intensity) 282 (8), 85 (100). Anal. Calcd for $C_{14}H_{20}NO_3SBr$: C, 46.41; H, 5.56; N, 3.87; O, 13.25. Found: C, 46.51; H, 5.56; N, 3.87; O, 13.35.

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**Supplementary Material Available:** Synthetic procedure for 3-hydroxy-4-pentenylamines **1a-m**, 4-hydroxy-5-hexenylamines, and their N-protected derivatives **2a-m**, **9a-m**, and **14a,b** and their spectral data (IR, $^1H$, $^{13}C$ NMR) (9 pages). Ordering information is given on any current masthead page.

# 2-Iminooxetane Chemistry. 2. General Synthesis from Ketene Imine-Aldehyde Cycloadditions[1]

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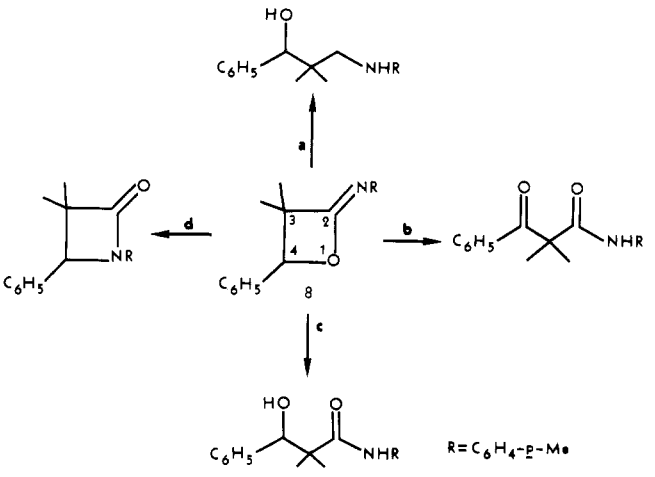
2-Iminooxetanes, versatile synthons of highly functionalized γ-amino alcohols, β-keto amides, β-hydroxy amides, and β-lactams, are synthesized by regiospecific 2 + 2 cycloadditions of aldehydes to ketene imines in the presence of lanthanide shift reagents ($Yt^{3+}$ or $Eu^{3+}$). In a few cases, the nature of the peripheral substitution on the reagents influences the selectivity of the cycloaddition, causing the formation of other isomeric products.

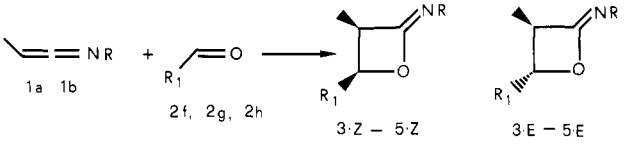
We have recently described the cycloaddition of dimethylketene *N*-*p*-tolylimine (**1d**) with benzaldehyde (**2f**),[1] in the presence of 1 mol % of lanthanide shift reagents, such as $Yt(fod)_3$ or $Eu(fod)_3$,[2] yielding the oxetane **8** as sole regioisomer. An exploratory investigation (Scheme I) showed that **8** is the intermediate key that can be transformed into the corresponding γ-amino alcohol (path a), β-keto amide (path b), and β-hydroxy amide (path c), depending on the medium. In addition, the catalyzed ring isomerization (path d) produced the regioisomeric β-lactam.

The possibility of developing a new strategy for syntheses of β-lactams having diverse functionality, via path d directly, or via β-keto amides and β-hydroxy amides as intermediates, prompted us to test the generality of our procedure for the synthesis of 2-iminooxetanes. So far we have studied the role of peripheral substituents in the reagents on the stereoselectivity of the heterocycloaddition among a selected number of ketene imines and aldehydes. This preliminary investigation is essential because alternative sources are not available for the production of 2-iminooxetanes. In fact, the literature reports only a few examples of photochemically induced cycloadditions of ketene imines and aldehydes or ketones.[3] However, these reactions produced only moderate amounts of mixtures of the regioisomeric 2- and 3-iminooxetanes, the latter being more often the major isomers. The thermally induced cycloaddition of diphenylketene *N*-*p*-tolylimine with the electron-deficient bis(trifluoromethyl) ketone to give the corresponding 2-iminooxetane has also already been described.[4]

**Scheme I**




**Scheme II**




R: a = $C_6H_4$-p-OMe; b = $C_6H_4$-p-Me

$R_1$: f = $C_6H_5$; g = n-Pr; h = i-Pr

| | R | $R_1$ |
|---|---|---|
| 3: | a | $C_6H_5$ |
| 4: | a | n-Pr |
| 5: | b | i-Pr |

(1) Barbaro, G.; Battaglia, A.; Giorgianni, P. *Tetrahedron Lett.* **1987**, *28*, 2995.

(2) The IUPAC and, in parentheses, the commercial names of the lanthanides used were as follows: tris(6,6,7,7,8,8,8-heptafluoro-2,2-dimethyl-3,5-octanedionato)ytterbium or -europium [$Yt(fod)_3$ or $Eu(fod)_3$]; tris(2,2,6,6-tetramethyl-3,5-heptanedionato)ytterbium [$Yt(thd)_3$]; tris-[3-[(heptafluoropropyl)hydroxymethylene]-(+)-camphorato]ytterbium or -europium [$Yt(hfc)_3$ or $Eu(hfc)_3$]; tris[3-[(trifluoromethyl)hydroxymethylene]-(+)-camphorato]europium [$Eu(tfc)_3$].

(3) (a) Singer, L. A.; Bartlett, P. D. *Tetrahedron Lett.* **1964**, 1887. (b) Singer, L. A.; Davis, G. A.; Muralidharan, V. P. *J. Am. Chem. Soc.* **1969**, *91*, 897 and references therein.

(4) Weidler-Kubanek, A.; Litt, M. *J. Org. Chem.* **1968**, *33*, 1844.

0022-3263/88/1953-5501$01.50/0 

Table I. Relevant $^1H$ and $^{13}C$ NMR Spectral Data ($CDCl_3$) of *E* and *Z* $C_3$-Monosubstituted 2-Iminooxetanes

| | $HC_3Me$ | | $HC_3Me$ | | $HC_4O$ (*J*, Hz) | | $C_2$ | | $C_3$ | | $C_4$ | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| no. | *E* | *Z* | *E* | *Z* | *E* | *Z* | *E* | *Z* | *E* | *Z* | *E* | *Z* |
| **3** | 1.56 | 0.95 | 3.4–3.8 | 3.8–4.2 | 5.22 (4.5) | 5.72 (7.0) | 160.2 | 161.0 | 50.5 | 46.0 | 84.2 | 80.2 |
| **4** | 1.43 | 1.30 | 3.1–3.4 | 3.6–3.9 | 4.35 (4.5) | 4.75 (7.0) | 161.2 | 162.1 | 46.7 | 43.2 | 84.6 | 80.3 |
| **5** | 1.44 | 1.37 | 3.1–3.6 | 3.6–4.0 | 3.96 (4.5) | 4.25 (6.5) | 161.6 | 162.4 | 44.6 | 42.7 | 89.1 | 85.0 |
| **6** | 1.30 | 1.20 | 2.9–3.3 | 3.4–3.9 | 4.30 (4.5) | 4.70 (7.0) | 162.0 | 163.0 | 45.7 | 42.2 | 83.2 | 79.1 |
| **15** | 1.47 | 1.27 | 3.4–3.7 | 3.7–4.0 | 4.75 (4.5) | – | 159.3 | 160.2 | 48.1 | 45.0 | 83.7 | 79.9 |
| **17** | 1.43 | 1.28 | 3.3–3.6 | 3.7–4.0 | 4.70 (4.5) | 5.15 (7.0) | 160.6 | 161.6 | 48.0 | 44.8 | 84.1 | 80.3 |
| **18** | 1.47 | 1.47 | 3.5–3.9 | 3.6–4.0 | 4.80 (4.5) | 5.28 (6.8) | 159.3 | 160.2 | 50.2 | 45.2 | 71.5 | 69.7 |
| **19** | 1.70 | 1.20 | 3.7–4.0 | 4.1–4.5 | 5.67 (4.2) | 6.10 (7.0) | 159.1 | 159.8 | 50.9 | 46.4 | 82.1 | 78.4 |
| **20** | 1.60 | 1.00 | 3.6–4.0 | 4.0–4.4 | 5.40 (4.5) | 5.87 (7.2) | 159.8 | 160.3 | 49.2 | 46.2 | 83.6 | 79.8 |
| **21** | 1.50 | 1.22 | 3.5–3.7 | 3.8–4.2 | 5.14 (4.5) | 5.62 (7.2) | – | – | 48.6 | 46.7 | 76.2 | 74.1 |
| **22** | 1.54 | 1.36 | 3.7–4.0 | 3.9–4.3 | 4.70 (4.7) | 5.16 (7.5) | 158.2 | 158.7 | 47.4 | 45.5 | 77.3 | 75.1 |

Table II

| ketene imine (mmol) | aldehyde (mmol) | mL of $CCl_4$ (°C, h) | cat.[a] | 2-iminooxetane | *E*:*Z*[b] | *E*[c] | *Z*[c] | overall yield[c] |
|---|---|---|---|---|---|---|---|---|
| **1a** (1.86) | **2f** (2.00) | 10 (20, 24) | a | **3** | 1.00 | 22 | 43 | 65 |
| **1a** (4.20) | **2g** (4.30) | 10 (20, 24) | b | **4** | 1.22 | 50 | 33 | 83 |
| **1b** (1.86) | **2h** (2.00) | 10 (25, 36) | b | **5** | 1.30 | 36 | 28 | 64 |
| **1c** (3.45) | **2g** (3.60) | 10 (20, 48) | a | **6** | 1.00 | 20 | 7 | 27 |
| **1d** (5.20) | **2f** (8.99) | 20 (35, 36) | a | **8** | | | | 80 |
| **1d** (3.15) | **2h** (4.20) | 20 (45, 72) | c | **9** | | | | 72 |
| **1d** (5.00) | **2k** (2.78) | 15 (35, 48)[d] | a | **10** | | | | 71 |
| **1e** (3.80) | **2i** (4.70) | 15 (40, 48) | b | **11** | 0.22 | 16 | 72 | 86 |
| **1d** (4.70) | **2j** (5.40) | 10 (40, 72) | c | **12** | | | | 85 |
| **1a** (3.79) | **2j** (4.00) | 6 (20, 24) | a | **15** | 2.00 | – | – | – |
| **1a** (8.20) | **2i** (8.55) | 20 (25, 30) | c | **17** | 0.82 | – | – | – |
| **1a** (3.48) | **2l** (3.67) | 15 (20, 48) | a | **18** | 1.00 | 36 | 21 | 57 |
| **1a** (3.73) | **2m** (4.00) | 10 (20, 30) | a | **19** | 1.18 | 47 | 40 | 87 |
| **1a** (2.23) | **2n** (2.25) | 10 (20, 15) | a | **20** | 0.83 | 30 | 28 | 58 |
| **1a** (1.13) | **2o** (1.15) | 2 (25, 5) | b | **21** | 0.82 | – | – | – |
| **1b** (3.45) | **2p** (3.63) | 10 (20, 24) | – | **22** | 1.22 | 40 | 32 | 72 |

[a] Catalyst (1.5 mmol % with respect to **1a–e**): a = $Yt(fod)_3$; b = $Yt(hfc)_3$; c = $Eu(hfc)_3$. [b] Measured on the crude reaction mixture. [c] Isolated yield of chemically pure compounds after flash chromatography. [d] In $CH_2Cl_2$.

## Results and Discussion

**A. Synthesis of $C_3$-Methyl-Monosubstituted 2-Iminooxetanes from Ketene Imines 1a,b and Aliphatic and Aromatic Aldehydes 2f–h.** Attempts to react ketene imines **1a,b** and aldehydes **2f–h** under thermal conditions failed, and catalysis by Lewis acids ($AlCl_3$, $Et_2AlCl$, $BF_3$, $TiCl_4$) was inefficient due to very fast oligomerization processes of the ketene imines.[5] However, the presence of traces (1.5 mol %) of lanthanide shift reagents catalyzed the cycloaddition of benzaldehyde (**2f**) and of *n*-butyraldehyde (**2g**) to ketene imine **1a** at 20 °C ($CCl_4$), the reactions being complete within 30 h. The same conditions were used in the reaction of the sterically hindered isobutyraldehyde (**2h**) with ketene imine **1b**. A $^1H$ NMR analysis revealed, in each experiment, the presence of the isomeric cis (*Z*) and trans (*E*) pair of 2-iminooxetanes (**3**-*Z*/**3**-*E*, **4**-*Z*/**4**-*E*, and **5**-*Z*/**5**-*E* respectively) as the only regioisomers (Scheme II).

Structures were assigned on the basis of their IR spectra, which showed an intense absorption in the 1745–1760-$cm^{-1}$ region (lit.[3] 1735–1750), 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, viz., the ketene imine and aldehyde, along one axis, and the isocyanate and the ethylene derivative, along the other one. The cis- and trans-configurational assignment was based on the upfield effect, exerted on the methyl at $C_3$ of the cis isomers by the substituent at $C_4$ (Table I).[6] Consequently, the hydrogens at $C_3$ and at $C_4$ of cis isomers resonate at a lower field. Finally, larger coupling-constant values for the vicinal hydrogens at $C_3$ and at $C_4$ are found for the cis isomers.[6] The $^{13}C$ NMR spectra (Table 1) showed selected resonances ranging from 45 to 52 ppm attributed to $C_3$, from 78 to 89 for $C_4$, and from 158 to 165 for $C_2$. As a general rule, the $C_2$ and $C_3$ of the trans isomers resonate at lower field with respect to the cis ones. An opposite trend has been found for $C_4$. Attempts to separate the two isomers by column chromatography ($SiO_2$, *n*-hexane–ethyl acetate, 2:1) were frustrated by the conversion of the 2-iminooxetane into the corresponding β-hydroxy amide, by hydrolysis.[7] This has also been reported by Singer.[3] However, in all cases, hydrolysis could be reduced by using flash chromatography over silica preheated in an oven and by eluting with carefully dried solvents. With these precautions, the isomers were isolated in most cases (Table II), but they were contaminated by the corresponding erythro and threo β-hydroxy amides. The last two products could be quantitatively removed by filtration, after the oily iminooxetane was dissolved in *n*-pentane and left at −20 °C for a few hours. The internal cis:trans isomer ratio observed after chromatographic workup is substantially different from the initial ratio evaluated by $^1H$ NMR

(5) Barbaro, G.; Battaglia, A.; Dondoni, A.; Giorgianni, P. *J. Org. Chem.* **1984**, *49*, 2200.

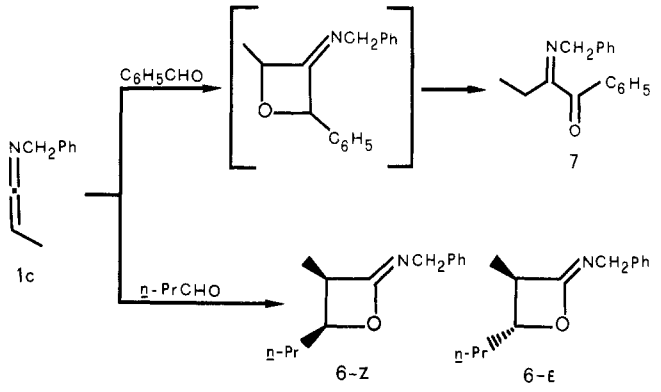
(6) Jackmann, L. M.; Sternhell, S. In *Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry*; Barton, D. H. R., Doering, W., Eds.; International Series of Monographs in Organic Chemistry; Pergamon: Oxford, 1969; Vol. 5, Chapter 3–8, p 234. Larger coupling-constant values of the vicinal hydrogens at $C_3$ and $C_4$ in the cis isomers are also observed in related small-ring heterocycles, as oxetanes and azetidines. See, for example: (a) Aben, R. W. M.; Smit, R.; Schreen, J. W. *J. Org. Chem.* **1987**, *52*, 365. (b) Shreen, H. W.; Aben, R. W. M.; Ooms, P. H. J.; Nivard, R. J. F. *J. Org. Chem.* **1977**, *42*, 3128.

(7) A detailed study on the hydratative ring opening of the 2-iminooxetanes will be reported in a separate paper.

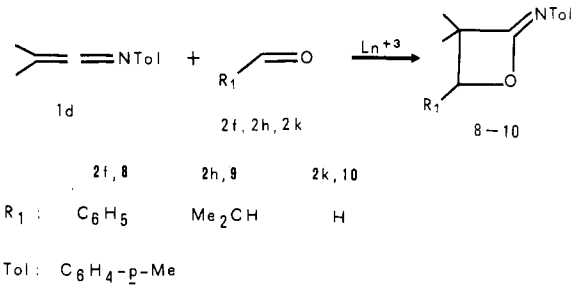
**Table III. Dependence of the Cis/Trans Isomer Distribution on the Nature of the Lanthanide Catalyst**

| no. | $Yt(thd)_3$ | $Yt(fod)_3$ | $Eu(fod)_3$ | $Yt(hfc)_3$ | $Eu(hfc)_3$ | $Eu(tfc)_3$ |
|---|---|---|---|---|---|---|
| 3 | 1.85 | 1.00 | 0.89 | 1.20 | 1.00 | 1.00 |
| 4 | 1.60 | 0.86 | 0.92 | 0.82 | 0.78 | 1.00 |
| 5 | 2.04 | 0.78 | 1.08 | 0.77 | 0.67 | 0.72 |
| 18 | 1.62 | 1.00 | | 0.78 | | |
| 19 | 1.86 | 0.85 | | 1.00 | | |

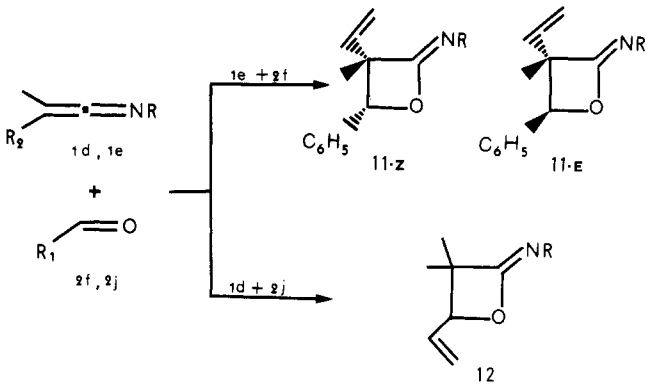
**Scheme III**




**Scheme IV**




**Scheme V**




of the crude reaction mixture. However, a careful comparison of the spectra of pure cis and trans isomers with the spectrum of the crude material revealed that the formation of the 2-iminooxetanes can be considered quantitative. The 2-iminooxetanes were obtained as bright yellow oils after purification. The products become darker on standing for a few days or when heated under vacuum (0.1 Torr) at 60–100 °C for a few hours. Even so, no significant alteration of the isomer distribution was observed.

Table III reports the isomer distribution of a selected number of 2-iminooxetanes depending on the type of lanthanide catalyst. This distribution is not greatly affected by the nature of the aldehyde, and the less hindered isomer, trans, is only slightly favored. It is worth noting that $Yt(thd)_3$, whose catalytic efficiency is substantially reduced with respect to the other fluorine activated lanthanides, seems to favor the cis isomer, even in the sterically disfavored oxetane **5**.

An exception to the reactivity pattern described is provided by methylketene *N*-benzylimine (**1c**), which showed variable regioselectivity, depending on the nature of the aldehyde (Scheme III).

Reaction with the aliphatic *n*-butyraldehyde (**2g**) gave the two 2-iminooxetanes **6-*Z*** and **6-*E*** quantitatively. On the other hand, reaction with the aromatic benzaldehyde (**2f**) gave the butyrophenone **7**, and only traces of the expected 2-iminooxetane could be detected in the crude reaction mixture (weak IR absorption at 1750 $cm^{-1}$). Relevant spectroscopic data, supporting the structure of **7**, are given in the Experimental Section. Compound **7** arises from a Michael-type addition of the central carbon of the ketene imine to that of the carbonyl of **2f**, followed by 1,3 migration of the carbonylic hydrogen to the terminal carbon of **1c**. The presence of a 3-iminooxetane intermediate could not be proved. Heterocycles of this kind appear to be stable even under chromatographic workup and should have been detected, if present, in the crude product.

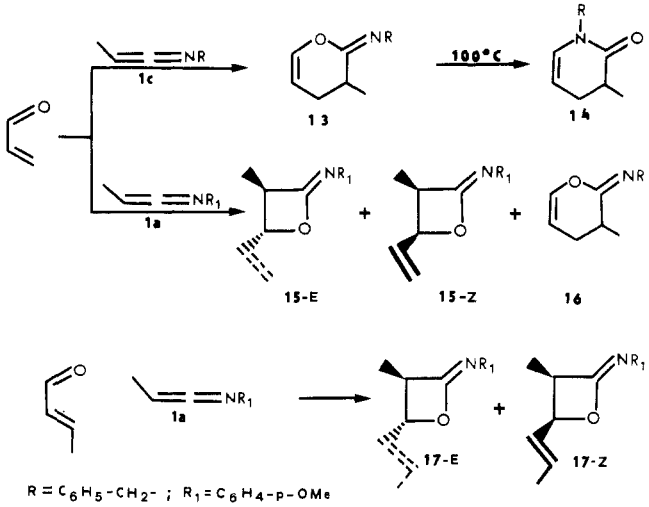
**B. Synthesis of Sterically Hindered $C_3$,$C_3$-Dimethyl-Substituted 2-Iminooxetanes with Dimethylketene *N*-*p*-Tolylimine (1d) and Aldehydes 2f, 2h, and 2k.** Disubstitution on the terminal carbon of the ketene imine **1d** is expected to inhibit the 1,2-cycloaddition across the C=C double bond of the heterocumulene, due to the formation of a highly hindered quaternary carbon center. Consequently, different sites of the molecule might be involved in the reaction. Nevertheless, the cyclocondensation of **1d** with benzaldehyde (**2f**), isobutyraldehyde (**2h**), and paraformaldehyde (**2k**) occurs smoothly at 40 °C with 1 mol % of catalyst (Scheme IV). The corresponding 2-iminooxetanes **8**, **9**, and **10** were the only regioisomers isolated in 70–90% yields directly from flash chromatography.

**C. 2-Iminooxetanes from C-Vinyl-Substituted Ketene Imine 1e or C-Vinyl-Substituted Aldehydes 2j and 2i.** The presence of vinyl substituents on the terminal carbon of the C=C=N unit can produce an alternative pericyclic pattern for involvement of the dienic fragment of the molecule, i.e., the C=C double bond of the heterocumulene and that of the vinyl substituent.[9] Such 1,4-hetero cycloaddition may give, in principle, less

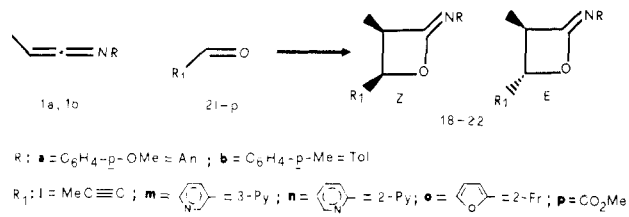
(8) For example, cycloadditions of thiobenzophenone to ketene imines take place at different sites of the cumulene. C-Monosubstituted ketene imines undergo 1,2-cycloaddition by the C=S bond of the thione across the cumulene C=C bond to give four-membered 1:1 adducts, viz., 2-iminothietanes. On the other hand, C,C-disubstituted ketene imines whose nitrogen is flanked by a phenyl undergo 1,4-cycloaddition by the C=S bond of the thione across the formal heterodiene system formed by the C=N bond of the cumulene and one of the C=C bonds of the *N*-aryl group to yield as final products six-membered ring adducts, viz., 4*H*-3,1-benzothiazines. See: Battaglia, A.; Dondoni, A.; Giorgianni, P. *J. Org. Chem.* **1980**, *45*, 3766.

(9) (a) Barbaro, G.; Battaglia, A.; Giorgianni, P. *J. Org. Chem.* **1987**, *52*, 3289. (b) Ghosez, L.; De Perez, C. *Angew. Chem., Int. Ed. Engl.* **1971**, *10*, 184.

Scheme VI




Scheme VII




| | R | $R_1$ |
|---|---|---|
| 18 | An | MeC≡C |
| 19 | An | 3-Py |
| 20 | An | 2-Py |
| 21 | An | 2-Fr |
| 22 | Tol | $CO_2Me$ |

strained six-membered heterocycles. In addition, a competition between a hetero 1,2-cycloaddition involving the C=O group of a vinyl aldehyde or a 1,4-hetero Diels–Alder reaction involving the C=CC=O fragment of the same molecule has also been observed.[10] We have exploited these possibilities with vinylmethylketene *N*-*p*-tolylimine (**1e**), acrylaldehyde (**2j**), and crotonaldehyde (**2i**). Ketene imine **1e** cycloadds regiospecifically to benzaldehyde (**2f**) and forms quantitatively the *trans*- and *cis*-2-iminooxetanes **11**-*E* and **11**-*Z*, in a 4.4:1 ratio (Scheme V).

Assignment of stereoconfiguration was based on the assumption that the methyl group at $C_3$ of the minor isomer *E* is at a higher field than that of the major isomer *Z*, due to the upfield effect exerted by its syn vicinal phenyl substituent. Formation of 2-iminooxetane **12** was also observed in the reaction of **2d** with acrylaldehyde (**2j**). C-Methyl-substituted ketene imines **1a** and **1c** behave differently from the C,C-dimethyl-substituted ketene imine **1d**. In fact, the reaction of methylketene *N*-benzylimine (**1c**) with **2j** leads under different catalytic conditions to 2-(benzylimino)-3,4-dihydro-2*H*-pyran derivative **13** exlusively (see Experimental Section), the reagents being totally inert in the absence of catalysts. This cycloadduct was obtained by 1,4-cycloaddition of the C=C bond of **1c** to the C=CC=O unit of **2j** (Scheme VI). Compound **13** was sufficiently pure to be spectroscopically characterized as the crude product (see Experimental Section), but could not be recovered from a chromatographic column (silica, *n*-hexane–ethyl acetate, 2:1), due to its partial polymerization and formation of many other products. However, pyrolysis of **13** (100 °C, 2 h; see Experimental Section) produced the regioisomeric *N*-benzyl-3-methyl-1,2,3,4-tetrahydro-2-oxopyridine (**14**) (Scheme VI), thus providing a further support to the supposed structure for compound **13**. On the other hand, the reaction of **1a** with acrylaldehyde (**2j**) was not stereocontrolled. In fact, $^1H$ and $^{13}C$ NMR spectra of the crude reaction mixture showed a complex pattern, revealing the presence of some resonances which were ascribed to the presence of cis and trans diasteroisomeric 2-iminooxetanes **15**-*E* and **15**-*Z*. Other signals were assigned to a 2-iminopyran derivative **16**. Attempts to isolate **15**-*E* and **15**-*Z*, as well as compound **16**, by column chromatography were frustrated by the formation of some amounts of the corresponding β-hydroxy amides and other unidentified products. For these reasons, the isomer distribution could not be estimated. In contrast, high regioselectivity was found in the reaction of **1a** with *trans*-2-butenal (**2i**), which gave the cis and trans isomeric 2-iminooxetanes **17**-*E* and **17**-*Z* exclusively. Attempts to separate them by column chromatography in anhydrous conditions afforded mostly polymeric material with some amounts of products of hydrolysis, which however could not be isolated. Better results were obtained when the hydrolysis was performed with a water-saturated mixture of *n*-hexane–ethyl acetate (1:1) on a silica column. Under these conditions, a mixture of isomeric erythro and threo β-hydroxy amides (13%) and of δ-hydroxy amides (30%) was isolated.[7]

**D. Reaction of Highly Functionalized Aldehydes.** In order to control how general and useful this approach may be for the syntheses of 2-iminooxetanes, we tested some highly functionalized aldehydes: namely, tetrolaldehyde (**2l**), 3- and 2-pyridinecarbaldehyde (**2m** and **2n**), and 2-furancarbaldehyde (**2o**) with **1a** and methyl glyoxylate (**2p**) in the reaction with **1b**. These aldehydes reacted in a few hours at room temperature with 1 mol % of lanthanide catalyst, leading to the corresponding 2-iminooxetanes (Table II, Scheme VII). The possibility of reaction of dimethylformamide with **1a** was also tested, but without success.

These reactions deserve a few significant comments. The presence of a carbalkoxymethyl substituent renders the aldehyde **2p** sufficiently electrophilic for the reaction to occur even in the absence of catalyst: however, the lanthanides increase the rate (see Experimental Section). Hence, the electrophilicity of the aldehyde plays a pivotal role in reactivity, as inferred from the results obtained with **2p** and bis(trifluoromethyl) ketone[4] when compared with *N*-dimethylformamide. Secondly, compounds **21**-*E* and **21**-*Z*, from 2-furancarbaldehyde (**2o**) and ketene imine **1a**, were thermally less stable than all the other 2-iminooxetanes. In fact, $^1H$ NMR analysis, performed at intervals during the reaction course, showed a relatively fast conversion of these two cycloadducts into the corresponding β-lactams (see Scheme I and ref 1), so that **21**-*E* and **21**-*Z* could be only partially characterized as transient species by spectroscopical means. After 40 h, **21**-*E* and **21**-*Z* had totally disappeared. Chromatography allowed the isolation of the corresponding β-lactams in 60% yields.[11]

## Conclusions

An exhaustive account of the stereochemical versatility of the catalyzed ketene imine–aldehyde cycloadditions is

(10) Danishefsky, S. J.; Larson, E.; Askin, D.; Kato, N. *J. Am. Chem. Soc.* **1985**, *107*, 1246 and references therein.

(11) A detailed account on the ring isomerization of compound **21**-*E* and **21**-*Z*, as well as of other 2-iminooxetanes to the corresponding β-lactams, will be reported in a separate paper.

beyond the scope of this paper. In spite of our efforts, many problems remain open: e.g., the anomalous change of regioselectivity in the reaction of methylketene *N*-benzylimine (**1c**) with benzaldehyde (**2f**) (Scheme III). A complete rationalization of the mechanism of this reaction might open a possible new entry to β-diketones, very important intermediates in organic synthesis.

Owing to the extremely low differences in activation energies involved, only very sophisticated theoretical approaches can be used to rationalize the stereochemical results.[12] For these reasons, the interplay between steric and electronic effects could not be completely understood. For example, while the reaction of the C-disubstituted ketene imine **2d** with acrylaldehyde (**2j**) is totally regioselective, the C-monosubstituted **1a** gave, unexpectedly, a mixture of regioisomers. These results can be qualitatively explained by a greater sensitivity of the 1,4-cycloaddition, compared with that of the 1,2-cycloaddition, to steric effects. Such behavior, which appears to be in conflict with expectations, seems further confirmed by the quantitative formation of *cis*- and *trans*-2-iminooxetanes in the reaction of **1a** with *trans*-2-butenal (**2i**). Even so, the complete stereocontrol of the reaction of methylketene *N*-benzylimine (**1c**) with acrylaldehyde (**2j**), leading to the pyran **13**, remains still to be explained, the result suggesting that electronic effects may also closely compete with the steric ones. Nevertheless, our goal to verify the generality of this approach for syntheses of 2-iminooxetanes was successfully achieved. This provides a new source of intermediates for syntheses of β-lactams, via both β-keto amides and β-hydroxy amides, or via catalytic ring isomerization of the 2-iminooxetane ring. As for the last point, the result of 2-furancarbaldehyde is very interesting in view of promoting a facile ring isomerization to β-lactams of 2-iminooxetanes obtained from α-oxygenated aldehydes.

## Experimental Section

**General Methods.** $^1H$ NMR and $^{13}C$ NMR spectra were recorded on a 90-MHz Varian EM 390 and Varian CFT-80 spectrometers respectively, and chemical shifts, measured in $CDCl_3$, were given as δ values in parts per million from $Me_4Si$. IR spectra ($CCl_4$) were determined on a Perkin-Elmer 257 grating spectrometer, and the absorbance values are given in $cm^{-1}$. Low-resolution mass spectra were recorded at an ionizing voltage of 70 eV on a Varian MAT 112 S spectrometer. For MS, IR, and $^1H$ and $^{13}C$ NMR data of 2-iminooxetanes, with the exception of compounds **3-*E***, **3-*Z***, **15-*E***, and **15-*Z***, see the paragraph at the end of the paper regarding supplementary material. Flash chromatography used E. Merck silica gel 60 (230–400 mesh). All solvents were purified before use.[14]

**Starting Materials.** The aldehydes and the lanthanide shift reagents were commercially available from Aldrich. Ketene imines were prepared according to the literature. In particular, **1a** and **1c** were prepared for the first time (lit.[15]). Methylketene *N*-(*p*-methoxyphenyl)imine (**1a**): bp 77–79 °C (0.2 Torr); IR 2010; $^1H$ NMR 1.67 (d, 3 H, Me), 3.78 (s, 3 H, Me), 3.97 (q, 1 H, $J$ = 7.40 Hz), 6.8–7.3 (m, 4 H, arom). Methylketene *N*-benzylimine (**1c**): bp 74–76 °C (0.2 Torr); IR 2010; $^1H$ NMR 1.52 (d, 3 H, Me), 3.42 (m, 1 H, $J_{HCH_3}$ = 7.20 Hz, $J_{HCH_2}$ = 2.10 Hz), 4.42 (d, 2 H), 7.2–7.3 (br, 5 H, arom).

**General Procedure for the Synthesis of 2-Iminooxetanes.** The ketene imine and the aldehyde, dissolved in $CCl_4$, were introduced to a vial containing the catalyst (1.5 mol % with respect to ketene imine). After the vial was sealed, the reaction mixture was thermostated at the selected temperature for the time required. The cis/trans isomer distribution, when diastereomeric pairs of 2-iminooxetanes are formed, was evaluated from $^1H$ NMR analysis of the reaction mixture. A flash chromatography on $SiO_2$ preheated in an oven, with eluant ethyl acetate–*n*-hexane, 1:2 (unless otherwise indicated), yielded the 2-iminooxetanes, together with some of the corresponding β-hydroxy amides. The latter compounds were removed by filtration, after dissolving the oily 2-iminooxetanes in *n*-pentane. Reaction conditions, cis/trans isomer distribution, and yields of pure 2-iminooxetanes as obtained after chromatographic workup are given in Table I. The isomer distribuiton with the type of catalyst was done on a $^1H$ NMR scale. Equimolar (0.05 mmol, $CCl_4$) amounts of the ketene imine and aldehyde were reacted in the presence of 1.5 mol % of the lanthanide. Results are collected in Table III. A typical procedure for 2-iminooxetanes **3-*Z*** and **3-*E***, together with their spectroscopic and analytical data, is described below.

***cis*- and *trans*-2-[(4-Methoxyphenyl)imino]-3-methyl-4-phenyloxetane (3-*Z* and 3-*E*).** Ketene imine **1a** (0.30 g, 1.86 mmol) was reacted with **2f** (0.21 g, 2.0 mmol) in the presence of $Yt(fod)_3$ (0.03 g, 0.028 mmol) in $CCl_4$ (10 mL) at 20 °C. After disappearance of **1a**, an $^1H$ NMR analysis of the crude reaction mixture revealed the presence of both **3-*E*** and **3-*Z*** in a 1:1 ratio. Chromatographic workup gave, in order, **3-*E*** (0.11 g, 0.41 mmol, 22%) and **3-*Z*** (0.22 g, 0.82 mmol, 43%). **3-*E***: oil; IR 1750; $^1H$ NMR 1.56 (d, 3 H, Me of $HC_3Me$, $J$ = 7.3 Hz), 3.4–3.8 (m, 1 H of $HC_3Me$), 3.7 (s, 3 H, Me), 5.2 (d, 1 H of HCO, $J$ = 4.5 Hz), 6.65–6.9 (m, 2 H, arom), 7.1–7.5 (m, 7 H, arom); $^{13}C$ NMR 14.5 (Me of $HC_3Me$), 50.5 (CH of $HC_3Me$), 55.4 (Me), 84.2 (CH of HCO), 114.0 (2 CH), 125.37 (2 CH), 125.7 (2 CH), 128.8 (2 CH), 129.0 (CH), 137.0 (C), 138.44 (C), 156.71 (C), 160.16 (C of OC=N); mass spectrum, $m/e$ 267 ($M^+$), 161, 149, 118, 106. Anal. Calcd for $C_{17}H_{17}NO_2$: C, 76.38; H, 6.41; N, 5.24. Found: C, 76.85; H, 6.12; N, 5.61. **3-*Z***: oil; IR 1750; $^1H$ NMR 0.95 (d, 3 H, Me of $HC_3Me$, $J$ = 7.0 Hz), 3.7 (s, 3 H, Me), 3.8–4.2 (m, 1 H of $HC_3Me$), 5.72 (d, 1 H of HCO, $J$ = 7.0 Hz), 6.6–7.0 (m, 2 H, arom), 7.1–7.4 (m, 7 H, arom); $^{13}C$ NMR 11.41 (Me of $HC_3Me$), 46.0 (CH of $HC_3Me$), 56.1 (Me), 80.2 (CH of HCO), 114.0 (2 CH), 125.32 (2 CH), 125.8 (2 CH), 128.4 (CH), 128.5 (2 CH), 135.8 (C), 137.0 (C), 156.7 (C), 161.0 (C of OC=N); mass spectrum, $m/e$ 267 ($M^+$), 161. Anal. Calcd for $C_{17}H_{17}NO_2$: C, 76.38; H, 6.41; N, 5.24. Found: C, 76.78; H, 6.17; N, 5.07.

***cis*- and *trans*-2-[(4-Methoxyphenyl)imino]-3-methyl-4-*n*-propyloxetane (4-*Z* and 4-*E*).** Anal. Calcd for $C_{14}H_{19}NO_2$: C, 72.07; H, 8.21; N, 6.00. Found for **4-*E***: C, 71.65; H, 8.67; N, 6.49. Found for **4-*Z***: C, 72.60; H, 8.55; N, 5.73.

**2-(*p*-Tolylimino)-3,3-dimethyl-4-isopropyloxetane (9).** Anal. Calcd for $C_{15}H_{21}NO$: C, 77.88; H, 9.15; N, 6.06. Found: C, 78.21; H, 9.23; N, 5.99.

**2-(Benzylimino)-1-butyrophenone (7).** Ketene imine **1c** (0.24 g, 1.65 mmol) was reacted with benzaldehyde (**2f**) (0.17 g, 1.65 mmol) in the presence of $Yt(fod)_3$ (0.020 g, 0.018 mmol), in $CCl_4$ (4 mL) at 20 °C, for 30 h. Chromatographic workup of the reaction mixture ($SiO_2$, $CH_2Cl_2$) afforded **7** (0.35 g, 1.39 mmol, 84%): oil; IR ($CCl_4$) 1715, 1710, 1670 $cm^{-1}$; $^1H$ NMR 1.04 (t, 3 H, Me, $J$ = 7.5 Hz), 2.4 (q, 2 H, $CH_2$), 4.97–5.04 (br, 2 H, $CH_2$ of $NCH_2$), 7.20–7.35 (br, 5 H, arom), 7.3–7.7 (m, 5 H, arom); $^{13}C$ NMR 9.7 (Me), 31.8 ($CH_2$), 49.4 ($CH_2$), 127.36 (CH), 127.76 (2 CH), 128.27 (2 CH), 128.5 (2 CH), 128.7 (2 CH), 132.3 (CH), 136.0 (C), 137.5 (C), 174.2 (C), 177.4 (C); mass spectrum, $m/e$ 251 ($M^+$), 174, 146. Identical results were obtained in the following five experiments: **1c** (0.0485 g, 0.33 mmol) was reacted with **2f** (0.04 g, 0.38 mmol) in $C_6H_6$ (0.5 mL) at 20 °C in the presence of 0.0045 mmol of $Yt(fod)_3$, $Eu(fod)_3$, $Yt(hfc)_3$, $Eu(hfc)_3$, and $Yt(thd)_3$. Anal. Calcd for $C_{17}H_{17}NO$: C, 81.24; H, 6.82; N, 5.57. Found: C, 81.92; H, 6.44; N, 5.29.

**2-(Benzylimino)-3-methyl-3,4-dihydro-2*H*-pyran (13).** Ketene imine **1c** (0.5 g, 3.44 mmol) was reacted with acrylaldehyde (**2j**) (0.2 g, 3.57 mmol) in the presence of $Yt(fod)_3$ (0.05 g, 0.047 mmol), in $CCl_4$ (10 mL) at 20 °C for 30 h. $^1H$ NMR analysis of the crude product revealed the presence of compound **13** as a unique regioisomer. Flash chromatography of the reaction mixture

(12) An account on this type of problem in ketene imine cycloadditions is given: ref 9a. For a more general account, see also: (a) Burnier, J. S.; Jorgensen, W. L. *J. Org. Chem.* **1984**, *49*, 3001. (b) Ghosez, L.; O'Donnell, M. J. In *Pericyclic Reactions and Orbital Symmetry*; Cambridge University: Cambridge, 1979.

(13) Bose, A. K.; Saha, D. P.; Manhas, M. S. *J. Org. Chem.* **1981**, *46*, 1229.

(14) Weissberger, A. *Technique of Organic Chemistry*; Interscience: New York, 1955; Vol. VII.

(15) (a) Battaglia, A.; Dondoni, A.; Giorgianni, P. *J. Org. Chem.* **1982**, *47*, 3998. (b) Bestmann, H. J.; Lienert, J.; Mott, L. *Justus Liebigs Ann. Chem.* **1968**, *24*, 718.

($SiO_2$, *n*-hexane–ethyl acetate, 2:1) afforded polymeric material and unidentified products. Spectroscopic analysis of the crude product gave the following:[16] IR 1700, 1665; $^1H$ NMR 1.25 (d, 3 H, Me of $HC_3Me$, $J$ = 6.9 Hz), 1.7–2.5 (m, 2 H of $CH_2$), 2.6–2.9 (m, 1 H of $HC_3Me$), 4.5–4.6 (br, 2 H of $NCH_2$), 4.9–5.2 (m, 1 H), 6.4–6.5 (m, 1 H of HCO, $J$ = 6.0 Hz), 7.0–7.5 (br, 5 H, arom); $^{13}C$ NMR 17.5 (Me, 27.2 ($CH_2$), 32.1 (CH of $HC_3Me$), 49.6 (CH of $NCH_2$), 102.7 (CH), 126.3 (CH), 127.6 (2 CH), 128.2 (2 CH), 140.7 (CH and C), 157.4 (C of OC=N); mass spectrum, $m/e$ 201 ($M^+$), 186. Compound **13** was also obtained as a unique cycloadduct when **1c** (0.05 g, 0.344 mmol) and **2j** (0.02 g, 0.357 mmol) were reacted in $CCl_4$ (0.5 mL), at 30 °C for 30 h, in the presence of 0.0045 mmol of $Yt(hfc)_3$, $Eu(fod)_3$, $Yt(fod)_3$, and $Yt(thd)_3$. The crude compound **13** (0.34 g, 1.6 mmol) was heated in a sealed ampule at 110 °C for 1 h. Chromatographic workup of the residue ($SiO_2$, $CH_2Cl_2$) yielded *N*-benzyl-3-methyl-1,2,3,4-tetrahydro-2-oxopyridine (**14**) (0.212 g, 65%): oil; $^1H$ NMR 1.26 (d, 3 H, Me of $HC_3Me$, $J$ = 6.9 Hz), 2.0–2.6 (m, 2 H, $CH_2$), 2.43–2.77 (m, 1 H of $HC_3Me$), 4.68 (s, 2 H of $NCH_2$), 5.0–5.3 (m, 1 H of CH=CH), 5.93–6.11 (m, 1 H of CH=C*H*N, $J$ = 7.8 Hz), 7.17–7.4 (br, 5 H, arom); $^{13}C$ NMR 15.95 (Me), 28.48 ($CH_2$), 35.58 (CH), 49.14 ($NCH_2$), 105.67 (CH), 127.4 (CH), 127.6 (2 CH), 128.6 (2 CH), 129.3 (CH), 137.5 (C), 172.54 (C); IR 1680; mass spectrum, $m/e$ 201 ($M^+$), 186, 158, 91. Anal. Calcd for $C_{13}H_{15}NO$: C, 77.58; H, 7.51; N, 6.96. Found: C, 77.06; H, 7.45; N, 7.02.

***cis*- and *trans*-2-[(4-Methoxyphenyl)imino]-3-methyl-4-vinyloxetane (15-*Z* and 15-*E*) and 2-[(4-Methoxyphenyl)imino]-3-methyl-3,4-dihydro-2*H*-pyran (16).** Ketene imine **1a** (0.61 g, 3.79 mmol) and acrylaldehyde (**2j**) (0.22 g, 4.0 mmol) were reacted in the presence of $Yt(fod)_3$ (0.05 g, 0.047 mmol) in $CCl_4$ (6 mL) at 20 °C for 24 h. $^1H$ NMR analysis of the crude reaction mixture revealed the presence of **15-*Z***, **15-*E***, and **16** in a ca. 1:2.0:1.5 ratio. In another experiment, with **1a** (0.48 g, 2.98 mmol) and **2j** (0.18 g, 3.2 mmol), in $CCl_4$ (5 mL), but in the presence of $Eu(hfc)_3$-*d* (0.058 g, 0.049 mmol), an isomer distribution of **15-*Z*–15-*E*–16** of 1:2:3.3 was found. Flash chromatography yielded the corresponding β-hydroxy amides and unidentified products. Spectroscopic analysis of the crude reaction mixture gave the following results:[16] $^1H$ NMR ($CCl_4$) 1.27 (d, 3 H, of $HC_3Me$ of **15-*Z***, $J$ = 6.5 Hz), 1.35 (d, 3 H, Me of $HC_3Me$ of **16**, $J$ = 6.5 Hz), 1.47 (d, 3 H, Me of $HC_3Me$ of **15-*E***, $J$ = 6.5 Hz), 1.75–2.6 (m, 2 H of $CH_2$ of **16**), 2.6–2.95 (m, 1 H of $HC_3Me$ of **16**), 3.35–3.7 (m, 1 H of $HC_3Me$ of **15-*E***), 3.73 (s, 3 H, Me), 3.75–4.0 (m, 1 H of $HC_3Me$ of **15-*Z***), 4.6–4.9 (m, 1 H of HCO of **15-*E***, $J_{HC_4CH}$ = 7.5 Hz), 4.87–5.23 (m, 1 H of C*H*$CH_2$ of **16**, and 1 H of HCO of **15-*Z***), 5.2–5.6 (m, 2 H of HC=C$H_2$ of **15-*E*** and **15-*Z***), 5.7–6.23 (m, 1 H of *H*C=$CH_2$ of **15-*E*** and **15-*Z***), 6.27–6.47 (m, 1 H of HCO of **16**, $J_{HCCH}$ = 6.0 Hz, $J_{HCH_2}$ = 1.5 Hz), 6.57–7.5 (m, H's, arom); $^{13}C$ NMR selected resonances were for **15-*E*** at 14.07 (Me), 48.1 (CH of $HC_3Me$), 83.74 (HCO), 159.3 (C of OC=N), for **15-*Z*** at 9.84 (Me), 44.98 (CH of $HC_3Me$), 79.85 (CH of HCO), 160.2 (C of OC=N), for **16** at 17.5 (Me), 27.06 ($CH_2$), 32.49 (CH of MeCH), 103.11 (CH), 140.87 (CH), 156.62 (C of OC=N); IR 1750 (OC=N of **15-*E*** and **15-*Z***), 1700 (OC=N of **16**), 1680; mass spectrum, $m/e$ 217 ($M^+$), 202, 161, 149, 68, 56.

***trans*- and *cis*-2-[(4-Methoxyphenyl)imino]-3-methyl-4-(3-pyridyl)oxetane (19-*E* and 19-*Z*).** Ketene imine **1a** (0.6 g, 3.73 mmol) was reacted with 3-pyridinecarbaldehyde (**2m**) (0.4 g, 4.0 mmol), in the presence of $Yt(fod)_3$ (0.061 g, 0.058 mmol), in $CCl_4$ (10 mL) at 20 °C for 24 h. After the total disappearance of **1a** (IR, 2010), a $^1H$ NMR analysis of the reaction mixture revealed a **19-*E*–19-*Z*** isomer ratio of 1.2:1. Attempts to separate the two isomers by flash chromatography ($SiO_2$, ethyl acetate) failed. Only a mixture of pure trans and cis isomers in a 1.2:1 ratio (0.88 g, 3.26 mmol, 87.4%) was recovered.

***trans*- and *cis*-2-[(4-Methoxyphenyl)imino]-3-methyl-4-(2-furyl)oxetane (21-*E* and 21-*Z*).** Ketene imine **1a** (0.183 g, 1.13 mmol) was reacted with 2-furancarbaldehyde (**2o**) (0.11 g, 1.15 mmol) in the presence of $Yt(hfc)_3$ (0.02 g, 0.016 mmol) in $CDCl_3$ (2 mL) at 20 °C. After 4 h, the $^1H$ NMR analysis of the crude reaction mixture revealed the presence of unreacted reagents (ca. 40% of their initial amount) and of **21-*E*** and **21-*Z*** (0.8:1). In addition, other resonances were barely detectable, which increased with time, while that of **21-*E*** and **21-*Z*** did not undergo any further increase. After the total disappearance of the reagents (24 h), the amount of **21-*E*** and **21-*Z*** decreased. After 72 h, **21-*E*** and **21-*Z*** disappeared, while the resonances, which could be attributed to the regioisomeric azetidin-2-ones, reached their maximum values. Evaporation of the solvent and chromatographic workup of the oily residue afforded a mixture of the corresponding regioisomeric *trans*- and *cis*-azetidin-2-ones in 60% yield.[11]

***trans*- and *cis*-2-(4-Tolylimino)-3-methyl-4-carbomethoxyoxetane (22-*E* and 22-*Z*).** In one experiment, ketene imine **1b** (0.01 M) and aldehyde **2n** (0.01 M) were reacted in $CCl_4$ (10 mL) in the absence of catalyst. The reaction was followed directly in an IR cell (1 mm) at room temperature by measuring the disappearance of the peak of **1c** at 2010 $cm^{-1}$. The reaction showed a half-lifetime of 45 min. The same reaction, but in the presence of $Yt(fod)_3$ (0.000 15 M), showed a half-lifetime of 7 min.

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**Registry No. 1a**, 113742-53-3; **1b**, 116749-11-2; **1c**, 116749-12-3; **1d**, 18779-86-7; **1e**, 42463-98-9; **2f**, 100-52-7; **2g**, 123-72-8; **2h**, 78-84-2; **2i**, 4170-30-3; **2j**, 107-02-8; **2k**, 30525-89-4; **2l**, 624-67-9; **2m**, 500-22-1; **2n**, 1121-60-4; **2o**, 98-01-1; **2p**, 96-35-5; **3-*E***, 116748-86-8; **3-*Z***, 116748-87-9; **4-*E***, 116748-88-0; **4-*Z***, 116748-89-1; **5-*E***, 116748-90-4; **5-*Z***, 116748-91-5; **6-*E***, 116748-92-6; **6-*Z***, 116748-93-7; **7**, 116749-08-7; **8**, 113200-68-3; **9**, 116749-07-6; **10**, 116749-15-6; **11-*E***, 116749-13-4; **11-*Z***, 116749-14-5; **12**, 116749-16-7; **13**, 116749-09-8; **14**, 116749-10-1; **15-*E***, 116748-94-8; **15-*Z***, 116748-95-9; **16**, 116749-09-8; **17-*E***, 116748-96-0; **18-*E***, 116748-97-1; **18-*Z***, 116748-98-2; **19-*E***, 116748-99-3; **19-Z**, 116749-00-9; **20-*E***, 116749-01-0; **20-*Z***, 116749-02-1; **21-*E***, 116749-03-2; **21-*Z***, 116749-04-3; **22-*E***, 116749-05-4; **22-*Z***, 116749-06-5; $Yt(FOD)_3$, 18323-96-1; $Yt(HFC)_3$, 80464-74-0; $Eu(FOD)_3$, 17631-68-4; $Yt(THD)_3$, 15492-52-1; $Eu(HFC)_3$, 34788-82-4; $Eu(TFC)_3$, 34830-11-0.

**Supplementary Material Available:** Tables of IR, mass, $^1H$ NMR, and $^{13}C$ NMR spectral data of 2-iminooxetanes (8 pages). Ordering information is given on any current masthead page.

(16) $^1H$ NMR and $^{13}C$ NMR spectra of the title compound were recorded directly on the crude reaction mixture, the purification by column chromatography being impossible. Consequently, any eventual slight shifts of the absorption values, due to the presence of 1.5 mol % of lanthanides, were unavoidable.

(17) Kelly, T. R.; Schmidt, T. E.; Haggerty, J. G. *Synthesis* **1972**, 544.