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Kinetic Resolution

Kinetic Resolution in the [2+2] Cycloaddition of Ketenes: An Experimental and Theoretical Study

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Abstract: The kinetic resolution of *Z* and *E* olefins by [2+2] cycloaddition with ketenes allows the isolation of pure *E* olefin, as well as the synthesis of pure *cis*-cyclobutanones, starting from *Z*/*E* mixtures. A computational rationale for this kinetic difference is reported. The obtained difference of energy of activation matches with the experimental results.

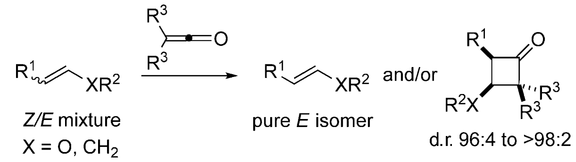

Figure 1. Kinetic resolution of olefins with ketenes.

The [2+2] cycloaddition of two olefins certainly represents the most useful method for the synthesis of cyclobutanes, which abound in nature as biologically active substances and are also key synthetic intermediates toward medicinal compounds.[1] In this area, the thermal [2+2] cycloaddition of ketenes with olefins offers a unique and very selective entry to a wide array of cyclobutanones.[2] This cycloaddition proceeds regio-, stereo-, and often chemioselectively as a result of the orbital-controlled transformation in a concerted asynchronous mechanism.[3] The stereochemistry of the alkene partner is therefore conserved in the cyclobutanone product: a *Z*-alkene leads to a *cis*-cyclobutanone and a *E*-alkene leads to a *trans*-cyclobutanone. Another very interesting feature of this reaction, overall far less documented, is the enhanced reactivity of *Z*-alkenes over *E*-alkenes.[2,4] This interesting property is not only underused, but in addition no theoretical study has been undertaken to explain this unusual kinetic difference. In this communication, we will first test the usefulness of this feature and next address theoretically the effect of olefin stereochemistry in the cycloaddition process in regard to the energetic and stereoselective aspects of the reaction in its intermolecular version. (Figure 1)

Despite numerous progresses, the selective formation of stereodefined olefins remains a challenge for the synthesis of a number of substrates. For instance, methods for synthesizing stereodefined silyl enol ethers are scarce: with most methods, *E* and *Z* mixtures of olefins are obtained.[5] Even a simple olefin such as the commercially available crotyl alcohol is sold as a *Z*/*E* mixture. In this regard, *E*-olefins are often formed as the major isomer, but rarely as the unique isomer, as opposed to *Z*-olefins, more easily accessible by selective hydrogenation of triple bonds. In addition, the separation of the two isomers of an alkene is often impossible by standard chromatographic techniques.[6] Considering the potential kinetic resolution of *Z*- and *E*-olefin in the [2+2] cycloaddition with ketenes, we decided to test the efficiency and synthetic utility of the process with the aim to selectively expunge *Z*-olefins from *Z*/*E* mixtures.[7] Indeed, as *Z*-olefins are meant to be much more reactive in the [2+2] cycloaddition with ketenes, it could be exploited to gain access to pure *E* isomer of a broad range of alkenes otherwise very difficult, or often impossible to isolate.

The first substrate chosen to test the kinetic resolution was triisopropylsilyl crotyl ether **1**, directly obtained from crotyl alcohol, commercially available as a 5:95 *Z*/*E* mixture of isomers. Treated with 0.15 equivalent of in situ-generated dichloroketene, the pure *E* triisopropylsilyl allylic ether (*E*)-**1** was isolated in 90% yield (Table 1, entry 1). In this process, there was no trace of remaining *Z*-alkene in the crude reaction mixture. This first experiment showed the great *Z*/*E* kinetic difference as only a few percent of *Z*-olefin reacted not only preferentially but seemingly exclusively. A second experiment was conducted with a 12:88 mixture of methyl oleate and methyl elaidate **2**: upon addition of 0.25 equivalent of dichloroketene, no trace of the *Z*-olefin (methyl oleate) remained in the crude product. Methyl elaidate (*E*)-**2** could thus be obtained in pure form in an outstanding 98% yield out of the 88% present in the starting material (Table 1, entry 2). The cycloaddition thus represents a practical method for obtaining pure methyl *trans*-9-octaenoate, with the *trans* isomer being twelve to twenty times more expensive than the *cis* isomer. Commercial cyclodode-

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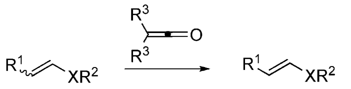
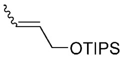
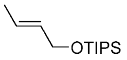
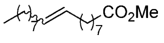
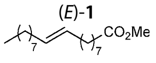
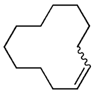
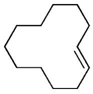
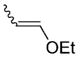
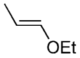
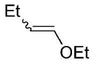
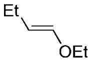
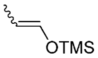
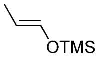
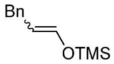
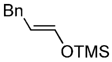
Table 1. Isolation of the *E* isomer starting with a *Z*/*E* mixture of isomers.



Z/*E* mixture
X = O, CH_2

pure *E* isomer

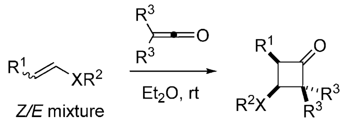
Entry	Alkene	*Z*/*E*[a]	R^3[b]	Recovered alkene	Yield[c]
1	 **1**	5:95	Cl (0.15)	 (*E*)-**1**	90[d]
2	 **2**	12:88	Cl (0.25)	 (*E*)-**2**	98[d]
3	 **3**	71:29	Cl (1.0)	 (*E*)-**3**	78[d]
4	 **4**	63:37	Ph (0.8)	 (*E*)-**4**	81[e] (50)[d]
5	 **5**	83:17	Ph (1.08)	 (*E*)-**5**	66[e]
6	 **6**	70:30	Ph (0.88)	 (*E*)-**6**	77[e]
7	 **7**	64:36	Ph (1.55)	 (*E*)-**7**	89[e]

[a] Determined by using ^1H NMR spectroscopy. [b] Equivalent of ketene in parenthesis. [c] Based on the proportion of the *E* isomer in the starting material. [d] Isolated pure product. [e] Yield based on the cyclobutane/*E* enol ether ratio; see the Supporting Information.

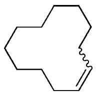
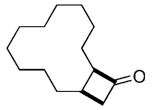
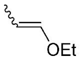
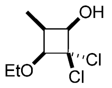
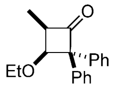
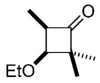
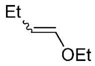
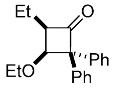
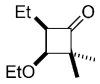
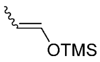
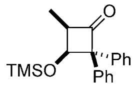
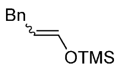
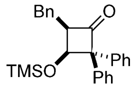
cene **3** is also sold as a mixture of *Z*/*E* isomers (71:29). The separation of the two isomers has been realized through multiple recrystallizations of their silver complex.[6] With dichloroketene, only the *Z* isomer reacted, affording the pure, less abundant *E* isomer in a single operation in 78% yield (Table 1, entry 3). Starting from simple alkene, the preferential reactivity of the *Z* isomer is a unique feature allowing for the isolation of the pure *E*-olefin. The isolation of enol ethers in pure isomeric form, hardly possible to access by standard methods, was next undertaken. Enol ethers are much more reactive than simple alkenes in [2+2] cycloaddition with ketene: it was thus decided to use the less reactive diphenylketene to test the kinetic resolution in this case. The reaction of diphenyl ketene (1.2 equiv to the olefin) with ethyl propenyl ether **4** (*Z*/*E*= 63:37) led to the pure *E* enol ether: this enol ether could be isolated by simple distillation from the crude reaction mixture in 50% yield. The same result was obtained with enol ether **5**. With silyl enol ethers (**6** and **7**, Table 1, entry 5 and 7), the cycloaddition also occurred only with the *Z* isomer, regardless of the substituent on the enol ether. In all cases, no trace of the *Z* isomer remained in the crude product, and only few percent of the *E* isomer reacted. The [2+2] cycloaddition of ketene thus represents a very practical solution for the chemical separation of isomeric mixture of olefins, to isolate pure *E*-olefins, either alkenes or enol ethers.

A useful complement to the isolation of pure *E*-olefins by using kinetic resolution is the selective synthesis of *cis*-cyclobutanones starting from *Z*/*E* mixtures of olefins. By treatment of dichloro, dimethyl, or diphenyl ketenes with alkenes or enol ethers, only the *cis*-cyclobutanones were obtained, with complete conversion of the *Z* material, thus affording the *cis*-cycloadduct in high yields and with excellent diastereoselectivity (Table 2). For instance, the treatment of dichloroketene with cyclododecene **3** followed by dechlorination led to cyclobutanone **8** as a single diastereoisomer (Table 2, entry 1). The cycloaddition of dichloroketene with ethyl propenyl ether **4** followed by reduction led to cyclobutanol **9** in moderate yield

Table 2. Isolation of *cis*-cyclobutanones starting with a *Z*/*E* mixture of isomers.



Z/*E* mixture
X = O, CH_2

Entry	Alkene	*Z*/*E*[a]	R^3[b]	Product	Yield[c]	d.r.[a]
1	 **3**	71:29	Cl (0.9)	 **8**	57[d]	98:2
2	 **4**	63:37	Cl (0.7)	 **9**	48[e]	96:4
3	**4**		Ph (0.8)	 **10**	99	98:2
4	**4**		Me (4.0)	 **11**	88	>98:2
5	 **5**	83:17	Ph (1.1)	 **12**	86	98:2
6	**5**		Me (5.0)	 **13**	94	>98:2
7	 **6**	70:30	Ph (0.9)	 **14**	63	97:3
8	 **7**	64:36	Ph (0.8)	 **15**	90	98:2

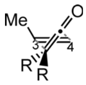
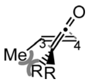
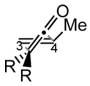
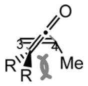
[a] Determined by using NMR spectroscopy. [b] Equivalent of ketene in parenthesis. [c] Yield of the isolated product based on proportion of starting enol ether. [d] Yield for two steps: cycloaddition and dechlorination. [e] Yield for two steps: cycloaddition and reduction with $LiAlH_4$.

and high diastereoselectivity (Table 2, entry 2). With the same enol ether, the reaction of either dimethyl or diphenylketene with enol ether **4** was much more efficient, both in terms of yield and diastereoselectivity: the *cis*-cyclobutanones **10** and **11** were obtained in good to excellent yields with good to excellent diastereoselectivities (Table 2, entries 3 and 4). Similar results were obtained with ethyl butenyl ether **5** (Table 2, entries 5 and 6). Finally, silyl enol ethers **6** and **7** were also converted into the corresponding *cis*-cyclobutanones **14** and **15** with only traces of the *trans* products (Table 2, entries 7 and 8). Overall, in [2+2] cycloaddition involving ketenes, diastereomerically enriched cyclobutanones can easily be obtained regardless of the stereochemical purity of the starting olefins.

Having experimentally proven the kinetic non-equivalence of *Z*/*E*-olefin in [2+2] cycloadditions, it seemed important to gain insight into the mechanistic origin of this dichotomy. To the best of our knowledge, no theoretical studies have been realized on this *Z*/*E* reactivity since the first theoretical study on the cycloaddition of ketene with alkene.[3] The mechanistic basis of ketene–alkene [2+2] cycloaddition were set by the groups of Houk[8a] and Moyano[8b] in the 1990s. They first showed the importance of the nearly perpendicular approach of the ketene to the alkene, and also that the quasi-pericyclic $[\pi 2_s+(\pi 2_s+\pi 2_s)]$ reaction mechanism is more relevant than a concerted asynchronous $(\pi 2_s+\pi 2_a)$ cycloaddition.[8,9] Their reactivity investigation was realized using respectively ab initio (HF and MP2 for the simplest examples) and semi-empirical calculations (AM1). In these works, the difference of reactivity of *Z*/*E*-alkenes was not addressed. However, the enhanced reactivity of the *Z*-alkene over the *E*-alkene has tentatively been justified by simple steric interactions arguments[10] or by assuming that the energetic effects of the alkenes substituents would be additive.[8a] Applying this shortcut would lead to opposite results based on Houk or Moyano's results (inversion of relative stability between TS3 and TS4: Table 3, entry 1 and 2). It was thus worthwhile examining simple cycloaddition of ketenes and *Z*/*E*-alkenes at the DFT level.

Performing calculations using Gaussian 09 D.01 at DFT B3LYP/6-31+G(d,p) level,[11] a trend of reactivity similar to the results of Houk and Moyano was found for all four transition states (TS). These calculations confirm, without surprise, the importance of the regioselectivity of the process through stabilization of the positive charge by the methyl group (TS1-2 < TS3-4), and a particular unfavorable steric interaction between the substituent of the alkene and the ketene (TS1 < TS2 and TS3 < TS4; Table 3). These results also confirm that TS3 is lower than TS4, following the previous order reported by Houk, but opposite to the one reported by Moyano (Table 3, entries 1 and 2). In addition, these results also show that TS2 is always lower in energy than TS3, as reported by Moyano, but opposite to the results of Houk: hence, the interaction of the alkene substituent is greater with the ketene substituent compared with the ketene carbonyl (in combination with the less favorable initial charge development at C3; Table 3).

Table 3. Relative activation energy [kcal mol^{-1}] for the transition states of propene with ketenes.

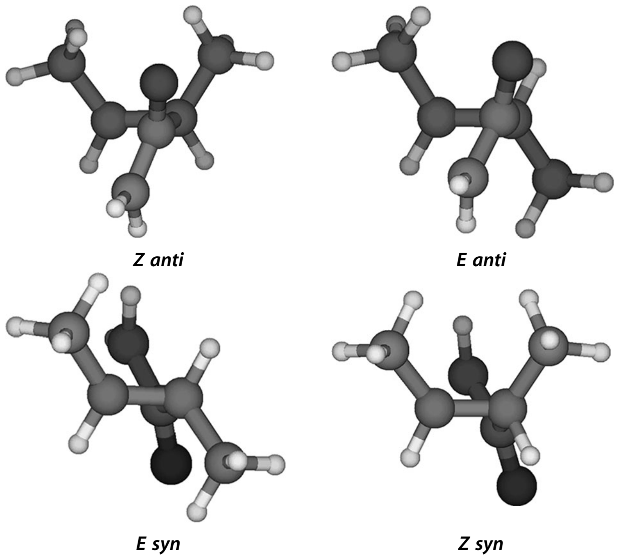
Entry	R	 TS1	 TS2	 TS3	 TS4
1	H[a]	0	4.9	4.5	6.9
2	H[b]	0	1.2	6.8	6.0
3	H[c]	0	2.9	5.2	6.0
4	Me[c]	0	4.3	4.8	8.6
5	Cl[c]	0	3.5	5.5	9.1
6	Ph[c]	0	4.3	5.7	10.7

[a] Results reported by Houk et al. (RHF/3-31G).[8a] [b] Results reported by Moyano et al. (AM1).[9b] [c] Our calculations (B3LYP/6-31+G(d,p)).

Simply based on these results, it would be very unreliable to predict the outcome of the cycloaddition for disubstituted alkenes: assuming that the energetic effects of methyl substitution are additive is not satisfactory. Moreover, both steric repulsion and the effect of positive charge stabilization are intertwined, and therefore cannot justify that the *Z*-alkenes are more reactive than the *E*-alkenes. Calculations on the cycloaddition between symmetrically substituted ketene and disubstituted *Z*/*E*-but-2-ene were therefore next performed. For each isomer, there are two approaches: one, called "*anti*", in which the alkene molecule approaches the ketene with its substituents as far as possible from the ketene substituents, and a second, called "*syn*", in which the olefin approach takes place with alkene substituents close to the ketene substituents. The results showed that the transition states of disubstituted alkenes are very similar to those of mono-substituted alkenes, with the ketene approaching in a slightly bent perpendicular fashion (Table 4). The calculated difference of energy of activation between *E*- and *Z*-olefins correlates nicely with the experimental results: the lowest activation energy ($\Delta G^{\neq}$) is always associated with the TS *Z anti* (Table 4). The increase of size of the ketene results in an increase of this difference of activation energy: from 1.2 to 5.5 kcal mol^{-1} with nonsubstituted- and diphenylketene, respectively. It turned out that the steric repulsion between the alkene substituents either at C3 or at C4 and the smaller substituent of the ketene, which points toward the alkene, is of crucial importance, much more important than the carbonyl interaction with the alkene. The *E anti* and *E syn* transition states are relatively close in energy, especially for bulkier ketenes, in which a more perpendicular approach leads to the merge of the two trajectories. Finally, the TS *Z syn* is energetically the highest one since it combines steric repulsions between the ketene substituent with both C3 and C4 alkene substituents.

As enol ethers are commonly used in the [2+2] cycloaddition with ketene, and also proved to be good substrate for kinetic resolution, the computational study of their *Z*/*E* difference of reactivity in [2+2] cycloaddition was next investigated. With enol ethers, their *s-cis* or *s-trans* conformation should be considered, but it has previously been shown for Diels–Alder and [3+2] cycloaddition that in the transition state, the *s-trans* conformation is always preferred, regardless of the ground state.[14] For [2+2] cycloaddition, we also confirm that despite a preference for the *s-cis* conformation for *E*-enol ethers with

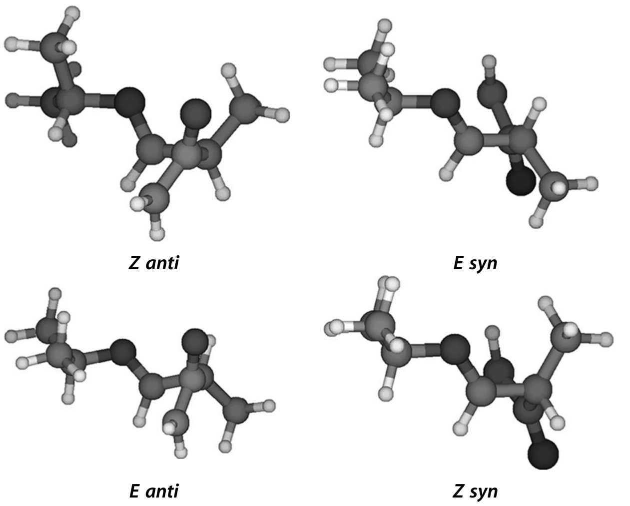
Table 4. Transition structures and activation energy [kcal mol^{-1}] of *Z*- and *E*-butene with ketenes.[a]



Entry	R	*Z anti*	*E anti*	*E syn*	*Z syn*	$\Delta\Delta G^{\neq}$ [b]
1	H	39.4	40.6	42.9	43.3	1.2
2	Me	36.5	40.9	42.1	44.6	4.4
3	Cl	24.5	29.0	29.3	31.7	4.7
4	Ph	38.4	44.7	43.9	48.4	5.5

[a] Drawings thanks to molden;[13] calculation using B3LYP/6-31+G(d,p). [b] *Z/E* difference of energy of activation: $\Delta G^{\neq}$(***E anti***)−$\Delta G^{\neq}$(***Z anti***).[12]

Table 5. Transition structures and activation energy [kcal mol^{-1}] of *Z*- and *E*-isopropyl propenyl ether with ketenes.[a]



Entry	*Z anti*	*E syn*	*E anti*	*Z syn*	$\Delta\Delta G^{\neq}$ [b]
R=H	33.2	33.3	33.7	34.6	0.1
R=Me	31.8	34.3	36.0	36.6	2.5
R=Cl	17.6	20.8	21.9	23.2	3.3
R=Ph	29.7	34.8	37.3	35.5	5.2

[a] Drawings thanks to molden;[13] calculation using B3LYP/6-31+G(d,p). [b] *Z/E* difference of energy of activation: $\Delta G^{\neq}$(***E syn***)−$\Delta G^{\neq}$(***Z anti***).[12]

small substituents (H, Me, Et) on the oxygen, the *s-trans* conformation is always the preferred conformation in the transition state in the reaction with ketenes (see Supporting Information). There are eight potential approaches of the ketene to the enol ether, but only four of them would develop an oxygen-stabilized positive charge. Hence, only the four energetically lowest approaches were evaluated (Table 5). Again, the *Z anti* transition state shows the lowest activation energy with all ketenes, and *Z syn* the highest, except for diphenyl ketene in which the *E anti* is the highest (Table 5). Unlike with butene, the *E syn* approach is now preferred in all cases over the *E anti* structure, probably a result of the more favorable ketene oxygen interaction over the ketene. As expected, as the ketene hindrance increase, the difference of reactivity between *Z*- and *E*-butene also increases: from 0.1 to 5.2 kcal mol^{-1} with nonsubstituted- and diphenylketene, respectively. The obtained energies are also consistent with the higher reactivity of enol ethers over alkenes.

In summary, the higher reactivity of *Z*- over *E*-olefins in [2+2] cycloaddition originates from the steric repulsion between the ketene substituent and the substituents of the olefin. These results are valid for alkenes, and also for enol ethers as substrates in [2+2] cycloaddition reaction with ketenes. The bulkiest the ketene substituents are, the more *Z*-selective the reaction is. This high difference of reactivity allowed for the kinetic resolution of *Z/E* mixture of olefins in the cycloaddition with ketenes, affording pure *E*-olefins. Moreover, the [2+2] cycloaddition can be conducted with *Z/E* mixtures of olefins, producing with good diastereoselectivity only the *cis*-cyclobutanones.

Experimental Section

Typical experimental procedure

The resolution of olefin with dichloroketene: Trichloroacetyl chloride (0.15 to 1.0 equiv) was added dropwise to a suspension of Zn/Cu (0.5 to 2.0 equiv) and the *Z/E* mixture of alkene (1 equiv) in dry Et_2O (1.5 mL) at 25 °C under an argon atmosphere. After stirring the reaction mixture for 2 h at room temperature, pentane was then added to precipitate zinc salts, the resulting mixture filtered over Celite, and the solid washed twice with pentane. The filtrate was dried over Na_2SO_4 and concentrated under reduced pressure. Purification of the crude product by flash chromatography on silica gel (0 to 5 % Et_2O in pentane) afforded the pure *E*-alkene.

Resolution of enol ethers with diphenylketene: Diphenyl ketene (1.2 equiv) was slowly added at 0 °C to a *Z/E* mixture of enol ether (1.0 equiv of *Z*) and the orange solution was subsequently stirred at 0 °C for 20–24 h. Purification of the crude mixture by flash chromatography on silica (0 to 5 % Et_2O in pentane) afforded the pure *E*-alkene.

Synthesis of *cis*-cyclobutanones: Distilled isobutyryl chloride (4.0 equiv) in toluene was added to a solution of *Z/E* mixture of enol ether (1.0 equiv) and Et_3N (4.0 equiv) in anhydrous toluene (1 mL, 0.1 M) at 70 °C over 4 h. The reaction mixture was stirred for further 14 h after completion of addition and then quenched by addition of water. The aqueous phase was extracted with Et_2O and the combined organic layers were successively washed with a solution of HCl (1 N), a solution of NaOH (1 N) and brine, dried over anhydrous $MgSO_4$, filtered, and the filtrate concentrated under reduced pressure. Purification of the crude mixture by flash chromatography on silica gel (0 to 5% Et_2O in pentane) afforded the desired *cis*-cyclobutanone.

Computational details

All geometries were fully optimized and all optimizations were followed by a frequency calculation to check the nature of the structures: minima or transition states. ΔG Values were deduced from the frequencies calculations in the gas phase at $T=298$ K and $P=1$ atm.

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Keywords: cycloaddition · ketenes · kinetic resolution · olefins · stereochemistry

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COMMUNICATION

Kinetic Resolution

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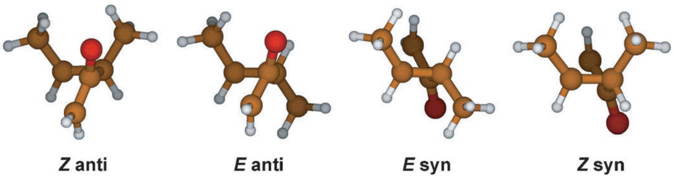
Kinetic Resolution in the [2+2] Cycloaddition of Ketenes: An Experimental and Theoretical Study



Resolved by reactivity: The effect of *Z*/*E*-olefin stereochemistry in [2+2] cycloaddition with ketenes is presented from both experimental and theoretical aspects. This difference of reactivity allowed pure *E*-olefins to be isolated from *Z*/*E* mixtures of alkenes or enol ethers by kinetic resolution (see figure).