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CYCLOCONDENSATION REACTIONS OF OPTICALLY ACTIVE α-ALKOXY ALDEHYDES TO KETENE IMINES: SYNTHESIS OF CHIRAL 2-IMINOOXETANES

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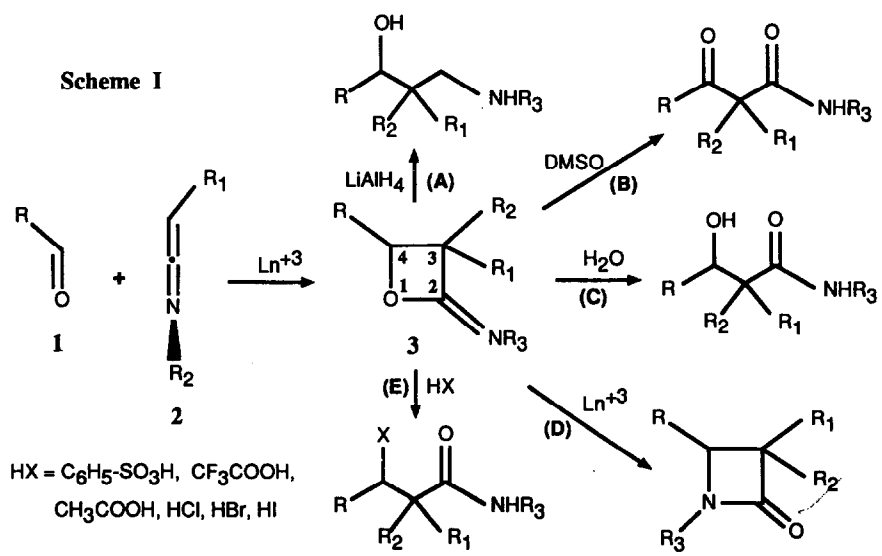
Abstract: The Lewis acid promoted hetero-cycloaddition of a series of ketene imines to stereogenic (*S*)-α-alkoxy aldehydes is regiospecific and gives diastereomeric mixtures of the corresponding optically active 2-iminooxetanes. The possibility of achieving a "chelation" or "non-chelation" controlled facial selectivity is investigated. The non-chelating Lewis acids ($BF_3.Et_2O$ and $ZnCl_2.Et_2O$) govern the selectivity of the cycloaddition, *anti*-Cram products being preferentially formed with low and medium size ketene imines. In contrast, *syn*-Cram configured isomers are preferentially formed whith the sterically demanding *tert*-butylketene *N*-*p*-methoxyphenylimine in the presence of catalytic amounts of lanthanide catalysts.

We have recently investigated the synthesis and reactivity of 2-iminooxetanes (**3** of Scheme I).[1, 2]

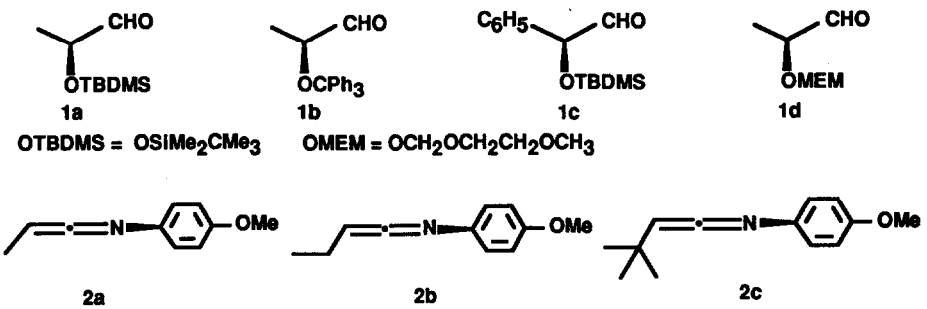
Scheme I



These heterocycles can be regarded as useful starting materials for synthetic routes to highly functionalized intermediates. In fact, 2-iminooxetanes undergo a variety of electrophilically initiated ring opening

reactions leading to γ-aminoalcohols (A),[2] β-ketoamides (B),[2] β-hydroxyamides (C),[3] β-lactams (D),[2] and β-derivatized amides (E).[4] For this reason we have developed a strategy for synthesis of 2-iminooxetanes with different functions at C3 and C4,[1] utilizing lanthanide-induced [2+2]-hetero-cycloadditions of aldehydes to ketene imines (Scheme I). The high regioselectivity[5] of the cyclocondensations prompted us to investigate the possibility of preparing optically active 2-iminooxetanes using chiral aldehydes as reagents. In order to gain a better knowledge about chiral induction in these reactions we can choose two different models, which create two pairs of new chiral centers at the binding sites. According to the first model, rigid chiral auxiliaries are attached to the carbonyl center of the aldehyde. The esters of optically active alcohols of glyoxylic acid are suitable candidates for this model, as they have already been used in asymmetric induction studies of oxetane forming photocycloadditions to electron-rich olefins.[6] We will report the results of our studies using this type of approach in a separate paper. The other model relies on the temporary conversion of a conformationally mobile acyclic chiral aldehyde to a more rigid cyclic one. This can be obtained, for example, when a chiral derivative of an α-alkoxy aldehyde is chelated with a Lewis acid metal catalyst and product distribution is the result of a "chelation-controlled diastereofacial selectivity".[7] If the metal does not form a good chelate the diastereofacial selectivity may be predicted by other models for which the selectivity is regulated by electronic and/or steric factors (non-chelation control).[8] In this case, a dipolar model that would place the polar alkoxy substituent *anti* to the carbonyl would lead to products with the relative stereochemistry opposite to that predicted by the "chelation control" model. In contrast to the successful investigations of 1, 2-like induction in Lewis acids induced hetero-Diels Alder reactions with chiral aldehydes,[9] systematic investigations on high induction are lacking in Lewis acid induced 1,2-hetero cycloadditions of cumulenes. Due to this lack we have exploited, as an extension of our previous studies[1] with racemic reagents, the possibility of controlling chelation or non-chelation in diastereogenic 1,2-hetero cycloadditions of chiral α-alkoxy aldehydes to racemic unsymmetrically monosubstituted ketene imines.

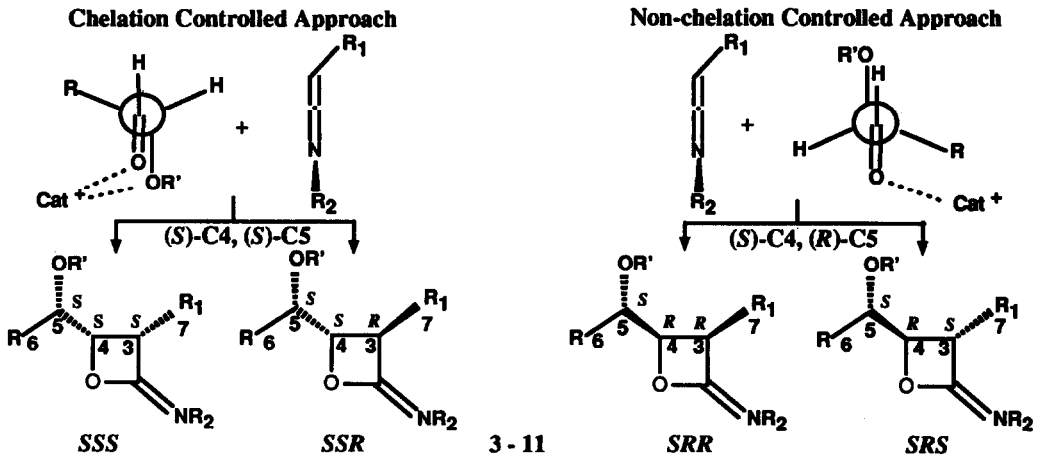
Results and Discussion



The optically active (*S*)-α-alkoxy aldehydes **1a-d** were reacted with C-monosubstituted ketene imines **2a-c** in the presence of lanthanide shift reagents [Yt(fod)$_3$, Yt(hfc)$_3$, Eu(fod)$_3$, Eu(tfc)$_3$],[10] chromium acetylacetonate [Cr(acac)$_3$], and the etherate complexes of $MgBr_2$, BF_3, and $ZnCl_2$. Depending on the substituents in the reagents and the type of catalyst, variable mixtures of four stereoisomers of oxetanes **3-11** (Scheme II) were obtained having an absolute configuration of *SRR*, *SSR*, *SSS*, *SRS* with respect to the C5, C4 and the C3 carbon atoms of the oxetane mojety. Product distribution is regulated by a "diasterofacial selectivity" and by a

"simple diastereoselectivity". "Diasterofacial selectivity" is responsible for a stereodifferentiation around C4-C5 of the oxetane and originates from a chelation or a non-chelation controlled approach with the metal catalyst of the chiral α-alkoxy aldehyde to the racemic ketene imine. The stereochemical consequence is the formation of the (*S*)-C4,(*S*)-C5 and the (*S*)-C4,(*R*)C5 stereoisomers, respectively.

Scheme II



3 - 11

3: R = R_1 = Me, R' = TBDMS; 4: R = R_1 = Me, R' = CPh_3; 5: R = Me, R_1 = Et, R' = CPh_3;
6: R = Me, R_1 = Et, R' = TBDMS; 7: R = C_6H_5, R_1 = Et, R' = TBDMS; 8: R = Me, R_1 = Me_3C, R' = CPh_3;
9: R = C_6H_5, R_1 = Me_3C, R' = TBDMS; 10: R = R' = MEM,; 11: R = Me, R_1 = Me_3C, R' = MEM

Instead, "simple diastereoselection"[11] is responsible for a *cis-trans* stereodifferentiation around C3-C4 carbon atoms of the oxetane moiety. Structures were assigned on the basis of their IR spectra which showed an absorption in the 1730-1750 cm^{-1} (lit. 1735-1760[1,5]) attributed to the exocyclic O-C=N function. Mass spectra revealed, besides the peak of the molecular ion, a fragmentation pattern of four peaks deriving from two different retrocycloadditions along the two main axes of the ring, namely the isocyanate and the ethylene derivative along one axis, and the ketene imine and the aldehyde along the other. All the isomers exhibited consistent ^1H and ^{13}C NMR spectral data. Attached Proton Test (APT) and HETCOR experiments were performed to distinguish the different carbons. The stereostructures were assigned by ^1H and ^{13}C NMR, mostly on the basis of the relative ^1H-^1H coupling constants for the vicinal hydrogens at C3-C4 and at C4-C5 ($J_{3,4}$ and $J_{4,5}$, Table I) and on the basis of NOE experiments. The ^{13}C NMR spectra showed selected resonances ranging from 41.3 to 58.9 ppm attributed to C3, from 80.5 to 86.8 for C4, from 67.3 to 76.9 for C5, and from 158.1 to 161.4 for C2. The assignment of stereoconfiguration around C3-C4 was particularly straightforward. In fact, previous investigations on 2-iminooxetanes[1] showed that the coupling constants of vicinal protons in the ring, $J_{cis} > J_{trans}$, may be used to distinguish the isomers. The range of coupling constants in this study was $J_{3,4}$ = 3.6-4.6 for the C3-C4 *trans* couple of diastereomers *SRS*, *SSR* and $J_{3,4}$ = 6.5-7.0 Hz for the *cis* couple *SRR*, *SSS*. Consistently, the C4-H hydrogen of the *cis* resonates at a lower field than the *trans*. The ^1H NMR correlations were supported by ^{13}C NMR analysis. In fact, as a general rule, the C4 carbon of the *trans* couple resonates at a lower field than the *cis* one. The stereorelationship between C4-C5 was more difficult to define.

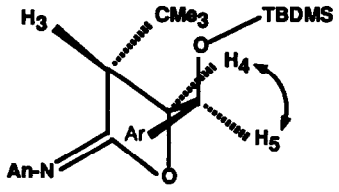
Table I. Relevant ^{13}C and ^{1}H NMR Chemical Shifts (ppm) and $J_{3,4}$ and $J_{4,5}$ (Hz) Coupling Constants Values and Optical Rotations ($[a]_D^{20}$) of 2-Iminooxetanes **3-11**

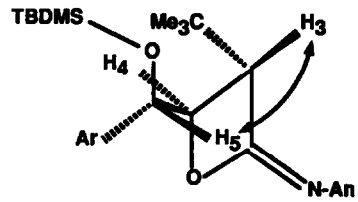
Entry	Oxetane	^{13}C NMR				^{1}H NMR			$[a]_D^{20}$
		C3	C5	C4	C=N	C4-H	$J_{3,4}$	$J_{4,5}$	
1	**3**-*SRR*	42.0	67.8	82.9	161.2	4.40	6.8	8.5	-
2	**3**-*SSS*	43.0	67.3	81.8	161.4	4.40	6.8	6.0	-
3	**3**-*SRS*	42.8	69.3	86.8	160.4	4.15	4.3	6.0	-
4	**3**-*SSR*	41.3	67.6	86.3	160.7	4.12	3.8	3.5	-
5	**4**-*SRR*	42.6	69.0	81.5	161.1	4.58	6.9	8.5	+ 133.7
6	**4**-*SSS*	43.2	68.7	82.0	161.1	4.49	6.9	5.6	-
7	**4**-*SRS*	42.6	69.9	84.5	160.5	3.90	4.0	6.0	-
8	**4**-*SSR*	42.8	69.5	86.0	160.7	4.01	4.2	3.5	-
9	**5**-*SRR*	49.7	69.0	81.4	160.5	4.54	7.0	7.5	-
10	**5**-*SSS*	50.2	68.9	82.0	160.7	4.45	7.0	4.5	+ 47.0
11	**5**-*SRS*	49.0	70.0	82.6	159.8	4.01	4.2	5.6	-
12	**5**-*SSR*	49.1	69.3	83.9	159.9	4.08	4.0	3.1	- 73.3
13	**6**-*SSS*	50.1	67.6	81.8	160.8	4.43	6.6	6.0	-
14	**6**-*SSR*	48.0	65.5	84.5	160.2	4.22	3.6	3.6	-
15	**6**-*SRR*	48.3	67.7	82.6	160.6	4.43	7.0	8.0	-
16	**6**-*SRS*	49.1	69.2	84.7	-	4.24	4.3	5.9	-
17	**7**-*SRR*	49.6	74.8	82.2	160.8	4.90	6.9	7.9	- 32.6
18	**7**-*SSS*	50.7	74.1	81.6	160.4	4.80	6.5	5.6	+ 57.0
19	**7**-*SRS*	49.7	76.7	84.7	159.3	4.39	4.2	6.6	- 8.4
20	**7**-*SSR*	47.2	73.6	84.9	159.9	4.39	4.0	2.7	-
21	**8**-*SRS*	57.9	70.1	79.8	158.8	4.07	4.0	4.0	-
22	**8**-*SSR*	58.3	69.5	80.9	158.9	4.22	4.0	2.5	-
23	**9**-*SRS*	58.5	76.9	81.3	158.2	4.40	4.1	6.3	- 49.3
24	**9**-*SSR*	55.9	73.7	81.6	158.6	4.44	3.8	2.7	+ 44.3
25	**10**-*SRR*	42.4	71.1	81.8	160.8	4.56	6.9	9.5	-
26	**10**-*SSS*	43.2	71.9	80.8	161.0	4.53	6.8	6.5	-
27	**10**-*SRS*	43.6	73.2	85.7	159.9	4.26	4.6	7.1	-
28	**10**-*SSR*	42.2	71.8	85.3	160.4	4.26	4.3	4.3	-
29	**11**-*SSS*	58.9	73.4	80.5	158.1	4.37	6.5	4.2	- 44.1
30	**11**-*SSR*	57.6	71.9	85.2	158.6	4.36	3.8	3.2	+ 6.4

Inspection of the Dreiding models of the *SSS* and *SRR* stereoisomers showed that in these C3-C4 *cis* compounds there is a strong repulsive interaction between the methyl group of the hydroxyethyl side-chain and the alkyl chain C3. This interaction favours an "*anti*" H4-H5 conformation in the *SRR* isomers and a "*gauche*" conformation in the *SSS*. On this basis, a larger $J_{4,5}$ value in the *SRR* isomers than in *SSS* is to be expected. Typically, the $J_{4,5}$ coupling constants of the *SRR* isomers ranged between 7.5-9.5 Hz, those of *SSS* between 4.2-6.5 Hz. A similar behaviour has been also observed in related heterocycles, such as the 2-azetidinones.[12]

In the case of the C3-C4 *trans* compounds (*SRS* and *SSR*) an inspection of the Dreiding models suggests that the alkoxy protecting group should be aligned antiperiplanar to the oxygen atom of the oxetane in the more stable conformation. In line with this model an "*anti*" H4-H5 conformation is adopted by *SRS* and a "*gauche*" by the *SRR* isomers. Accordingly, the larger $J_{4,5}$ coupling constants, ranging between 4.0-7.1 Hz, were found for the *SRS* isomers, while those of *SSR* ranged between 2.5-4.3 Hz. The absolute configuration

about C4-C5 was further confirmed by means of NOE difference spectra performed on the couple 9-*SRS* and 9-*SSR*. In fact, as expected from the proposed model, a NOE signal enhancement between the H5 and H3 protons was detected only in the minor isomer 9-*SRS*. In addition, NOE measurements indicate that the H4-H5 protons are closer in the *SSR* isomer.





9-*SSR* An = p-MeO-C_6H_4; Ar = C_6H_5 9-*SRS*

The above criteria allowed the assignment of stereoconfiguration of oxetanes **11**. These cycloadducts were isolated as a pair of stereoisomers having a different stereochemistry about C3-C4: namely a *cis* has been assigned to that of entry 29 ($J_{3,4}$ = 6.5 Hz) and a *trans* to that of entry 30 ($J_{3,4}$ = 3.8 Hz). As a consequence, an *SSS* stereostructure ($J_{4,5}$ = 4.2 Hz) was assigned to the oxetane of entry 29 and an *SSR* configuration ($J_{4,5}$ = 3.2 Hz) to that of entry 30. Product distribution was determined by HPLC on the crude products, associated with ^{1}H NMR spectroscopy when some pairs of diastereomers were not resolved. Control experiments, performed on pure isolated diastereomers, did not result in any isomerization.

Entries 1-14 of Table II report the product distribution of lanthanide-induced cycloadditions of the ketene imines **2a-c** and aldehydes **1a-d**. The reactions were performed under very mild conditions (25-30 °C) and the catalysts were employed in truly catalytic amount (typically, 1.5-2.0 %). These were inefficient only in the reaction involving the sterically demanding (*S*)-2-(triphenylmethyloxy) propanal (**1b**) and *tert*-butylketene imine (**2c**). In this case the oxetanes **8** were obtained in the presence of an equimolar amount of $MgBr_2.Et_2O$ (entry 15, Table II). Typically, entries 4-8 of Table II show the variation of this distribution for the reaction of (*S*)-2-(triphenylmethyloxy)-propanal (**1b**) and ethylketene *N*-*p*-methoxyphenylimine (**2b**) with a series of lanthanide catalysts and $Cr(acac)_3$. As can be seen from the reported data, no significant facial selectivity was observed. This type of selectivity is here expressed as the C4-C5-facial selectivity ratio (FS) of the amount of chelate to non-chelate isomers [FS = (*SSS* + *SSR*)/(*SRS* + *SRR*)]. It appears that lanthanides favor cycloaddition via non-chelation control but with only a slight degree of selectivity, as the FS ratio ranged between 0.44 [$Yt(fod)_3$] to 0.83 [$Eu(fod)_3$]. Similar results are reported for the aldol additions of litium enolates to α-alkoxy aldehydes and can be partially attributed to the presence of the bulky trityloxy protecting group that prevents chelation control. The type of lanthanide promoter also influences the extent of "simple diastereoselection", expressed as the C3-C4-simple selectivity ratio (SS) of the amount of *Z*- to *E*-isomers [SS = (*SSS* + *SRR*)/(*SRS* + *SSR*)], this ratio ranged between 0.40 with $Eu(tfc)_3$ to 1.65 with $Yt(fod)_3$, depending on the nature of the metal ligand and on the organic residue linked to the metal, when the same metal is used. To achieve a better diastereoselectivity, we have explored the effect of the peripheral substituents in the reagents. As to the effect of the protecting group of the aldehyde, we have reacted the methylketene *N*-*p*-methoxyphenylketene imine (**2a**) with the (*S*)-lactaldehyde derivatives bearing the 2-(methoxyethoxy)methyloxy (O-MEM) (**1d**) substituent or the sterically demanding *tert*-butyldimethylsilyloxy (**1a**), and trityloxy (**1b**) substituents. These reactions were performed in the presence of $Yt(fod)_3$ and

afforded the oxetanes **3**, **4**, and **10**, respectively. Whatever the nature of the protecting group, the non-chelation controlled products are preferentially formed (entries 1, 2, and 12, Table II).

Table II. Dependence of the Isomer Distribution of Oxetanes **3-11** on the Type of Catalyst.

Entry	Catalyst	Oxetane	*SRR*	*SSS*	*SRS*	*SSR*	FS[a]	SS[b]
1	$Yt(fod)_3$	**3**	35.1	22.2	25.2	17.5	0.66	1.34
2	$Yt(fod)_3$	**4**	45.0	13.0	21.0	21.0	0.51	1.38
3	$Eu(fod)_3$	**4**	38.5	11.9	26.8	22.8	0.53	1.02
4	$Yt(fod)_3$	**5**	49.7	12.6	19.8	17.9	0.44	1.65
5	$Yt(hfc)_3$	**5**	28.1	15.8	28.2	27.9	0.78	0.78
6	$Eu(fod)_3$	**5**	23.0	27.0	32.0	18.0	0.83	1.0
7	$Eu(tfc)_3$	**5**	11.0	17.4	45.8	25.8	0.76	0.40
8	$Cr(acac)_3$	**5**	32.3	30.0	24.4	13.3	0.76	1.65
9	$Yt(fod)_3$	**6**	30.1	18.1	20.9	29.9	0.9	1.0
10	$Yt(fod)_3$	**7**	20.7	52.0	15.2	12.1	1.78	2.66
11	$Yt(fod)_3$	**9**	-	-	16.6	83.4	5.02	*trans*
12	$Yt(fod)_3$	**10**	36.5	32.2	21.3	10.2	0.74	2.17
13	$Yt(hfc)_3$	**10**	29.1	32.6	14.5	23.8	1.29	1.61
14	$Yt(fod)_3$	**11**	-	47.8	-	52.2	> 10	0.92
15	$MgBr_2$	**8**	-	-	41.0	59.0	1.43	*trans*
16	$ZnCl_2$	**4**	45.3	8.0	32.3	14.4	0.29	1.14
17	BF_3	**4**	6.7	5.2	75.9	12.2	0.21	0.14
18	$ZnCl_2$	**5**	40.1	4.0	50.3	5.6	0.11	0.79
19	BF_3	**5**	6.7	1.8	82.0	9.5	0.13	0.10

a. FS = C4-C5-Facial selectivity (*SSS+SSR/SRS+SRR*). b. SS = C3-C4-Simple selectivity (*SSS+SRR/SRS+SSR*)

This is quite surprising, since the MEM protecting group of **1d** would seem likely to direct the selectivity in the way predicted by "Cram's cyclic model", due to the presence of two additional oxygen atoms, so that chelation involving a "crown-ether" effect would be possible. However, an improvement in the chelation diastereocontrol was achieved when **1d** was reacted in the presence of $Yt(hfc)_3$ (FS = 1.29, entry 13 of Table II).

It was observed that the nature of the substituent (R) in the aldehyde produces a noticeable variation in diastereoselectivity. This variation is shown in Table II which reports the product distribution of oxetanes **6** and **7** obtained from the $Yt(fod)_3$ induced cycloaddition of ethylketene *N-p*-methoxyphenylimine **1b** with OTBDMS derivatives of the (*S*)-lactaldehyde **1a** (R = methyl) and of the (*S*)-mandelic aldehyde **1c** (R = phenyl), respectively. Interestingly, the phenyl substituent of **1c** favored a chelation diastereocontrol and a *cis*-C3-C4 diasteroselectivity (FS = 1.78, SS = 2.66, entry 10) with respect to the methyl of **1a** (FS = 0.9, SS = 1.0, entry 9). The net result is that the phenyl substituent of the mandelic aldehyde favored the formation of the *SSS* stereoisomer which was obtained as the major one in 52 % amount.

Diasteroselectivity increased with the size of the alkyl substituent in the keten imine. For instance, the bulky *tert*-butyl substituent of **2c** gave a good (*S*)-C4,(*S*)-C5 diastereoselection, the same as predicted by the chelation control, irrespective of the type of the aldehyde. In fact, a FS ratio of 5.0 was obtained in the reaction of **2c** with the O-*tert*-butyldimethylsilyl protected mandelic aldehyde **1c** (entry 11, Table II).

Similarly, a total chelation-controlled selectivity was observed in the cycloaddition of **2c**, in the presence of $Yt(fod)_3$, to the MEM protected aldehyde **1d** (entry 14, Table II). In contrast, poor selectivity was observed with the less sterically demanding methylketene *N-p*-methoxyphenylimine with the same aldehydes (FS = 1.8 and 0.74, respectively). The (*S*)-C4,(*S*)-C5 diastereoselectivity, caused by the sterically demanding *tert*-butyl substituent of ketene imine **2c**, can be predicted by a Cornforth's dipolar model that places the alkoxy groups *anti* to the carbonyl. According to this mechanism, the determining factor which influences the FS ratio appears to be the relative bulk of the *tert*-butyl substituent *versus* the α-alkoxy protecting group of the aldehyde which disfavour the non-chelation controlled approach. As far as the effect of the substituents on the simple diasteroselectivity is concerned, it is worthwhile noting that a good level of *trans*-C3-C4 diastereocontrol was achieved only when both reagents were loaded by bulky substituents. In fact, no selectivity was found around C3-C4 when the sterically demanding *tert*-butylketene imine **2c** reacted with the

Table III. Dependence of the Facial Selectivity (FS) on the Temperature and on the Amount[a] of $Yt(fod)_3$ in the Reaction of Ketene Imine **2a** with Aldehyde **1a** Leading to 2-Iminooxetane

% of $Yt(fod)_3$	T°C	*SRR*	*SRS*	FS[b]
1.8	25.0	34.0	27.0	0.7
14.8	25.0	13.4	28.8	1.4
1.4	- 45.0	27.2	18.2	1.2
15.4	- 45.0	3.0	4.0	13.0

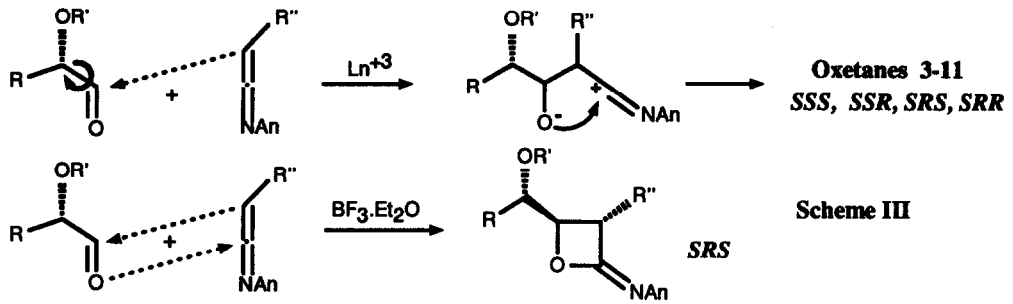
a. Molar % with espect to **2a**. b. FS = C4-C5-Facial selectivity (*SSS+SSR/SRS+SRR*).

less hindered MEM-protected aldehyde **1d**. In contrast, the reaction was totally *trans*-C3-C4 selective when **2c** reacted with the trityloxy and *tert*-butyldimethylsilyloxy substituted aldehydes **1b** and **1c**.

Table III reports the dependence of the facial selectivity with the temperature and with the amount of catalyst in the $Yt(fod)_3$ induced reaction of ketene imine **2a** with aldehyde **1a**, leading to the oxetane **3**. A (*S*)-C4,(*S*)-C5 diastereoselection was favored when this ketene imine of moderate bulk reacted at low temperatures and when the amount of catalyst was increased. For instance, at - 45 °C with a 15 molar % of $Yt(fod)_3$, the FS ratio was of 13. This experimental observation prompted us to try other Lewis acids, such as the 1:1 etherate complexes of $ZnCl_2$ and BF_3 that are generally used in stoichiometric amounts at lower temperatures.[13] Our aim was to improve *anti*-C4-C5 diastereoselection with ketene imines **2a** and **2b**, bearing linear alkyl substituents of moderate bulk, in the presence of Lewis acids incapable of chelation. The reactions, performed at - 50 °C, were completed within few minutes (BF_3) or a few hours ($ZnCl_2$). Product distributions are shown in Table II. It appears that, even when the steric environment is not demanding, both BF_3 and $ZnCl_2$ show significant levels of non-chelation control. However, a different behavior of the two catalysts was observed in the C3-C4-simple diastereoselection. Interestingly, the milder $ZnCl_2$ was not selective in this respect: a comparable amount of *SRR* and *SRS* isomers was obtained, while BF_3 was an excellent catalyst for the formation of the *SRS* isomers.

Our results show that lanthanides catalysts are unable to promote a good chelate bidentate, hence to favor a chelation diastereocontrol, irrespective of the type of substituents in the aldehyde. In line with these

results, absence of C3-C4 simple diastereoselection was also observed when substituents of medium size are present in the reagents. Such absence suggests a stepwise mechanism for the hetero-cycloaddition (Scheme III) involving an initial aldol-type addition of the nucleophilic terminal carbon atom of the ketene imine to the carbon of the lanthanide-coordinated aldehyde. In fact, theoretical calculations on the electronic population of the C=C bond in ketene imines[14] have shown that the resonance structures where the terminal carbon atom is negatively charged contribute significantly to the ground state structure. Such zwitterionic two-center transition state can be viewed as the result of a forbidden reaction, the dominant interaction occurring between the HOMO of the ketene imine and the LUMO of the lanthanide-coordinated aldehyde.



Scheme III

This forbidiness is a consequence of the lower efficiency of lanthanides in promoting ketene imine aldehyde hetero-cyloadditions with respect to stronger catalysts as boron trifluoride or zinc chloride and of a less pronounced 1,2-dipolar character of the ketene imines with respect to ketenes.[14] Substitution of lanthanides with boron trifluoride and zinc chloride reduces the HOMO (ketene imine) - LUMO (Lewis acid-coordinated aldehyde) energy gap, so that the transition state stabilization energy is increased. Moreover, another interaction between the HOMO of the aldehyde and the LUMO of the Lewis acid coordinated ketene imine, might compete for the energy stabilization of the transition state.[15] This stabilization increases the rate of the hetero-cycloadditions and affect the diastereoselectivity. In fact, these stronger interactions remove the forbidiness,[16] thus favoring more highly organized allowed transition states.[17] This sterically demanding transition state geometry results in a better *anti*-C3-C4 stereocontrol. This type of diastereocontrol, associated with a non-chelation approach of the reagents favors the formation of the *SRS* isomers.

Conclusions

Additional studies on chiral β or γ-alkoxy aldehydes, shown by Masamune[18] to display higher levels of chelation control, are worthy of examination. Notwithstanding, our efforts reveal some interesting points for which this reaction is attractive from a synthetic point of wiew. First, readily available starting materials are converted into 2-iminooxetanes in high yield with only trace amounts of catalyst, even if the system is loaded with sterically demanding peripheral substituents. This is rather important for the achievement of high diastereocontrol. In fact, we have demonstrated that through proper choice of sterically demanding substituents the formation of stereoisomers is reduced to two, with a considerable excess of the chelation controlled products, as in the reactions of entries 11, 14, and 15 of Table II. Second, both BF_3 and $ZnCl_2$ are excellent catalysts for non-chelating diastereocontrol with smaller ketene imines, the *SRS* isomers being obtained with boron trifluoride. Third, at variance with the carbon-carbon bond forming reactions of C-nucleophiles, such as Grignard reagents or enolates, these "acid" aldol condensations do not require any

particular precautions, such as carefully dried solvents and inert atmosphere. Fourth; these findings allow the synthesis of new chiral building blocks, such as amino-polialcohols ($RC^*HOR'C^*HOHC^*R_1R_2CH_2NHR_3$) via hydrogenolysis of the corresponding 2-iminooxetanes.[2] Another application is the synthesis of chiral β-haloamides, suitable intermediates for the synthesis of the corresponding β-lactams[3] (scheme I).

EXPERIMENTAL

General. The ^1H and ^{13}C NMR data were obtained as $CDCl_3$ solutions and the internal reference was tetramethylsilane. The differential NOE experiments were performed on a Varian Gemini 300 instrument using NOEDIFF sequences in NMR tubes degassed with freeze-pump-thaw technique. IR spectra were obtained as CCl_4 solutions. Mass spectra were recorded on a Varian MAT 112 S at an ionizing voltage of 70 eV. Product distribution was evaluated directly on the crude reaction mixtures by HPLC analysis using a 250 x 4.6 mm column of Hipersyl 5 MOS C_8- (230 nm). Buffer A: H_2O-CH_3CN (10:90); buffer B: H_2O; gradient: 30-25 buffer B in 25 min, then 25-30 buffer B in 5 min; flow 1.0 ml/min, temperature 23 °C. On the occasions when some pairs of diastereomers could not be resolved with this technique, the ^1H NMR analysis was associated with the HPLC one. The ketene imines[19] and the aldehydes[20] were prepared according to the literature. All the solvents were dried and purified according to standard procedures.

General Procedure for the Synthesis of 2-Iminooxetanes.

A) With Lanthanide Shift Reagents and Chromium Acetyl Acetonate Catalysts. The ketene imine and the aldehyde, in the presence of 1.0-2.0 mmol % of catalyst, were reacted in CCl_4 at the selected temperature for the time required. Removal of the solvent and flash chromatography of the residue afforded the isolation of pure diastereoisomers or of fractions containing one of the isomers as the major one. In several cases these fractions were rechromatographed in order to increase the relative amount of this isomer. Although chromatography was performed with dried solvents and with silica preheated in an oven, on occasions the oxetanes were contaminated by variable amounts (*ca* 5-10 %) of the corresponding β-hydroxyamides, formed by hydrolytic ring opening during the elution. These amides were quantitatively removed by filtration after the oxetanes had been dissolved in *n*-pentane and left at - 20 °C for one day. After the workup, the oxetanes were always obtained as oily viscous residues.

B) With $MgBr_2.Et_2O$, $BF_3.Et_2O$, and $ZnCl_2$ (1.0 M solution in diethyl ether). A solution of the catalyst in CH_2Cl_2 was cooled under nitrogen at - 50 °C and an equimolar solution of the aldehyde was added over 3 min. After 5 min the ketene imine was added and the reaction mixture was thermostated at the selected temperature for the time required under stirring. The reaction was quenched by adding a two mole excess of triethylamine. The solution was poured onto 100 ml of saturated aqueous sodium bicarbonate and extracted with ether. Work-up of the crude reaction mixture was as described above.

2-[(4-Methoxyphenyl)imino]-3-methyl-4-[(*S*)-1-[(*tert*-butyldimethylsilyl)-oxy]ethyl]oxetanes 3-*SSR*, 3-*SSS*, 3-*SRS*, and 3-*SRR*). The aldehyde **1a** (0.5 g, 2.6 mmol) and the ketene imine **2a** (0.64 g, 3.97 mmol) were reacted in the presence of $Yt(fod)_3$ (0.05 g, 0.046 mmol) at 25 °C for 24 h. Flash chromatography (*n*-pentane/ethyl ether, 2:1) gave 0.785 g (2.25 mmol, 87 %) of oxetanes. **3-*SSR***: this compound was obtained as the major product in a 3-*SSR*:3-*SSS* = 20:1 mixture. ^1H NMR: δ 0.0 (s, Me, 3), 0.05 (s, Me, 3), 0.8 (s, Me, 9), 1.10 (d, Me-6, 3), 1.40 (d, Me-7, 3), 3.65 (m, H-3, 1), 3.75 (s, OMe, 3), 4.07 (m, H-5, 1), 4.12 (m, H-4, 1), 6.8-7.3 (m, 4 H, arom); $J_{H,Me-7}$ = 7.0, $J_{H,Me-6}$ = 6.5, $J_{3,4}$ = 3.7, $J_{4,5}$ = 3.5 Hz. *Anal.* Calcd for

$C_{19}H_{31}NO_3Si$: C, 65.29; H, 8.94; N, 4.01. Found: C, 65.36; H, 8.90; N, 4.03. **3-*SSS***: this compound was obtained as the major product in a 3-*SSS*:3-*SSR* = 4:1 mixture. ^{1}H NMR δ 0.0 (s, Me, 3), 0.05 (s, Me, 3), 0.8 (s, Me, 9), 1.20 (d, Me-6, 3), 1.40 (d, Me-7, 3), 3.75 (s, OMe, 3), 3.80 (m, H-3, 1), 4.15 (m, H-5, 1), 4.40 (m, 4-H, 1), 6.8-7.3 (m, 4 H, arom); $J_{H,Me-7}$ = 7.0, $J_{H,Me-6}$ = 6.5, $J_{3,4}$ = 6.75, $J_{4,5}$ = 6.0 Hz. *Anal.* Calcd for $C_{19}H_{31}NO_3Si$: C, 65.29; H, 8.94; N, 4.01. Found: C, 65.43; H, 8.92; N, 3.97. **3-*SRS***: this compound was obtained as the major product in a 3-*SRS*:3-*SRR* = 20:1 mixture. ^{1}H NMR δ 0.1 (s, Me, 6), 0.9 (s, Me, 9), 1.20 (d, Me-6, 3), 1.42 (d, Me-7, 3), 3.35 (m, H-3, 1), 3.75 (s, OMe, 3), 4.00 (m, H-5, 1), 4.15 (m, H-4, 1), 6.8-7.3 (m, 4 H, arom); $J_{H,Me-7}$ = 7.3, $J_{H,Me-6}$ = 6.0, $J_{3,4}$ = 4.3, $J_{4,5}$ = 6.0. *Anal.* Calcd for $C_{19}H_{31}NO_3Si$: C, 65.29; H, 8.94; N, 4.01. Found: C, 65.25; H, 8.97; N, 4.04. **3-*SRR***: this compound was obtained as the major product in a 3-*SRR*:3-*SRS* = 5:1 mixture. ^{1}H NMR d 0.05 (s, Me, 3), 0.06 (s, Me, 3), 0.9 (s, Me, 9), 1.15 (d, Me-6, 3), 1.35 (d, Me-7, 3), 3.75 (m, H-3, 1), 3.75 (s, OMe, 3), 4.10 (m, H-5, 1), 4.40 (m, H-4, 1), 6.8-7.3 (m, 4 H, arom); $J_{H,Me-7}$ = 6.7, $J_{H,Me-6}$ = 6.3, $J_{3,4}$ = 6.7, $J_{4,5}$ = 8.5. *Anal.* Calcd for $C_{19}H_{31}NO_3Si$: C, 65.29; H, 8.94; N, 4.01. Found: C, 65.33; H, 8.98; N, 3.96. All the diastereoisomers showed identical mass and ir spectral data. Ms: m/z 349 (M^+), 292, 218, 161, 149; ir: ν 1737 (O-C=N), 1506 cm^{-1}.

2-[(4-Methoxyphenyl)imino]-3-methyl-4-[(*S*)-1-[(triphenylmethyl)-oxy]ethyl]oxetanes (4-*SSR*, 4-*SSS*, 4-*SRR*, and 4-*SRS*). *Procedure A*: The aldehyde **1b** (1.69 g, 5.4 mmol) and the ketene imine **2a** (0.86 g, 5.4 mmol) were reacted in the presence of Yt(fod)$_3$ (0.08 g, 0.074 mmol) at 25 °C for 5 days. Flash chromatography (*n*-pentane/ethyl ether, 2:1) gave 2.1 g (4.4 mmol, 82.0 %) of oxetanes. *Procedure B*: The aldehyde (0.34 g, 1.1 mmol) and the ketene imine (0.170 g, 1.1 mmol) were reacted in the presence of an equimolar amount of $BF_3.Et_2O$. There was obtained 0.378 g (0.792 mmol, 72 %) of oxetanes. **4-*SSR***: this compound was obtained (*Procedure A*) as the major product in a 4-*SSR*:4-*SRS* = 4:1 mixture. ^{1}H NMR δ 0.75 (d, Me-6, 3), 1.39 (d, Me-7, 3), 3.60 (m, H-3, 1), 3.78 (s, OMe, 3), 3.90 (m, H-5, 1), 4.01 (m, H-4, 1), 6.7-7.6 (m, 19 H, arom); $J_{H,Me-7}$ = 7.0, $J_{H,Me-6}$ = 6.0, $J_{3,4}$ = 4.2, $J_{4,5}$ = 3.5 Hz. *Anal.* Calcd for $C_{32}H_{31}NO_3$: C, 80.47; H, 6.54; N, 2.93. Found: C, 80.36; H, 6.58; N, 2.95. **4-*SSS***: this compound was obtained (*Procedure A*) as the major product in a 4-*SSS*:4-*SRS* = 10:1 mixture . ^{1}H NMR δ 0.99 (d, Me-6, 3), 1.21 (d, Me-7, 3), 3.73 (m, H-3, 1), 3.75 (s, OMe, 3), 3.82 (m, H-5, 1), 4.49 (m, H-4, 1), 6.7-7.6 (m, 19 H, arom); $J_{H,Me-7}$ = 7.0, $J_{H,Me-6}$ = 6.0, $J_{3,4}$ = 6.9, $J_{4,5}$ = 5.6 Hz; ^{1}H NMR relevant resonances in C_6D_6: δ 0.88 (d, Me-6, 3), 1.12 (d, Me-7, 3), 3.40 (m, H-3, 1), 3.82 (m, H-5, 1), 4.20 (m, H-4, 1). *Anal.* Calcd for $C_{32}H_{31}NO_3$: C, 80.47; H, 6.54; N, 2.93. Found: C, 80.55; H, 6.57; N, 2.90. **4-*SRR***: this compound was isolated as pure diastreoisomer (*Procedure A*). ^{1}H NMR δ 0.66 (d, Me-6, 3), 1.21 (d, Me-7, 3), 3.75 (m, H-3, 1), 3.75 (s, OMe, 3), 3.92 (m, H-5, 1), 4.58 (m, H-4, 1), 6.7-7.6 (m, 19 H, arom); $J_{H,Me-7}$ = 6.7, $J_{H,Me-6}$ = 6.0, $J_{3,4}$ = 6.9, $J_{4,5}$ = 8.5 Hz. *Anal.* Calcd for $C_{32}H_{31}NO_3$: C, 80.47; H, 6.54; N, 2.93. Found: C, 80.53; H, 6.50; N, 2.96. **4-*SRS***: this compound was obtained (*Procedure B*) as the major product in a 4-*SRS*:4-*SSR* = 10:1 mixture. ^{1}H NMR δ 0.84 (d, Me-6, 3), 1.33 (d, Me-7, 3), 3.42 (m, H-3, 1), 3.78 (s, OMe, 3), 3.90 (m, H-4, 1), 3.95 (m, H-5, 1), 6.7-7.6 (m, 19 H, arom); $J_{H,Me-7}$ = 7.4, $J_{H,Me-6}$ = 6.0, $J_{3,4}$ = 4.0, $J_{4,5}$ = 6.0 Hz. *Anal.* Calcd for $C_{32}H_{31}NO_3$: C, 80.47; H, 6.54; N, 2.93. Found: C, 80.39; H, 6.55; N, 2.90 All the diastereoisomers showed identical mass and ir spectral data. Ms: m/z 477 (M^+), 149, 147; ir: ν 1732 (O-C=N), 1506 cm^{-1}.

2-[(4-Methoxyphenyl)imino]-3-ethyl-4-[(*S*)-1-[(triphenylmethyl)-oxy]ethyl]oxetane (5-*SSS*, 5-*SRS*, 5-*SRR*, and 5-*SSR*). The aldehyde **1b** (0.873 g, 2.76 mmol) and the ketene imine **2b** (0.50 g, 2.85 mmol), were reacted in the presence of Yt(fod)$_3$ (0.05 g, 0.046 mmol) at 30 °C for 8 days. Flash chromatography (*n*-pentane/ethyl ether = 2:1) gave 1.15 g (2.34 mmol, 85.0 %) of oxetanes. **5-*SSS***: ^{1}H NMR δ 0.98 (t, Me, 3),

1.04 (d, Me-6, 3), 1.5-1.8 (m, CH_2, 2), 3.45 (m, H-3, 1), 3.77 (s, OMe, 3), 3.84 (m, H-5, 1), 4.45 (m, H-4, 1), 6.75-7.20 (m, 4 H, arom), 7.20-7.6 (m, 15 H, arom); $J_{3,4}$ = 7.0, $J_{4,5}$ = 4.5 Hz. *Anal.* Calcd for $C_{33}H_{33}NO_3$: C, 80.62; H, 6.77; N, 2.85. Found: C, 80.51; H, 6.78; N, 2.89. **5-*SRS***: this compound was obtained as the major product in a **5-*SSS*:5-*SRS*:5-*SRR*:5-*SSR*** = 0.8:2.0:1.0:0.9 mixture. ^{1}H NMR δ 0.87 (d, Me-6, 3), 0.97 (t, Me, 3), 1.7-1.9 (m, CH_2, 2), 3.33 (m, H-3, 1), 3.78 (s, OMe, 3), 3.80-3.95 (m, H-5, 1), 4.01 (m, H-4, 1), 6.75-7.20 (m, 4 H, arom), 7.2-7.6 (m, 15 H, arom); $J_{3,4}$ = 4.2, $J_{4,5}$ = 5.6 Hz. *Anal.* Calcd for $C_{33}H_{33}NO_3$: C, 80.62; H, 6.77; N, 2.85. Found: C, 80.75; H, 6.72; N, 2.81. **5-*SRR***: this compound was obtained as the major product in a **5-*SRR*:5-*SRS*** = 2.0:1.0 mixture. ^{1}H NMR δ 0.73 (d, Me-6, 3), 1.01 (t, Me, 3), 1.6-1.8 (m, CH_2, 2), 3.55 (m, H-3, 1), 3.79 (s, OMe, 3), 3.88 (m, H-5, 1), 4.54 (m, H-4, 1), 6.75-7.25 (m, 4 H, arom), 7.3-7.6 (m, 15 H, arom); $J_{3,4}$ = 7.0, $J_{4,5}$ = 7.5 Hz. *Anal.* Calcd for $C_{33}H_{33}NO_3$: C, 80.62; H, 6.77; N, 2.85. Found: C, 80.50; H, 6.79; N, 2.87. **5-*SSR***. ^{1}H NMR δ 0.73 (d, Me-6, 3), 1.00 (t, Me, 3), 1.7-1.9 (m, CH_2, 2), 3.55 (m, H-3, 1), 3.78 (s, OMe, 3), 3.80-3.95 (m, H-5, 1), 4.08 (m, H-4, 1), 6.70-7.25 (m, 4 H, arom), 7.3-7.6 (m, 15 H, arom); $J_{3,4}$ = 4.0, $J_{4,5}$ = 3.1 Hz.. *Anal.* Calcd for $C_{33}H_{33}NO_3$: C, 80.62; H, 6.77; N, 2.85. Found: C, 80.72; H, 6.81; N, 2.88. All the diastereoisomers showed identical mass and ir spectral data. Ms: m/z 491 (M^+), 243, 149; ir: ν 1735 (O-C=N), 1506 cm^{-1}.

2-[(4-Methoxyphenyl)imino]-3-ethyl-4-[(*S*)-1-[(*tert*-butyldimethylsilyl)-oxy]ethyl]oxetane (6-*SSS*, 6-*SSR*, 6-*SRR*, and 6-*SRS*). The aldehyde **1a** (0.627 g, 3.34 mmol) and the ketene imine **2b** (0.581 g, 3.32 mmol) were reacted in the presence of Yt(fod)$_3$ (0.045 g, 0.041 mmol) at 25 °C for 3 days. Flash chromatography (*n*-pentane/ethyl ether, 2:1) gave 1.06 g (2.92 mmol, 88 %) of oxetanes. **6-*SSS***: this compound was obtained as the major product in a **6-*SSS*:6-*SSR*** = 8.0:1.0 mixture. ^{1}H NMR δ 0.03 (s, Me, 3), 0.08 (s, Me, 3), 0.87 (s, Me, 9), 1.16 (t, Me-8, 3), 1.23 (d, Me-6, 3), 1.8-2.2 (m, CH_2, 2), 3.62 (m, H-3, 1), 3.78 (s, OMe, 3), 4.19 (m, H-5, 1), 4.43 (m, H-4, 1), 6.8-7.2 (m, 4 H, arom); $J_{3,4}$ = 6.6, $J_{4,5}$ = 6.0 Hz. *Anal.* Calcd for $C_{20}H_{33}NO_3Si$: C, 66.08; H, 9.15; N, 3.85. Found: C, 66.35; H, 9.10; N, 3.89. **6-*SSR***: this compound was obtained as the major product in a **6-*SSR*:6-*SRR*** = 5.0:1.0 mixture. ^{1}H NMR δ 0.02 (s, Me, 3), 0.06 (s, Me, 3), 0.86 (s, Me, 9), 1.06 (t, Me-8, 3), 1.14 (d, Me-6, 3), 1.7-2.2 (m, CH_2, 2), 3.56 (m, H-3, 1), 3.79 (s, OMe, 3), 4.11 (m, H-5, 1), 4.22 (m, H-4, 1), 6.8-7.2 (m, 4 H, arom); $J_{3,4}$ = 3.6, $J_{4,5}$ = 3.6 Hz. *Anal.* Calcd for $C_{20}H_{33}NO_3Si$: C, 66.08; H, 9.15; N, 3.85. Found: C, 65.89; H, 9.12; N, 3.87. **6-*SRR***: this compound was obtained as the major product in a **6-*SRR*:6-*SRS*** = 12.0:1.0 mixture. ^{1}H NMR δ 0.06 (s, Me, 3), 0.07 (s, Me, 3), 0.89 (s, Me, 9), 1.17 (d, Me-6, 3), 1.18 (t, Me-8, 3), 1.7-2.0 (m, CH_2, 2), 3.57 (m, H-3, 1), 3.78 (s, OMe, 3), 4.11 (m, H-5, 1), 4.43 (m, H-4, 1), 6.8-7.2 (m, 4 H, arom); $J_{3,4}$ = 7.0, $J_{4,5}$ = 8.0 Hz. *Anal.* Calcd for $C_{20}H_{33}NO_3Si$: C, 66.08; H, 9.15; N, 3.85. Found: C, 66.21; H, 9.19; N, 3.82. **6-*SRS***: this compound was obtained as the major product in a **6-*SRS*:6-*SRR*** = 10.0:1.0 mixture. ^{1}H NMR δ 0.09 (s, Me, 6), 0.90 (s, Me, 9), 1.06 (t, Me-8, 3), 1.19 (d, Me-6, 3), 1.8-2.0 (m, CH_2, 2), 3.28 (m, H-3, 1), 3.78 (s, OMe, 3), 4.01 (m, H-5, 1), 4.24 (m, H-4, 1), 6.8-7.2 (m, 4 H, arom); $J_{3,4}$ = 4.3, $J_{4,5}$ = 5.9 Hz. *Anal.* Calcd for $C_{20}H_{33}NO_3Si$: C, 66.08; H, 9.15; N, 3.85. Found: C, 66.01; H, 9.19; N, 3.87. All the diastereoisomers showed identical mass and ir spectral data. Ms: m/z 363 (M^+), 175, 149; ir: ν 1732 (O-C=N) cm^{-1}.

2-[(4-Methoxyphenyl)imino]-3-ethyl-4-[(*S*)-1-[(*tert*-butyldimethylsilyl)-oxy]benzyl]oxetane (7-*SSS*, 7-*SSR*, 7-*SRR*, 7-*SRS*). The aldehyde **1c** (0.495 g, 1.98 mmol) and the ketene imine **2b** (0.345 g, 1.97 mmol) were reacted in the presence of Yt(fod)$_3$ (0.036 g, 0.033 mmol) at 25 °C for 2 days. Flash chromatography (*n*-hexane/ethyl acetate, 4:1) gave 0.76 g (1.79 mmol, 90.0 %) of oxetanes. **7-*SSS***: ^{1}H NMR δ -0.21 (s, Me, 3), 0.02 (s, Me, 3), 0.88 (s, Me, 9), 1.02 (t, Me, 3), 1.8-2.0 (m, CH_2, 1), 2.05-2.25 (m, CH_2, 1), 3.60 (m, H-3,

1), 3.77 (s, OMe, 3), 4.80 (m, H-4, 1), 5.09 (m, H-5, 1), 6.8-7.2 (m, 4 H, arom), 7.2-7.4 (m, 5 H, arom); $J_{3,4}$ = 6.5, $J_{4,5}$ = 5.6 Hz. *Anal.* Calcd for $C_{25}H_{35}NO_3Si$: C, 70.54; H, 8.29; N, 3.29. Found: C, 70.66; H, 8.24; N, 3.33. **7-*SSR***: this compound was obtained as the major product in a **7-*SSR*:7-*SRR*:7-*SSS*** = 2.8:1.5:1.0 mixture. ^{1}H NMR relevant resonances were at δ 0.53 (t, Me, 3), 0.88 (s, Me, 9), 3.73 (m, H-3, 1), 4.39 (m, H-4, 1), 5.17 (m, H-5, 1); $J_{3,4}$ = 4.0, $J_{4,5}$ = 2.7 Hz. *Anal.* Calcd for $C_{25}H_{35}NO_3Si$: C, 70.54; H, 8.29; N, 3.29. Found: C, 70.70; H, 8.33; N, 3.32. **7-*SRR***: ^{1}H NMR δ -0.15 (s, Me, 3), 0.08 (s, Me, 3), 0.84 (s, Me, 9), 0.9 (t, Me, 3), 1.5-1.7 (m, CH_2, 1), 1.8-2.0 (m, CH_2, 1), 3.50 (m, H-3, 1), 3.80 (s, OMe, 3), 4.90 (4.58 in C_6D_6) (m, H-4, 1), 4.90 (4.76 in C_6D_6) (m, H-5, 1), 6.8-7.3 (m, 4 H, arom), 7.2-7.4 (m, 5 H, arom); $J_{3,4}$ = 6.9, $J_{4,5}$ = 7.9 Hz. *Anal.* Calcd for $C_{25}H_{35}NO_3Si$: C, 70.54; H, 8.29; N, 3.29. Found: C, 70.64; H, 8.34; N, 3.26. **7-*SRS***: ^{1}H NMR δ -0.06 (s, Me, 3), 0.08 (s, Me, 3), 0.61 (t, Me, 3), 0.89 (s, Me, 9), 1.2-1.8 (m, CH_2, 2), 3.20 (m, H-3, 1), 3.79 (s, OMe, 3), 4.39 (m, H-4, 1), 4.80 (m, H-5, 1), 6.7-7.2 (m, 4 H, arom), 7.2-7.4 (m, 5 H, arom) $J_{3,4}$ = 4.2, $J_{4,5}$ = 6.6 Hz. *Anal.* Calcd for $C_{25}H_{35}NO_3Si$: C, 70.54; H, 8.29; N, 3.29. Found: C, 70.39; H, 8.35; N, 3.33. All the diastereoisomers showed identical mass and ir spectral data. Ms: m/z 425 (M^+), 175, 149; ir: ν 1735 (O-C=N) cm^{-1}.

2-[(4-Methoxyphenyl)imino]-3-*tert*-butyl-4-[(*S*)-1-[(triphenylmethyl)-oxy]ethyl]oxetane (8-*SSR*, and 8-*SRS*). The aldehyde **1b** (1.06 g, 3.35 mmol) and the ketene imine **2c** (0.685 g, 3.37 mmol) were added to an equimolar amount of $MgBr_2$ at 25 °C for 24 hrs. Flash chromatography (*n*-hexane/ethyl acetate, 7:1) gave 1.52 g (2.93 mmol, 87.0 %) of the mixture of the two oxetanes. MS m/z 519 (M^+), 203, 149; ir: ν 1740 (O-C=N), 1506 cm^{-1}. *Anal.* Calcd for $C_{35}H_{37}NO_3$: C, 80.89; H, 7.18; N, 2.7O. Found: C, 80.64; H, 7.23; N, 2.72. **8-*SSR***. ^{1}H NMR δ 0.76 (d, Me-6, 3), 1.09 (s, Me, 9), 3.45 (m, H-3, 1), 3.81 (s, OMe, 3), 3.95 (m, H-5, 1), 4.22 (m, H-4, 1), 6.8-7.3 (m, 4 H, arom), 7.2-7.7 (m, 15 H, arom); $J_{3,4}$ = 4.0, $J_{4,5}$ = 2.5 Hz. **8-*SRS***. ^{1}H NMR δ 0.99 (d, Me-6, 3), 1.04 (s, Me, 9), 3.19 (m, H-3, 1), 3.81 (s, OMe, 3), 3.88 (m, H-5, 1), 4.07 (m, H-4, 1), 6.8-7.3 (m, 4 H, arom), 7.2-7.7 (m, 15 H, arom); $J_{3,4}$ = 4.0, $J_{4,5}$ = 4.0 Hz. **2-[(4-Methoxyphenyl)imino]-3-*tert*-butyl-4-[(*S*)-1-[(*tert*-butyldimethylsilyl)-oxy]benzyl]oxetanes (9-*SSR*, 9-*SRS*).** The aldehyde **1c** (0.89 g, 3.56 mmol) and the ketene imine **2c** (0.71 g, 3.50 mmol) were reacted in the presence of Yt(fod)$_3$ (0.084 g, 0.08 mmol) at 25 °C for three days. Flash chromatography (*n*-hexane/ethyl acetate, 7:1) gave in the order: **9-*SSR*** (0.24 g, 0.53 mmol, 15.0 %) and **9-*SRS*** (1.19 g, 2.62 mmol, 75.0 %). **9-*SSR***. ^{1}H NMR δ - 0.0 (s, Me, 3), - 0.02 (s, Me, 3), 0.75 (s, Me, 9), 0.89 (s, Me, 9), 3.48 (m, H-3, 1), 3.79 (s, OMe, 3), 4.44 (m, H-4, 1), 5.09 (m, H-5, 1), 6.8-7.3 (m, 4 H, arom), 7.3-7.5 (m, 5 H, arom); $J_{3,4}$ = 3.8, $J_{4,5}$ = 2.7 Hz. *Anal.* Calcd for $C_{27}H_{39}NO_3Si$: C, 71.48; H, 8.66; N, 3.09. Found: C, 71.39; H, 8.62; N, 3.13. **9-*SRS***. ^{1}H NMR δ - 0.07 (s, Me, 3), - 0.05 (s, Me, 3), 0.82 (s, Me, 9), 0.88 (s, Me, 9), 3.04 (m, H-3, 1), 3.79 (s, OMe, 3), 4.40 (m, H-4, 1), 4.80 (m, H-5, 1), 6.8-7.3 (m, 4 H, arom), 7.3-7.5 (m, 5 H, arom); $J_{3,4}$ = 4.1, $J_{4,5}$ = 6.3 Hz. *Anal.* Calcd for $C_{27}H_{39}NO_3Si$: C, 71.48; H, 8.66; N, 3.09. Found: C, 71.35; H, 8.69; N, 3.14. The two isomers showed identical mass and ir spectral data. Ms: m/z 453 (M^+), 203, 149; ir: ν 1742 (O-C=N) cm^{-1}.

2-[(4-Methoxyphenyl)imino]-3-methyl-4-[(*S*)-1-[(2-methoxyethoxymethyl)-oxy]ethyl]oxetane (10-*SSR*, 10-*SSS*, 10-*SRS*, and 10-*SRR*). The aldehyde **1d** (0.32 g, 1.98 mmol) and the ketene imine **2a** (0.332 g, 2.06 mmol) were reacted in the presence of Yt(fod)$_3$ (0.044 g, 0.042 mmol) at 25 °C for 24 hrs. HPLC analysis was performed on a 250 X 4.6 mm column Spherisorb 5 MOS C_8. Flash chromatography (*n*-pentane/Et_3N, 4:1) gave 0.549 g (1.70 mmol, 85 %) of oxetanes. **10-*SSR***: this compound was obtained as the major product in a **10-*SSR*:10-*SSS*** = 8.0:1.0 mixture. ^{1}H NMR δ 1.20 (d, Me-6, 3), 1.46 (d, Me-7, 3), 3.36 (s, OMe, 3), 3.45-3.6 (m, CH_2, 2), 3.65-3.75 (m, $CH_2$and H-3, 3), 3.76 (s, OMe, 3), 4.05-4.14 (m, H-5, 1),

4.26 (t, H-4, 1), 4.75-4.85 (m, CH_2, 2), 6.8-7.2 (m, 4 H, arom); $J_{H,Me-7}$ = 7.5, $J_{H,Me-6}$ = 6.7, $J_{3,4}$ = 4.3, $J_{4,5}$ = 4.3 Hz. *Anal.* Calcd for $C_{17}H_{25}NO_5$: C, 63.14; H, 7.79; N, 4.33. Found: C, 63.31; H, 7.84; N, 4.30. **10-*SSS***: this compound was obtained as the major product in a **10-*SSS*:10-*SSR*** = 4.0:1.0 mixture. ^{1}H NMR δ 1.31 (d, Me-6, 3), 1.46 (d, Me-7, 3), 3.38 (s, OMe, 3), 3.4-3.6 (m, CH_2, 2), 3.65-3.75 (m, CH_2, 2), 3.78 (s, OMe, 3), 3.80-4.0 (m, H-3, 1), 4.05-4.14 (m, H-5, 1), 4.53 (t, H-4, 1), 4.75-4.85 (m, CH_2, 2), 6.8-7.2 (m, 4 H, arom); $J_{H,Me-7}$ = 7.5, $J_{H,Me-6}$ = 6.7, $J_{3,4}$ = 6.8, $J_{4,5}$ = 6.5 Hz. *Anal.* Calcd for $C_{17}H_{25}NO_5$: C, 63.14; H, 7.79; N, 4.33. Found: C, 63.01; H, 7.75; N, 4.31. **10-*SRS***: this compound was obtained as the major product in a **10-*SRS*:10-*SRR*** = 4.0:1.0 mixture. ^{1}H NMR δ 1.22 (d, Me-6, 3), 1.45 (d, Me-7, 3), 3.36 (s, OMe, 3), 3.4-3.55 (m, CH_2, and H-3, 3), 3.65-3.75 (m, CH_2, 2), 3.78 (s, OMe, 3), 4.0-4.1 (m, H-5, 1), 4.26 (dd, H-4, 1), 4.78-4.82 (m, CH_2, 2), 6.8-7.2 (m, 4 H, arom); $J_{H,Me-7}$ = 7.5, $J_{H,Me-6}$ = 6.5, $J_{3,4}$ = 4.6, $J_{4,5}$ = 7.1 Hz. *Anal.* Calcd for $C_{17}H_{25}NO_5$: C, 63.14; H, 7.79; N, 4.33. Found: C, 62.93; H, 7.82; N, 4.36. **10-*SRR***: this compound was obtained as the major product in a **10-*SRR*:10-*SRS*** = 3.5:1.0 mixture. ^{1}H NMR δ 1.20 (d, Me-6, 3), 1.38 (d, Me-7, 3), 3.34 (s, OMe, 3), 3.4-3.55 (m, CH_2, 2), 3.65-3.75 (m, CH_2, 2), 3.78 (s, OMe, 3), 3.75-3.85 (m, H-3, 1), 4.05-4.15 (m, H-5, 1), 4.56 (dd, H-4, 1), 4.78-4.82 (m, CH_2, 2), 6.8-7.2 (m, 4 H, arom); $J_{H,Me-7}$ = 7.5, $J_{H,Me-6}$ = 6.5, $J_{3,4}$ = 6.9, $J_{4,5}$ = 9.5 Hz. *Anal.* Calcd for $C_{17}H_{25}NO_5$: C, 63.14; H, 7.79; N, 4.33. Found: C, 63.27; H, 7.82; N, 4.37. All the diastereoisomers showed identical mass and ir spectral data. Ms: m/z 323 (M^+), 161, 149; ir: ν 1730-1735 (O-C=N) cm^{-1}

2-[(4-Methoxyphenyl)imino]-3-*tert*-butyl-4-[(*S*)-1-[(2-methoxyethoxymethyl)-oxy]ethyl]oxetane (11-*SSR* and 11-*SSS*). The aldehyde **1d** (0.32 g, 1.98 mmol) and the ketene imine **2c** (0.40 g, 2.00 mmol) were reacted in the presence of Yt(fod)$_3$ (0.10 g, 0.095 mmol) at 25 °C for ten days. The reaction was stopped at 45 % conversion of the reagents and the product distribution (Table II) was directly evaluated on the crude by ^{1}H NMR. Flash chromatography (*n*-hexane/ethyl acetate, 1:2) yielded in the order: **11-*SSR*** (0.153 g, 0.42 mmol, 21.0 %) and **11-*SSS*** (0.127 g, 0.35 mmol, 17.5 %). **11-*SSR***. ^{1}H NMR δ 1.10 (s, Me, 9), 1.19 (d, Me-6, 3), 3.34 (s, 3H, OMe), 3.3-3.5 (m, CH_2 and H-3, 3), 3.6-3.7 (m, CH_2, 2), 3.78 (s, OMe, 3), 4.09 (m, H-5, 1), 4.36 (m, H-4, 1), 4.3-4.4 (m, CH_2, 2), 6.7-7.2 (m, 4 H, arom); $J_{H,Me-6}$ = 6.8, $J_{3,4}$ = 3.8, $J_{4,5}$ = 3.2 Hz. *Anal.* Calcd for $C_{20}H_{31}NO_5$: C, 65.73; H, 8.55; N, 3.83. Found: C, 65.80; H, 8.60; N, 3.88. **11-*SSS***. ^{1}H NMR δ 1.10 (s, Me, 9), 1.22 (d, Me-6, 3), 3.14 (d, H-3,1), 3.39 (s, 3H, OMe), 3.4-3.5 (m, CH_2, 2), 3.7-3.8 (m, CH_2, 2), 3.77 (s, OMe, 3), 3.90 (m, H-5, 1), 4.37 (m, H-4, 1), 4.75-4.85 (m, CH_2, 2), 6.7-7.2 (m, 4 H, arom); $J_{H,Me-6}$ = 6.5, $J_{3,4}$ = 6.5, $J_{4,5}$ = 2.2 Hz. *Anal.* Calcd for $C_{20}H_{31}NO_5$: C, 65.73; H, 8.55; N, 3.83. Found: C, 65.61; H, 8.58; N, 3.79. All the diastereoisomers showed identical mass and ir spectral data. Ms: m/z 365, (M^+), 162, 149; ir: ν 1735-1740 (O-C=N) cm^{-1}.

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