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Application of the Octacarbonyldicobalt-Catalyzed Carbonylation of Ethyl Diazoacetate for the One-Pot Synthesis of *N-tert*-Butyl-*trans*-α-ethoxycarbonyl-β-phenyl-β-lactam

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Dedicated to Professor László Markó on the occasion of his 80th birthday

Keywords: Cobalt / Carbene ligands / Carbonyl ligands / C–C coupling / Lactams / Density functional calculations

N-tert-Butyl-*trans*-α-ethoxycarbonyl-β-phenyl-β-lactam has been prepared in 95 % yield (GC) by the octacarbonyldicobalt-catalyzed carbonylation of ethyl diazoacetate in dichloromethane in the presence of *N-tert*-butylbenzaldimine at 10 °C and 75 bar pressure of carbon monoxide. The key step of the reaction is the catalytic formation of the highly reactive (ethoxycarbonyl)ketene from both of the intermediary complexes $[Co_2(CO)_7(CHCO_2Et)]$ and $[Co_2(CO)_6(CHCO_2Et)_2]$, which is in situ scavenged by the imine in a [2+2] cycloaddition reaction. DFT (PBEPBE/6-31G**) calculations revealed that the reaction follows a two-step mechanism via a noncyclic intermediate with a reaction free energy of –15.9 kcal/mol and a free-energy barrier of 24.7 kcal/mol for the second rate-limiting step. The computation also shows that the formation of the *trans* isomer is preferred both kinetically and thermodynamically.

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Introduction

β-Lactams have found broad medical applications in the form of penicillin and cephalosporin antibiotics. On the other hand, enantiopure β-lactams have become important as versatile building blocks in the asymmetric synthesis of proteinogenic and non-proteinogenic amino acids, peptidomimetics, heterocycles, and other types of compounds of biological importance.[1] To prepare β-lactams the Staudinger [2+2] cycloaddition reaction between an imine and a ketene[2,3] and its variants has been widely used.[4,5] Application of the Staudinger reaction with (ethoxycarbonyl)ketene, $EtO_2CCH=C=O$, however, is impeded by the fact that this highly reactive ketene cannot be isolated under ambient conditions.

The cobalt-catalyzed carbonylation of ethyl diazoacetate results in the formation of (ethoxycarbonyl)ketene, which can be scavenged by OH, NH, and suitable CH compounds.[6,7] We found that imines are also suitable scavengers for the in situ formed unstable ketene leading to β-lactams. Herein we report the selective one-pot synthesis of *N-tert*-butyl-*trans*-α-ethoxycarbonyl-β-phenyl-β-lactam by the octacarbonyldicobalt-catalyzed carbonylation of ethyl diazoacetate in the presence of *N-tert*-butylbenzaldimine.

It is generally assumed[8] that the [2+2] ketene/imine cycloaddition is a stepwise reaction involving a zwitterionic intermediate formed after a stereoselective attack by the nitrogen lone pair of the imine on the sp-carbon atom of the ketene. In the second rate-determining step, the intermediate undergoes an electrocyclic conrotatory ring-closure to give the final product, the β-lactam. The existence of zwitterionic intermediates was proved experimentally in the thermal reaction of ketenes with imidazoles by using IR spectroscopy at low temperature.[9] Some ab initio studies, however, predict that the mechanism for the reaction between formaldimine and ketene takes place by a concerted mechanism.[10] The two possible pathways of the Staudinger reaction are outlined in Scheme 1.

In the two-step mechanism, close similarity was found between the second transition state, corresponding to the electrocyclic conrotatory ring-closure of the zwitterionic intermediate, and the transition-state structures of the electrocyclic ring-opening of cyclobutenes described by Houk and co-workers.[11] The special stereoselectivity associated with such reactions is termed as torquoselectivity. The influence of substituents governing the torquoselectivity has been ex-

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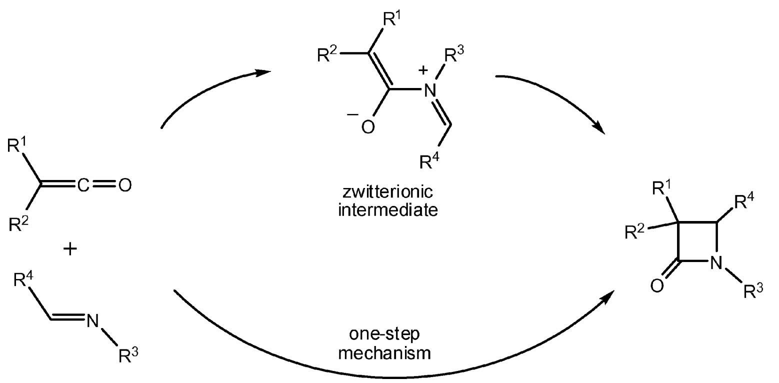

Scheme 1. Possible pathways for the [2+2] Staudinger reaction.

amined in various theoretical studies.[12] It was found that donor groups prefer outward rotation in the transition state, whereas strong acceptors prefer inward rotation.

The existence of a zwitterionic intermediate would suggest that the stabilization energy of the solvent plays an important role, especially if the inward–outward energy difference of the intermediates and transition-state structures are small.[13] Other studies have shown, however, that the introduction of solvation did not influence the diastereoselectivity or the overall reaction energetics.[14]

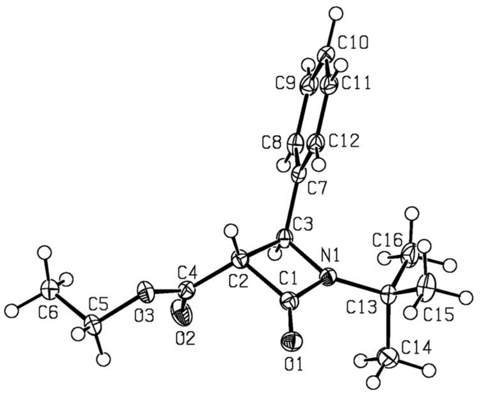

Figure 1. ORTEP drawing of *N*-*tert*-butyl-*trans*-α-ethoxycarbonyl-β-phenyl-β-lactam.

Results and Discussion

Catalytic Syntheses

We found that a stoichiometric mixture of ethyl diazoacetate (EDA) and *N*-*tert*-butylbenzaldimine (BTB) in CH_2Cl_2 solution in the presence of a catalytic amount of $[Co_2(CO)_8]$ can be converted under carbon monoxide pressure at room temperature into *N*-*tert*-butyl-*trans*-α-ethoxycarbonyl-β-phenyl-β-lactam (TBL) in up to 95% yield, as determined by quantitative IR spectroscopy and gas chromatography. The formation of this product can be monitored by its characteristic absorptions at 1756 and 1728 cm^{-1} in the IR spectra of the reaction mixture. Isolation by column chromatography resulted in a white crystalline product with a melting point of 82 °C. The literature has reported the *trans* isomer as a colorless oil at room temperature.[15] The ^1H NMR spectrum of our product revealed clearly the *trans* structure in solution (J_{HH} = 2.2 Hz for the *trans* methine protons), which we confirmed by X-ray crystallography of the crystalline product (see Figure 1 and Tables S1 and S2 of the Supporting Information). Most remarkable is the small torsion angle (4.2°) of C13–N1–C1–O1, which indicates that the hybridization of the lactam nitrogen atom is sp^2 rather than sp^3. Consequently, there is a strong overlap between N1 and C1, which is reflected in the observed short N1–C1 bond [1.350(2) Å].

By monitoring the yield of TBL with time in the carbonylation reaction (see Figure 2), a short induction period can be observed, and from the points thereafter the initial rate of formation of TBL between 1 and 3 h of reaction time can be estimated as $r_{TBL}[1–3\text{ h}; 10\text{ °C}; P(CO) = 50\text{ bar}] = 0.47 \times 10^{-5}\ \text{mol/dm}^3\,\text{s}$.

To see the effect of the concentrations of $[Co_2(CO)_8]$, EDA, and BTB, we performed experiments at 10 °C and 50 bar CO pressure over 3 h with various initial concentrations (Table 1). The data in Table 1 show that the amount of TBL formed is nearly linear with the initial concentrations of $[Co_2(CO)_8]$ and EDA, and independent of the BTB concentrations.

The effect of CO pressure on the TBL formation was investigated at 10 °C in experiments started with different CO pressures between 1 and 170 bar by using $[EDA]_0 = [BTB]_0 = 0.50\ \text{mol/dm}^3$ and $[Co_2(CO)_8]_0 = 0.025\ \text{mol/dm}^3$ and 3 h of reaction time. The data in Figure 3 show a maximum TBL yield at around 85 bar. Before this maximum the CO dependence is nearly linear between 10 and 75 bar CO pressure. Beyond the maximum the effect of rising CO pressure is slightly negative.

The composition of the cobalt complexes in the reaction mixture checked by IR spectroscopy after 3 h of reaction time shows the presence of three different cobalt complexes: $[Co_2(CO)_8]$, $[Co_2(CO)_7(CHCO_2Et)]$ (**1**), and $[Co_2(CO)_6(CHCO_2Et)_2]$ (**2**), which can be recognized in the mixtures by their characteristic ν(CO) bands at 2021, 2070, and 2080 cm^{-1}, respectively. Their ratio depends on the CO pres-

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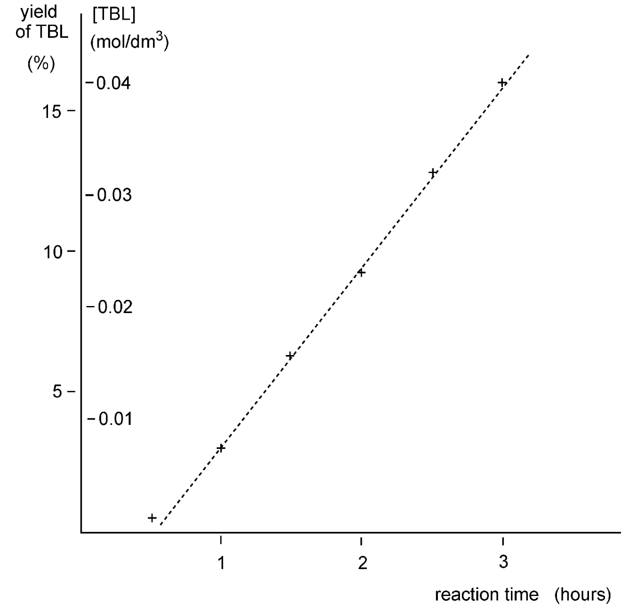


Figure 2. Yield of *N*-*tert*-butyl-*trans*-α-ethoxycarbonyl-β-phenyl-β-lactam (TBL) vs. reaction time in the [$Co_2(CO)_8$]-catalyzed carbonylation reaction of ethyl diazoacetate (EDA) in the presence of *N*-*tert*-butylbenzaldimine (BTB) at 10 °C and 50 bar CO pressure. Initial concentrations: $[Co_2(CO)_8]_0$ = 0.025 mol/dm^3; $[EDA]_0$ = $[BTB]_0$ = 0.25 mol/dm^3.

Table 1. Yield of *N*-*tert*-butyl-*trans*-α-ethoxycarbonyl-β-phenyl-β-lactam (TBL) from the [$Co_2(CO)_8$]-catalyzed carbonylation reaction of ethyl diazoacetate (EDA) in the presence of *N*-*tert*-butylbenzaldimine (BTB) at 10 °C and 50 bar CO pressure in 3 h of reaction time by using various initial concentrations of the reactants.

Entry	$[Co_2(CO)_8]_0$ [mol/dm^3]	$[EDA]_0$ [mol/dm^3]	$[BTB]_0$ [mol/dm^3]	Yield of TBL[a] [%]
1	0.003	0.25	0.25	2.4
2	0.006	0.25	0.25	4.3
3	0.013	0.25	0.25	10.8
4	0.025	0.25	0.25	19.7
5	0.050	0.25	0.25	25.0
6	0.025	0.13	0.25	3.0
7	0.025	0.25	0.25	16.6
8	0.025	0.50	0.25	37.9
9	0.025	0.75	0.25	52.1
10	0.025	0.25	0.12	15.2
11	0.025	0.25	0.25	16.6
12	0.025	0.25	0.50	16.1

[a] Determined by quantitative IR spectroscopy.

sure used in the experiment. At 1 bar CO pressure complex **2** prevails with >90% accompanied by <10% of complex **1**. At 50 bar CO pressure the reaction mixture contains <2% of complex **2**, around 80% of complex **1**, and <20% of [$Co_2(CO)_8$]. At 150 bar CO pressure >90% of the cobalt is in the form of [$Co_2(CO)_8$], the rest is in the form of complex **1**.

Our earlier investigations have shown that under ambient conditions the reaction of ethyl diazoacetate (EDA) with [$Co_2(CO)_8$] gives dinitrogen and (ethoxycarbonyl)carbene-bridged carbonyldicobalt complexes [$Co_2(CO)_7(CHCO_2Et)$] (**1**) and [$Co_2(CO)_6(CHCO_2Et)_2$] (**2**) depending on the molar ratio of EDA/[$Co_2(CO)_8$], in accord with Equations (1) and (2), respectively.[6]

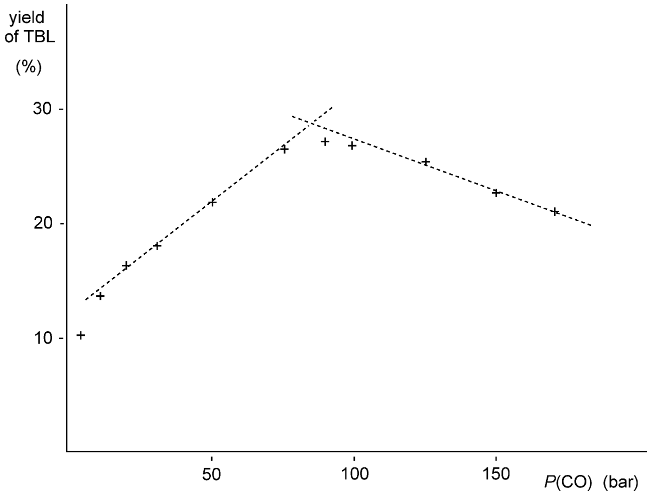


Figure 3. Effect of CO pressure on the yield of *N*-*tert*-butyl-*trans*-α-ethoxycarbonyl-β-phenyl-β-lactam (TBL) in experiments using $[EDA]_0$ = $[BTB]_0$ = 0.50 mol/dm^3 and $[Co_2(CO)_8]_0$ = 0.025 mol/dm^3 and 3 h of reaction time.

$$Co_2(CO)_8 + EtO_2CCHN_2 \longrightarrow \underset{\mathbf{1}}{Co_2(CO)_7(CHCO_2Et)} + N_2 + CO \qquad (1)$$

$$Co_2(CO)_8 + 2\ EtO_2CCHN_2 \longrightarrow \underset{\mathbf{2}}{Co_2(CO)_6(CHCO_2Et)_2} + 2\ N_2 + 2\ CO \qquad (2)$$

Under carbon monoxide the (ethoxycarbonyl)carbene ligand(s) of these complexes couple(s) with CO to give (ethoxycarbonyl)ketene, which is replaced under carbon monoxide by CO [see Equations (3) and (4)].[7]

$$\underset{\mathbf{2}}{Co_2(CO)_6(CHCO_2Et)_2} + 2\ CO \longrightarrow \underset{\mathbf{1}}{Co_2(CO)_7(CHCO_2Et)} + EtO_2CCH{=}C{=}O \qquad (3)$$

$$\underset{\mathbf{1}}{Co_2(CO)_7(CHCO_2Et)} + 2\ CO \longrightarrow Co_2(CO)_8 + EtO_2CCH{=}C{=}O \qquad (4)$$

Complex **2** reacts faster with carbon monoxide than complex **1**.[16] The highly reactive (ethoxycarbonyl)ketene formed as a short-living organic product in the above reactions either dimerizes or reacts with suitable scavengers such as alcohols, phenols, and amines to give the corresponding malonic ester derivatives in excellent yields [Equation (5)].[6,7]

$$EtO_2CCH{=}C{=}O + B{-}H \longrightarrow EtO_2CCH_2C({=}O)B \qquad (5)$$

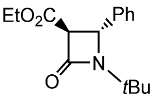
(B–H = alcohols, phenols, amines)

(Ethoxycarbonyl)ketene may react with the CH acid ethyl diazoacetate to give diethyl 2-diazo-3-oxoglutarate [Equation (6)].[6]

$$EtO_2CCH{=}C{=}O + EtO_2CCHN_2 \longrightarrow EtO_2CCH_2C({=}O)C(N_2)CO_2Et \qquad (6)$$

We found that among various imines PhCH=N*t*Bu is also an excellent scavenger of the in situ formed unstable (ethoxycarbonyl)ketene [Equation (7)]. Thus, the reaction of either complex **1** or complex **2** with carbon monoxide in the presence of PhCH=N*t*Bu gives the β-lactam TBL as a result of the 2+2 cycloaddition reaction in Equation (7).

$$EtO_2CCH{=}C{=}O + PhCH{=}NtBu \longrightarrow$$



(7)

We found that not only PhCH=N*t*Bu but other imines of the type PhCH=NR (R = Me and CH_2Ph) are also suitable scavengers for the in situ formed unstable (ethoxycarbonyl)ketene leading to β-lactams (see Exp. Sect.). On the other hand, diphenyl ketimine $Ph_2C{=}NH$, having an N–H bond, does not give as scavenger β-lactam, but affords the malonic ester derivative $EtO_2CCH_2C({=}O)N{=}CPh_2$ in excellent yield (see Exp. Sect.).

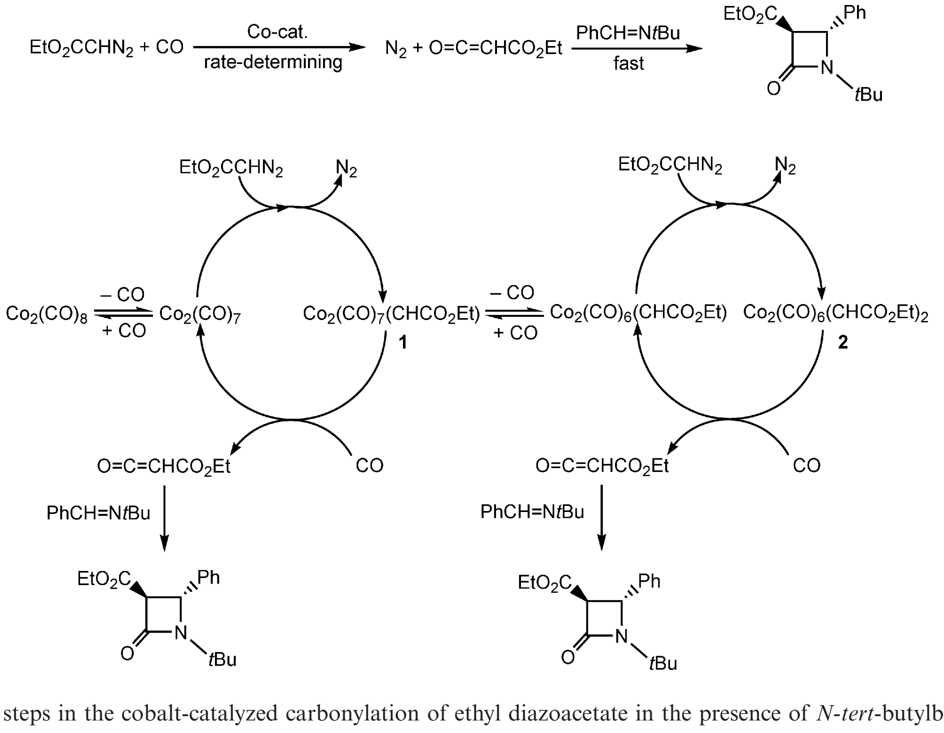
Because the intermediary (ethoxycarbonyl)ketene can be formed from both complexes **1** and **2** by the reaction with carbon monoxide,[6,7] two different catalytic cycles (see Scheme 2) can serve to produce the β-lactam in the subsequent fast reaction with the imine. In accord with the observed composition of the complexes in the reaction mixture, at a high pressure of carbon monoxide the operating catalytic cycle involves most probably $[Co_2(CO)_7]$ and $[Co_2(CO)_7(CHCO_2Et)]$ (**1**), whereas at a low pressure of carbon monoxide $[Co_2(CO)_6(CHCO_2Et)]$ and $[Co_2(CO)_6(CHCO_2Et)_2]$ (**2**) are the working catalytic species. This might explain the experimental observation obtained at various pressures of carbon monoxide depicted in Figure 3. The bottleneck in the catalytic reaction in the low-pressure range might be the rate-determining reaction of the intermediary complex **2** with carbon monoxide, whereas in the high-pressure range the formation of the intermediary complex **1** might be rate-determining.

To identify which step in the catalytic cycles is the real bottleneck under various reaction conditions a detailed kinetic investigation of all the assumed steps in Scheme 2 is underway.

Theoretical Results

The structures of the two possible β-lactam isomers possessing the ethoxycarbonyl group with the most favorable conformation were computed at the PBEPBE/6-31G(d,p) level of theory and are depicted in Figure 4. The *trans* isomer is designated as **TBL1** and the *cis* isomer is designated as **TBL2**. The bond lengths in **TBL1** are in reasonable agreement with the corresponding X-ray structure (see Table S1 and Figure 1). However, the difference between the experimental and computed C13–N1–C1–O1 dihedral angles is notable as the former is 4.2°, whereas the latter is 16.2°. Thus the *N-tert*-butyl substituent is somewhat bent out of the lactam plane.

TBL1 is 2.5 kcal/mol more stable than **TBL2** in terms of free energy, which may be attributed to the greater repulsion of the ethoxycarbonyl and the phenyl groups in the latter. This is also reflected in the longer C2–C3 distance in **TBL2**. The topological analysis of **TBL1** (see Figure 5) reveals that the electron density is unevenly distributed inside the ring. Interestingly, the distortion of the density distribution only slightly influences the position of the ring critical point.



Scheme 2. Assumed steps in the cobalt-catalyzed carbonylation of ethyl diazoacetate in the presence of *N-tert*-butylbenzaldimine.

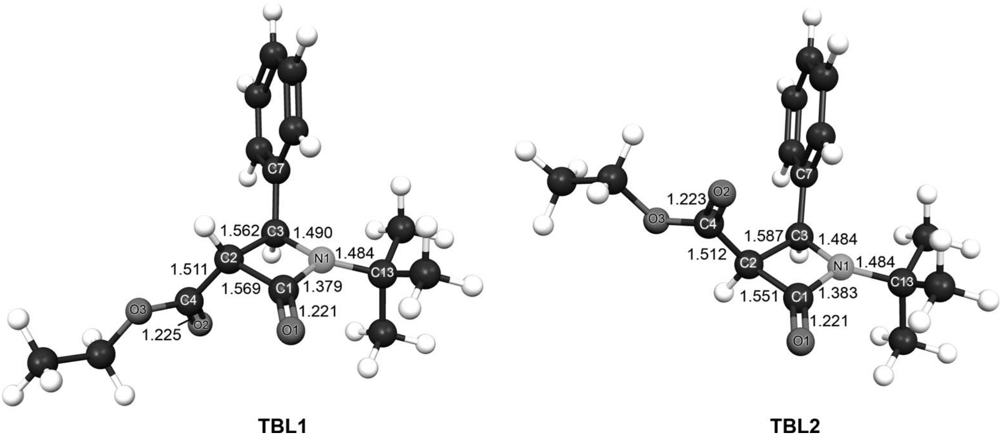


Figure 4. Computed structure of *N*-*tert*-butyl-*trans*-α-ethoxycarbonyl-β-phenyl-β-lactam (**TBL1**) and *N*-*tert*-butyl-*cis*-α-ethoxycarbonyl-β-phenyl-β-lactam (**TBL2**). Selected bond lengths are given in Å.

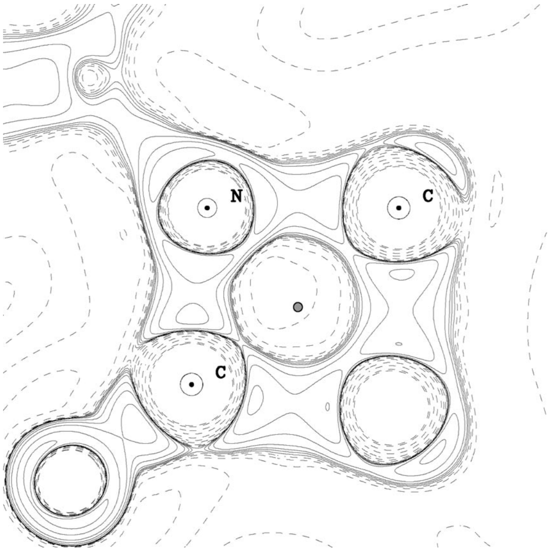


Figure 5. Contour line diagram of the Laplacian distribution $\nabla^2\rho(r)$ of **TBL1** in the plane of the lactam ring. Solid lines indicate charge concentration [$\nabla^2\rho(r) < 0$], dashed lines indicate charge depletion [$\nabla^2\rho(r) > 0$]. The grey dot indicates the ring critical point (RCP) in the lactam ring.

Within the framework of the atoms in molecules (AIM) analysis the bond ellipticity at the BCP can be determined, which can be used as a quantitative index of the π character of a bond. The analysis of **TBL1** shows that the ellipticity of the N1–C1 bond in the bond critical point is 0.178; thus, the charge density distribution is not cylindrical, predicting a double bond character. The electronic structure of the β-lactam ring has also been investigated within the framework of the natural bond orbital (NBO) analysis. The short N1–C1 bond is rationalized by the strong interaction of the N1 lone pair with the π* antibonding orbital between C1 and O1. For this donor–acceptor interaction the second-order perturbation energy is 45.3 kcal/mol; the $n_{N1} \rightarrow \pi^*_{N1-C1}$ overlap is depicted in Figure 6a. The occupancy of n_{N1} is reduced from 2 (the theoretical limit) to 1.65, whereas the occupancy of π^*_{N1-C1} is increased from 0 to 0.31. Owing to the hyperconjugative interaction of the O1 lone pair both σ_{C1-N1} and σ_{C1-C2} are weakened with perturbation energies of 22.1 and 23.6 kcal/mol, respectively (see Figure 7b and c).

The NMR parameters of **TBL1** and **TBL2** were predicted by using the GIAO methodology. The ^{13}C NMR chemical shifts are in accord with experimental values (see

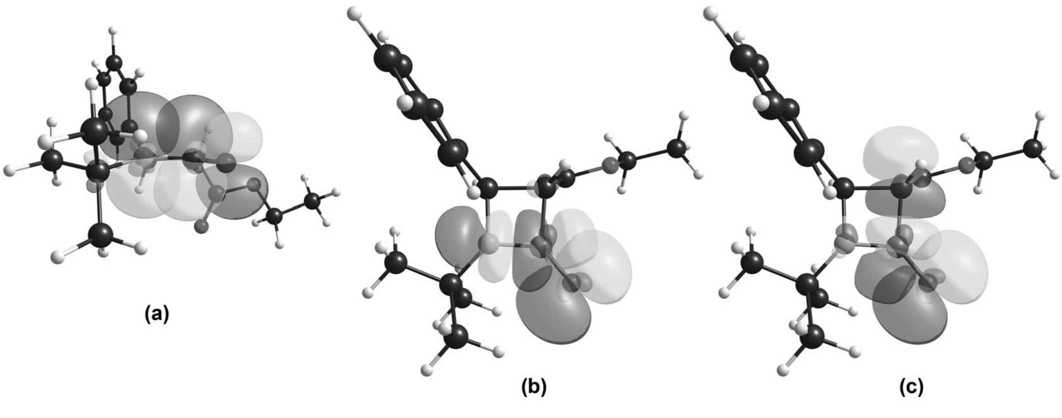


Figure 6. Second-order perturbation interactions of the natural bond orbitals of **TBL1**. (a) Interaction between the lone pair of N and the π^*_{C-N} antibonding orbital; (b) hyperconjugation between one of the lone pairs of O and the σ^*_{C-N} antibonding orbital; (c) hyperconjugation between one of the lone pairs of O and the σ^*_{C-C} antibonding orbital.

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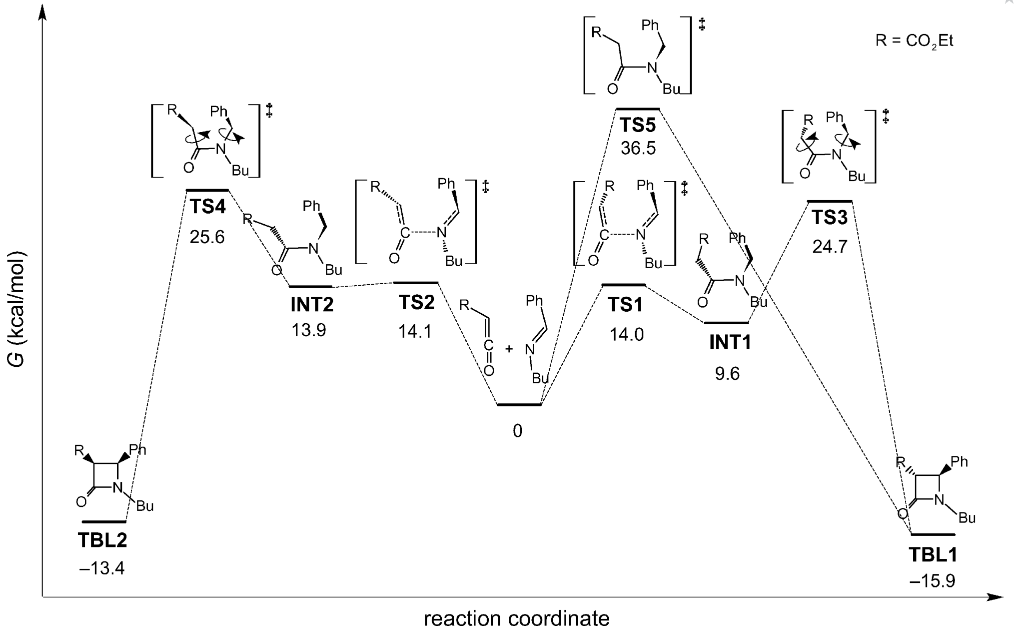

Figure 7. Gibbs free-energy profiles for the possible mechanisms of the reaction of *N*-*tert*-butylbenzaldimine with (ethoxycarbonyl)ketene.

Table 2); however, the shifts of the carbonyl carbon signals are underestimated by 8–10 ppm. Not surprisingly, comparing **TBL1** and **TBL2**, the biggest difference in chemical shifts is shown for the methine carbon atoms C2 and C3 as well as for the *ipso* carbon atom C7. The computed spin–spin coupling for the two methine protons in **TBL1** is 2.28 Hz, in excellent agreement with the experimental value of 2.23 Hz. For **TBL2** the corresponding value is J = 0.76 Hz.

Table 2. Computed ^{13}C NMR chemical shifts for **TBL1** and **TBL2**.

	δ [ppm]					
	C1	C2	C3	C4	C7	C13
trans (experimental)	162.1	62.4	56.4	167.1	139.1	55.1
trans (computed)	152.3	66.3	59.9	159.2	134.9	58.6
cis (computed)	151.9	61.9	61.8	159.0	131.2	58.5

The pathways of the [2+2] cycloaddition reaction of *N*-*tert*-butylbenzaldimine and (ethoxycarbonyl)ketene show close similarity to analogous reactions reported in the literature. The three possible pathways are (i) a two-step mechanism via a noncyclic intermediate and a subsequent conrotatory ring-closure resulting in the *trans* isomer **TBL1**, (ii) the analogous reaction resulting in the *cis* isomer **TBL2**, and (iii) a one-step reaction resulting in the *trans* isomer. We found no path to the *cis* isomer by a concerted pathway, probably for steric reasons. Note that the one-step pathway can be ruled out as a viable pathway leading to **TBL1** due to the high free-energy barrier associated with the transition state **TS5**. The proposed mechanistic pathways are depicted in Figure 7. Both isomers are formed in an exothermic reaction. The reaction free energy for the formation of **TBL1** is higher by 2.5 kcal/mol than that of **TBL2**, in accord with the higher thermodynamic stability of the former.

In the first step of the two-step pathways new σ_{C-N} bonds are formed that result in noncyclic intermediates **INT1** and **INT2** via transition states **TS1** and **TS2**, respectively, with free energy barriers of about 14 kcal/mol. The computed geometry of **INT1** is shown in Figure 8. The analogous intermediates are usually described in the literature to be of zwitterionic character; however, natural population analysis (NPA) revealed a rather covalent character for **INT1** with a partial charge of –0.284 for the N1 atom and –0.599 for the O1 atom. The corresponding partial charges in the product **TBL1** are –0.462 and –0.556, respectively, which indicate that N1 becomes more negative after ring closure, whereas the charge on O1 does not change significantly. Also notable is the difference in the charges on the C2 and C3 atoms in the cyclic and noncyclic compounds as the partial charge on C2 is more negative and the charge on C3 is more positive than those in **TBL1** or in **TBL2**. The NPA charges for **TBL1** or **TBL2** as well as those for **INT1** are summarized in Table 3.

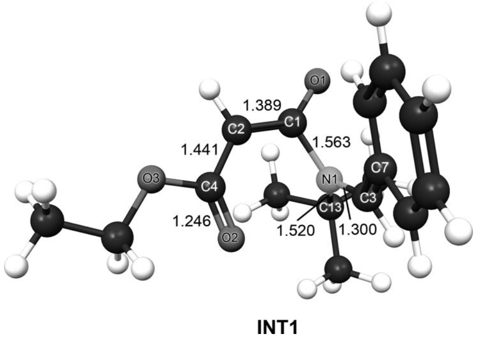

Figure 8. Computed structure of the formally zwitterionic intermediate **INT1**. Selected bond lengths are given in Å.

Table 3. Natural population analysis (NPA) charges of **TBL1**, **TBL2**, and **INT1**.

	O1	N1	C1	C2	C3	C4	O2	O3	C7	C13
TBL1	–0.556	–0.462	0.684	–0.440	–0.065	0.789	–0.577	–0.515	–0.067	0.125
TBL2	–0.559	–0.461	0.684	–0.439	–0.051	0.788	–0.562	–0.520	–0.081	0.125
INT1	–0.599	–0.284	0.535	–0.553	0.166	0.720	–0.655	–0.534	–0.126	0.130

In the second rate-limiting step the conrotatory ring-closure via transition states **TS3** and **TS4** results in **TBL1** and **TBL2**, respectively. The overall free-energy barrier is smaller for the *trans* isomer by 0.9 kcal/mol, which indicates that the formation of **TBL1** is also preferred kinetically over **TBL2**.

Conclusions

The present results have proved that *N*-*tert*-butyl-benzaldimine (BTB) is an effective scavenger of the intermediary (ethoxycarbonyl)ketene in the cobalt-catalyzed carbonylation of ethyl diazoacetate (EDA) and affords *N*-*tert*-butyl-*trans*-α-ethoxycarbonyl-β-phenyl-β-lactam (TBL) selectively, which can be isolated in good yields. Investigation of the mechanism of the catalysis has shown that the origin of the TBL product might be the result of two different catalytic cycles, both producing the intermediary (ethoxycarbonyl)ketene. In accord with the observed composition of the complexes in the reaction mixture, at a high pressure of carbon monoxide the operating catalytic cycle involves most probably [$Co_2(CO)_7$] and [$Co_2(CO)_7(CHCO_2Et)$] (**1**), whereas at a low pressure of carbon monoxide [$Co_2(CO)_6$-($CHCO_2Et$)] and [$Co_2(CO)_6(CHCO_2Et)_2$] (**2**) are the working catalytic species. In accord with the observed CO dependence of the catalytic reaction, the bottleneck in the catalytic reaction in the low-pressure range might be the rate-determining reaction of the intermediary complex **2** with carbon monoxide, whereas in the high-pressure range the formation of the intermediary complex **1** might be the rate-determining step. In agreement with experiments, computational studies revealed that the *trans* isomer of TBL (**TBL1**) is the preferred product both kinetically and thermodynamically. In contrast with the analogous reactions described in the literature it can be concluded that in the case of (ethoxycarbonyl)ketene the noncyclic intermediate of the two-step reaction is of a covalent rather than a zwitterionic character.

Experimental Section

General: Handling of the carbonylcobalt complexes was carried out in dry (P_4O_{10}) and deoxygenated (BTS contact, room temp.) argon or carbon monoxide by utilizing standard Schlenk techniques.[17] Solvents were dried and distilled under argon according to standard procedures.[18] IR spectra were recorded with a Thermo Nicolet Avatar 330 FTIR spectrometer by using 0.00265, 0.00765, 0.02095, or 0.05097 cm CaF_2 solution cells calibrated by the interference method.[19] Gas chromatographic analyses were performed with an HP 5890D instrument with FID by using a 30 m, 0.32 mm i.d., 0.25 μm SPB 1 column. The GC/MS analyses were performed with an Agilent 6890N instrument equipped with a mass-selective detector working at 70 eV and by using a 30 m, 0.25 mm i.d., 0.25 μm SPB 5 column. TLC tests were performed on Silica $60F_{254}$ plates (Merck, Fluka), and the R_f values refer to tests with ethyl acetate/hexanes (1:3) or dichloromethane. Flash chromatography[20] was carried out by using Kieselgel (200–400 mesh, 60 Å, Sigma–Aldrich) with ethyl acetate/hexanes (1:3) or dichloromethane as the eluent. ^1H NMR spectra were recorded with a Bruker 400 MHz spectrometer by using $CDCl_3$ as the solvent. Chemical shifts δ are reported in ppm relative to $CHCl_3$ (δ =5.24 ppm). ^{13}C NMR spectra were recorded with a Bruker 400 MHz spectrometer at 100 MHz by using CD_2Cl_2 as the solvent. Chemical shifts δ are reported in ppm relative to CH_2Cl_2 (δ =53.10 ppm). Microanalyses were performed by using a CHNS-O EA1108 Elemental Analyser (Carlo Erba). Octacarbonyldicobalt was prepared according to a literature procedure[23] and was twice recrystallized under carbon monoxide, first from dichloromethane and then from *n*-heptane. X-ray crystal structure determination: Intensity data were collected with a Rigaku R-axis Rapid IP diffractometer at ambient temperature with Mo-K_α radiation (λ = 0.7107 Å); the structure was solved by direct methods[21] and refined by full-matrix least squares[22] against F^2. CCDC-713051 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Preparation of *N*-*tert*-Butyl-*trans*-α-ethoxycarbonyl-β-phenyl-β-lactam: A solution of ethyl diazoacetate (0.106 mL, 1.0 mmol) and *N*-*tert*-butylbenzaldimine (0178 mL, 1.0 mmol) in CH_2Cl_2 (5.0 mL) and an open glass insert loaded with [$Co_2(CO)_8$] (17.1 mg, 0.05 mmol) was placed under carbon monoxide into a stainless-steel autoclave (total capacity 20 mL) and pressurized at room temperature with CO to 75 bar pressure. After shaking at 10 °C for 24 h, the pressure was slowly released. The IR spectrum of the brown solution showed weak bands of various carbonylcobalt complexes in the range of 1800–2100 cm^{-1}, very strong bands of *N*-*tert*-butyl-*trans*-α-ethoxycarbonyl-β-phenyl-β-lactam at 1756 and 1728 cm^{-1} (corresponding to 90% yield) and very weak bands of unreacted *N*-*tert*-butylbenzaldimine at 1640 and 1580 cm^{-1}. Gas chromatographic analyses with *n*-octane and *n*-hexadecane as internal references showed the presence of benzaldehyde (2%), *N*-*tert*-butylbenzaldimine (4%), and *N*-*tert*-butyl-*trans*-α-ethoxycarbonyl-β-phenyl-β-lactam (95%, based on the starting *N*-*tert*-butylbenzaldimine). TLC analyses showed that the *N*-*tert*-butyl-*trans*-α-ethoxycarbonyl-β-phenyl-β-lactam product separates well giving an isolated spot at R_f = 0.51 with ethyl acetate/hexanes (1:3) as eluent. The solvent from the crude reaction mixture was removed under vacuum, and the brown oily residue was subjected to flash chromatography on Kieselgel (200–400 mesh, 60 Å, i.d. 1 cm, height 45 cm) with ethyl acetate/hexanes (1:3) (60 mL) as the eluent. *N*-*tert*-Butyl-*trans*-α-ethoxycarbonyl-β-phenyl-β-lactam was obtained from the fractions after concentration in vacuo as a white crystalline solid (95.1 mg, 0.345 mmol, 34.5% isolated yield). M.p. 82 °C. $C_{16}H_{21}NO_3$ (275.34): calcd. C 69.79, H 7.69, N 5.09; found C 68.76, H 8.34, N 5.21. IR (CH_2Cl_2): $\tilde{\nu}$ (ε_M) = 1756 (1295), 1728 cm^{-1} (645 cm^2/mmol). ^1H NMR ($CDCl_3$): δ = 1.27 (s, 9 H,

CH_3), 1.29 (t, J_{HH} = 7.1 Hz, 3 H, CH_3), 3.67 (d, J_{HH} = 2.2 Hz, 1 H, CH), 4.21 (dq, J_{HH} = 2.2, 7.1 Hz, 2 H, CH_2), 4.82 (d, J_{HH} = 2.2 Hz, 1 H, CH), 7.3–7.42 (m, 5 H, Ph) ppm. ^{13}C NMR ($CDCl_3$): δ = 14.1 (CH_3), 28.0 [$C(CH_3)_3$], 55.1 [$C(CH_3)_3$], 56.4 (C_6H_5CH), 61.7 (CH_2), 62.4 (EtO_2CCH), 126.6 (*o*-C_6H_5), 128.7 (*p*-C_6H_5), 128.9 (*m*-C_6H_5), 139.1 (*ipso*-C_6H_5), 162.1 (N-CO), 167.1 (EtO-*C*O) ppm. The NMR spectra are identical to those in the literature.[15] GC/MS: *m*/*z* (%) = 275 (0.28) $[M]^+$, 176 (65), 148 (26), 131 (100), 103 (25).

Preparation of *N*-Benzyl-*trans*-α-ethoxycarbonyl-β-phenyl-β-lactam: By using *N*-benzylbenzaldimine (0190 mL, 1.0 mmol) in the above procedure the IR spectrum of the crude reaction product showed weak bands of various carbonylcobalt complexes in the range of 1800–2100 cm^{-1}, strong bands of *N*-benzyl-*trans*-α-ethoxycarbonyl-β-phenyl-β-lactam at 1767 and 1731 cm^{-1} (corresponding to a 32% yield), and very weak bands of unreacted *N*-benzylbenzaldimine at 1644, 1600, and 1580 cm^{-1}. Gas chromatographic analyses with *n*-hexadecane as the internal reference showed the presence of benzaldehyde (9%), *N*-benzylbenzaldimine (14%), and *N*-benzyl-*trans*-α-ethoxycarbonyl-β-phenyl-β-lactam (37%, based on the starting *N*-*tert*-butylbenzaldimine). TLC analyses showed that the *N*-benzyl-*trans*-α-ethoxycarbonyl-β-phenyl-β-lactam product separates well giving an isolated spot at R_f = 0.23 with dichloromethane. Flash chromatography was performed on Kieselgel (200–400 mesh, 60 Å, i.d. 1 cm, height 45 cm) with dichloromethane (190 mL) as the eluent. *N*-Benzyl-*trans*-α-ethoxycarbonyl-β-phenyl-β-lactam was obtained from the fractions after concentration in vacuo as a colorless oil (38.4 mg, 0.124 mmol, 13% isolated yield). IR (CH_2Cl_2): $\tilde{\nu}$ (ε_M) = 1767 (856), 1731 cm^{-1} (365 cm^2/mmol). ^1H NMR ($CDCl_3$): δ = 1.28 (t, J_{HH} = 7.1 Hz, 3 H, CH_3), 3.80 (d, J_{HH} = 15.3 Hz, 1 H, CH_2Ph), 3.89 (d, J_{HH} = 1.7 Hz, 1 H, CH), 4.22 (dq, J_{HH} = 2.1, 7.1 Hz, 2 H, CH_2), 4.68 (d, J_{HH} = 2.0 Hz, 1 H, CH), 4.85 (d, J_{HH} = 15.3 Hz, 1 H, CH_2Ph), 7.1–7.4 (m, 10 H, Ph) ppm. ^{13}C NMR ($CDCl_3$): δ = 14.1 (CH_3), 44.7 (*C*H_2Ph), 56.9 (CH), 61.7, (CH_2), 63.4 (CH), 126.7 and 127.8 (*o*-C_6H_5), 128.2 and 128.7 (*p*-C_6H_5), 129.0, 129.1 (*m*-C_6H_5), 134.6, 135.9 (*ipso*-C_6H_5), 162.3 (N-CO), 166.7 (EtO-*C*O) ppm. Both the ^1H and the ^{13}C NMR spectra are in accord with the spectra of the known *N*-benzyl-*trans*-α-ethoxycarbonyl-β-phenyl-β-lactam.[24]

Preparation of *N*-Methyl-*trans*-α-ethoxycarbonyl-β-phenyl-β-lactam: By using *N*-methylbenzaldimine (0.124 mL, 1.0 mmol) in the above procedure the IR spectrum of the crude reaction product showed weak bands of $[Co_2(CO)_8]$ at 2112, 2072, 2042, 2021, and 1843 cm^{-1}, weak bands of benzaldehyde at 1702, 1597, and 1583 cm^{-1}, and strong bands of *N*-methyl-*trans*-α-ethoxycarbonyl-β-phenyl-β-lactam at 1738 and 1652 cm^{-1} (corresponding to >70% yield). TLC analyses showed that the *N*-methyl-*trans*-α-ethoxycarbonyl-β-phenyl-β-lactam product separates well giving an isolated spot at R_f = 0.62 with dichloromethane/ethyl acetate (1:1) on Al_2O_3. Flash chromatography was performed on Al_2O_3 (Brockman I, neutral, i.d. 1 cm, height 45 cm) with dichloromethane/ethyl acetate (1:1) (130 mL) as the eluent. *N*-Methyl-*trans*-α-ethoxycarbonyl-β-phenyl-β-lactam was obtained from the fractions after concentration in vacuo as a colorless oil (25.1 mg, 0.108 mmol, 11% isolated yield). IR (CH_2Cl_2): $\tilde{\nu}$ (ε_M) = 1733 (270), 1648 cm^{-1} (493 cm^2/mmol). ^1H NMR ($CDCl_3$): δ = 1.16 (t, J_{HH} = 7.1 Hz, 3 H, CH_3), 2.20 (s, 3 H, NCH_3), 3.98 (d, J_{HH} = 1.2 Hz, 1 H, CH), 4.14 (dq, J_{HH} = 2.1, 7.1 Hz, 2 H, CH_2), 4.45 (d, J_{HH} = 1.2 Hz, 1 H, CH), 7.15–7.42 (m, 5 H, Ph) ppm. ^{13}C NMR ($CDCl_3$): δ = 14.0 (*C*H_3CH_2), 36.5 (CH_3N), 50.2 (CH), 58.1 (CH), 61.7, (CH_2), 127.9 (*o*-C_6H_5), 128.0 (*p*-C_6H_5), 128.5 (*m*-C_6H_5), 137.1 (*ipso*-C_6H_5), 165.0 (N-CO), 169.6 (EtO-*C*O) ppm. Both the ^1H and the ^{13}C NMR spectra are similar to the spectra of the known *N*-methyl-*trans*-α-methoxycarbonyl-β-phenyl-β-lactam.[25]

Preparation of Ethyl 3-[(Diphenylmethylene)amino]-3-oxopropanoate ($EtO_2CCH_2C(=O)N=CPh_2$): By using diphenyl ketimine (0.502 mL, 3.0 mmol), ethyl diazoacetate (0.315 mL, 3.0 mmol), and $[Co_2(CO)_8]$ (10.3 mg, 0.03 mmol) in the above procedure the IR spectrum of the crude reaction product showed strong bands of $EtO_2CCH_2C(=O)N=CPh_2$ at 1740, 1691, and 1635 cm^{-1} and weak bands at 1599 and 1579 cm^{-1}. TLC analyses showed that the $EtO_2CCH_2C(=O)N=CPh_2$ product separates well giving an isolated spot at R_f = 0.40 with ethyl acetate/hexanes (1:3) as eluent. Separation of 1/10 of the crude reaction mixture on preparative plates gave $EtO_2CCH_2C(=O)N=CPh_2$ (47.3, 0.16 mmol, 53% yield) as a yellow oil. The IR spectrum in CH_2Cl_2 is identical to that of the crude reaction mixture: $\tilde{\nu}$ (ε_M) = 1740 (411), 1691 (273), 1635 (260) 1599 (49) 1579 cm^{-1} (79 cm^2/mmol). $C_{18}H_{17}NO_3$ (295.33): calcd. C 73.20, H 5.80, N 4.74; found C 72.11, H 5.89, N 4.34. ^1H NMR ($CDCl_3$): δ = 1.17 (t, J_{HH} = 7.0 Hz, 3 H, CH_3), 3.25 (s, CH_2), 4.10 (q, J_{HH} = 7.0 Hz, 2 H, CH_2), 7.4–7.6 (m, 10 H, Ph) ppm. ^{13}C NMR ($CDCl_3$): δ = 14.0 (CH_3), 48.2 (CH_2), 61.3 (CH_2), 62.4 (EtO_2CCH), 128.2, 128.4, 129.4, 130.0 131.3, 136.0, 166.4, 166.5, 179.0 ppm.

Computational Details: All the geometries were calculated without any symmetry constraints by using the gradient-corrected exchange functional developed by Perdew, Burke and Ernzerhof in combination with a correlation functional also developed by the same authors and denoted as PBEPBE.[26] The 6-31G(d,p) basis set[27] was employed throughout this study. For all stationary points the Hessian was evaluated to characterize the genuine minima (no imaginary frequency) and the transition states (1 imaginary frequency). Thermal correction for the Gibbs free energy (at 298 K) has been estimated on the basis of the frequency calculations at the optimization level. Intrinsic reaction coordinate (IRC) analyses[28] were carried out throughout the reaction pathways to confirm that the stationary points are smoothly connected to each other. Natural population and natural bond orbital (NBO) analyses[29] were performed at the same level of theory as that used for geometry optimization. For the calculations the PC GAMESS 7.1.C[30] software was used. QTAIM (quantum theory of atoms in molecules) analyses of the wavefunctions were carried out with the XAIM software to investigate the structures of the electron densities of the optimized structures.[31]

Supporting Information (see footnote on the first page of this article): Bond lengths and bond and torsion angles for *N*-*tert*-butyl-*trans*-α-ethoxycarbonyl-β-phenyl-β-lactam.

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