>95/5	<2/98
11		Ph	$Eu(fod)_3$	**e**	59	98/2	>98/2
12			$SnCl_4$		83	93/7	<2/98
13			$Eu(fod)_3$	**f**	65	>98/2	>98/2
14			$SnCl_4$		61	>95/5	<2/98

[a] Reactions with $Eu(fod)_3$ (0.05 equiv) were refluxed in cyclohexane until the disappearance of the dienophile and reactions with $SnCl_4$ (0.5 equiv) were realized in CH_2Cl_2 at −78 °C during 3 h. [b] Purified yield. [c] Selectivity was determined from the ^{1}H NMR spectrum of the crude reaction mixture. [d] Yield representing the mixture of four isomers. [e] Not determined. [f] *Exo*-β/*exo*-α > 98/2.

(13) Telan, L. A.; Poon, C. D.; Evans, S. A., Jr. *J. Org. Chem* **1996**, *61*, 7455.
(14) Sera, A.; Ueda, N.; Itoh, K.; Yamada, H. *Heterocycles* **1996**, *43*, 2205.
(15) (a) Tietze, L. F.; Schulz, G. *Liebigs Ann.* **1995**, 1921. (b) Tietze, L. F.; Schneider, C.; Grote, A. *Chem. Eur. J.* **1996**, *2*, 139.
(16) Iriarte Capaccio, C. A.; Varela, O. *Tetrahedron Lett.* **2003**, *44*, 4023.
(17) Reetz, M. T. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 556.
(18) Such an interaction would not exist in the case of heterocycloadditions involving *N*-vinyloxazolidine-2-thiones, for which weak facial selectivities are observed (see ref 8).
(19) Gaulon, C. Ph.D. Thesis, University of Maine, Le Mans, 2003.

NMR (entry 6 vs entry 8). The effectiveness of these cycloadditions prompted us to test the reaction with another diene, the trimethoxybenzylidene pyruvate methyl ester **12**[20] (entries 9−14, Table 3). Under the optimized conditions established, **12** was opposed to various dienophiles and afforded the expected dihydropyranes **13d−f** with high *endo* and facial selectivities. From the heteroadduct **13f,** more elaborated molecules like norlignans[21] (some of them have shown some antitubuline activities and are inhibitors of topoisomerase II)[22] could be prepared as represented in Scheme 2.

Scheme 2. Synthesis of Norlignans from Dihydropyrans



For this purpose, the oxidative cleavage of the double bond to yield the aldehyde **14**, a reaction already performed on similar substracts in our team, is now in progress.

In this paper, we have described the first examples of hetero-Diels−Alder reactions between chiral β-substituted *N*-vinyloxazolidinones and 1-oxabutadienes, affording original cycloadducts with high *endo* and facial selectivities. The choice of the Lewis acid proved critical, affording selectively either the *endo* α adduct using $Eu(fod)_3$ as the catalyst or *endo* β if the promotor was $SnCl_4$. The ability to modulate the substituents on the heterodiene and the dienophile without affecting the stereoselectivity and the yield is very promising to envision the access to a large diversity of interesting structures, especially of the lignan-type.

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Supporting Information Available: Materials and methods, experimental procedures, X-ray crystal structures, and ^1H and ^{13}C NMR data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(20) Brown, E.; Dujardin, G.; Maudet, M. *Tetrahedron* **1997**, *53*, 9679.
(21) For a recent review see: Chang, J.; Reiner, J.; Xie, J. *Chem. Rev.* **2005**, *105*, 4581.
(22) Gupta, R. S. *J. Natl. Cancer Inst.* **1985**, *74*, 159.