The Paternò-Büchi Reaction

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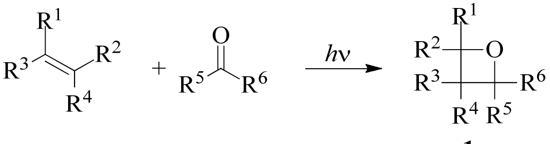
CHAPTER ONE

INTRODUCTION

The Paternò–Büchi Reaction

The Paternò–Büchi reaction originally referred to a [2+2]-photocycloaddition between an alkene and the excited state of a carbonyl compound to give the corresponding oxetane **1** (Scheme 1). As outlined in this chapter, this reaction can be further generalized as a photochemical reaction between an unsaturated compound and a compound with a carbon–heteroatom double bond, mainly aldehydes and ketones. Also, the notion that the reaction occurs through interaction of the excited state of the carbonyl compound with the ground state of the alkene does not always hold. Examples of the converse situation are also presented where the excited state of the alkene reacts with a carbonyl compound in its ground state [1].



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Scheme 1

The Paternò–Büchi reaction represents a method for preparing small, heterocyclic rings, some of which are contained in natural and biologically active compounds (Figure 1). Among such compounds are paclitaxel (**2**), an antitumor drug [2] isolated in *T. brevifolia* [3], merrilactone (**3**) (isolated in *Illicium merrillianum* and showing neurotrophic activity) [4], and oxetanocin (**4**) (isolated in *Bacillus megaterium* NK84-0218 [5] and possessing anti-HIV activity) [6]. In addition, thromboxane A_2 (**5**), mitrephorone A (**6**) (isolated in *Mitrephora Glabra Scheff* and possessing anticancer activity) [7], and maoecrystal I (**7**) (isolated in *Isidon japonicus* and showing cytotoxic activity) [8], all contain oxetane rings.

Furthermore, oxetane **8** displays several biological activities [9], dictyoxetane (**9**) (isolated in *Dictyoadatichotoma algae*) [10], oxetin (**10**) (isolated from the fermentation broth of *Streptomyces* sp.OM-2317) [9a], bradyoxetin (**11**) (a bioactive compound isolated from *Bradyrhizobium japonicum*) [11], laureatin (**12**) (isolated from *Laurentia nipponica* and showing larvicidal activity) [12], parthoxetine (**13**) (isolated from *Parthenium fruticosum*) [13], and a sesquiterpene dimer (**14**) (isolated from *Xylopia aromatic*) [14] all contain an oxetane ring.

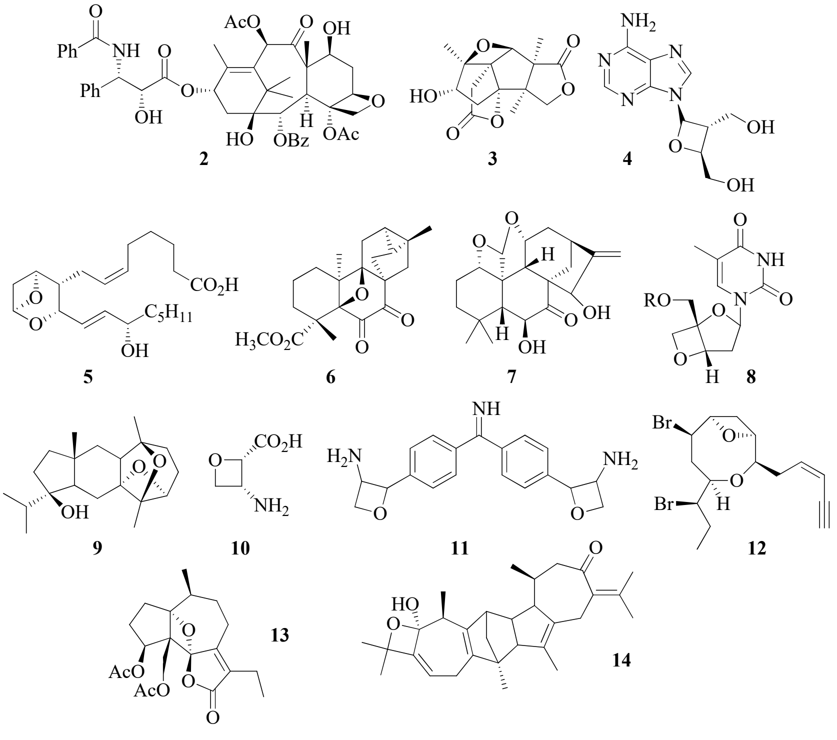


Figure 1. Bioactive compounds containing the oxetane ring.

It is noteworthy that several patents for new drugs containing an oxetane ring have been registered [15]. Interestingly, only compound **4** and oxetin (**10**) have been synthesized to date using a Paternò–Büchi reaction. However, the compounds reported in Figure 1 represent future challenges for synthetic applications of this photochemical reaction.

Several reviews have previously been published covering different aspects of the Paternò–Büchi reaction [16].

Historical Background

The exact origin of the Paternò–Büchi reaction is not easily discerned because the discovery of this process involved a controversy between Ciamician and Paternò [17]. In 1909, Paternò, while studying the photochemical reaction of benzaldehyde with amylene (2-methyl-2-butene), showed that the corresponding [2+2]-cycloadduct was formed [18]. It was not possible for Paternò to distinguish between the two possible constitutional isomers of the oxetane and all of the possible stereoisomers could not be determined.

In 1909, Ciamician also reported a reaction where the same type of photochemistry was described involving the photoreaction of safrole and isosafrole with benzaldehyde and claimed the formation of addition products [19]. However, structures were not provided for the photoproducts.

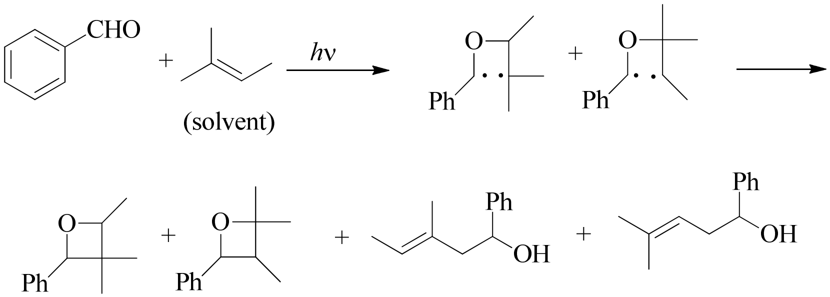
Despite its potential, the Paternò–Büchi reaction was essentially forgotten. In 1949, it was reported that aliphatic aldehydes (ethanal) irradiated in a quartz tube in the presence of an alkene (1-octene) gave, after distillation of the crude product, little of the corresponding ketone (2-decanone). However, no oxetane product was isolated [20]. It was only in 1954 that Büchi repeated the reaction described by Paternò, and identified the oxetane product [21].

CHAPTER TWO

MECHANISM AND STEREOCHEMISTRY

Mechanism

Since the first reports on this subject, the reaction of benzaldehyde with 2-methyl-2-butene was suggested to involve the triplet state of the carbonyl compound reacting with the alkene ground state to form the most stable biradical intermediate (Scheme 2) [21]. However, the photoisomerization of 5-hexen-2-one (see below) and the absence of any effects due to the presence of oxygen allow one to speculate that a triplet state is not involved in this reaction [22].



15 **16** (15%)

1.6:1 (64%)

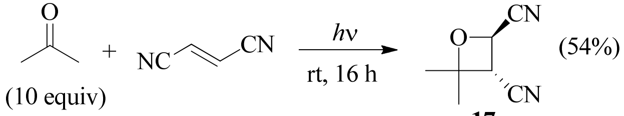
Scheme 2

In the reactions of biaryl ketones, the cycloaddition occurs only with carbonyl compounds that can access n→π* triplet states [23]. The reaction of benzaldehyde with 2-methyl-2-butene gives mainly the corresponding oxetanes (64%) along with a mixture of 1-phenyl-3-methyl-3-pentenyl-1-ol and 1-phenyl-4-methyl-3-penten-1-ol (in a combined yield of 15%) as well as some dihydrobenzoin (11%) [24]. The oxetane mixture is mainly compound **15**, but some of the isomer **16** is also present (**15**/**16** = 1.6:1) (Scheme 2). The relative stereochemistry of these products has not been determined.

The quantum yield for the formation of the oxetanes **15** and **16** is 0.45 ± 0.05. Benzophenone and acetophenone react with 2-methyl-2-butene to give the corresponding oxetanes higher regioselectivity (>90%) than for benzaldehyde. The quantum yields for oxetane formation are similar to those obtained with benzaldehyde when benzophenone is the carbonyl compound, while acetophenone gives a lower value (0.1). All of these carbonyl compounds can access an n→π* triplet state. 1- and 2-Naphthaldehyde give the corresponding oxetanes (70%) when reacting with 2-methyl-2-butene. The regioisomeric ratio between the two possible oxetanes is 3:2 in favor of that corresponding to **15** and the quantum yields are 0.05. 2-Naphthyl phenyl ketone reacts with 2-methyl-2-butene to give the oxetanes in 62% overall yield with a regioselectivity similar to that shown by benzophenone and with a quantum yield of 0.005. 1- and 2-Acetylnaphthalene do not react with all the alkenes tested. Naphthaldehyde and naphthyl methyl ketone have a π,π* triplet state. 9-Anthraldehyde also shows the involvement of a π→π* triplet state. However, it gave a Paternò–Büchi reaction when irradiated in the presence of 2-methyl-2-butene. To justify the reactivity of this compound, the internal conversion between the n→π* and π→π* triplet states could be lower than that for the naphthaldehydes, leading to a higher reactivity. The n→π* triplet state of 9-anthraldehyde reacts with 2-methyl-2-butene, giving the corresponding oxetane with high regioselectivity, giving only the regioisomer derived from the most stable biradical intermediate.

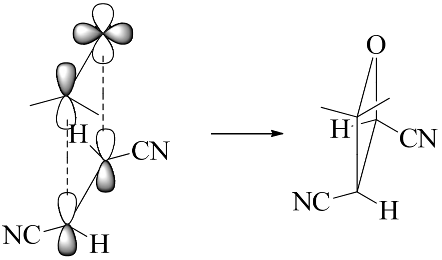
The triplet excited state of the carbonyl compound can undergo an electron transfer process with an alkene to provide the corresponding radical-ion pair. This process occurs with electron-rich alkenes and carbonyl compounds in polar solvents [25].

Kinetic Data. Some aliphatic ketones such as acetone react with (*E*)-1,2-dicyanoethene, giving the corresponding oxetanes in good yields (54%) while maintaining the configuration of the alkene in the product (Scheme 3) [26]. The fluorescence of acetone is quenched by the addition of dicyanoethene.



17

Scheme 3



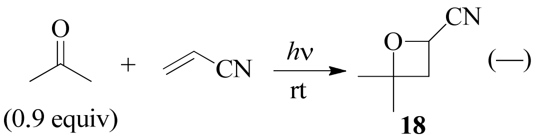
Scheme 4

Oxetanes are also obtained in the reaction of the same aliphatic ketones in the presence of maleic anhydride in good yields (67%). Triplet quenchers (1,3-pentadiene, 2,5-dimethyl-2,4-hexadiene, and naphthalene) do not inhibit the reactions. Thus, the reactions seem to occur from a singlet excited n→π* state either through a concerted process or through a rapid closure of an intermediate biradical species.

The formation of **17** is only slightly affected by the addition of 1,3-pentadiene (a triplet quencher), and the reaction is quite inefficient ($\phi = 0.026$–0.054). The Stern–Volmer plot of the formation of **17** as a function of (*E*)-1,2-dicyanoethene concentration is in agreement with the formation of an exciplex intermediate.

The cycloaddition occurs through a concerted or a "quasi-concerted" attack of the nucleophilic π system of the singlet n→π* state of acetone on the π system of the ground state of 1,2-dicyanoethene (Scheme 4). The observed stereospecificity demands that bond formation is faster than bond rotation.

In the Paternò–Büchi reaction between acetone and acrylonitrile, only oxetane **18** is formed (Scheme 5) [27]. This observation is more consistent with an addition of the higher electron-density carbon lobe of the LSOMO orbital of the ketone to the most electron deficient end of the acrylonitrile double bond. The reaction occurs *via* the formation of an exciplex.

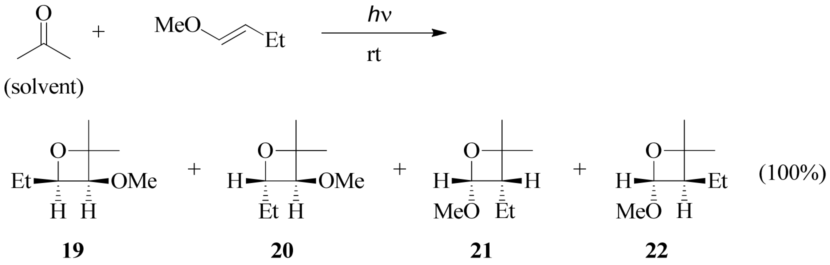


18

Scheme 5

Kinetic data confirms the involvement of the triplet state in the Paternò-Büchi reaction of benzaldehyde with 2,3-dimethyl-2-butene. The overall reaction follows 0^{th}-order kinetics. A Stern–Volmer plot of the reaction taking place in the presence of piperylene shows that the reaction occurs via a single reactive state (n→π* triplet) with a quantum yield of 0.55 [28]. Furthermore, when 9-anthraldehyde is used as a starting material, a quantum yield of 0.024 is found. A Stern–Volmer plot of the quenching experiment of the reaction between 9-anthraldehyde and 2,3-dimethyl-2-butene in the presence of di-*tert*-butyl nitroxide indicates that there are two different reactive species. The energy gap between the n→π* singlet state and the low-lying triplet state of anthraldehyde is considerably larger than that of benzaldehyde, and the rate of radiationless transition between these two states may become sufficiently slow to be competitive with the rate of singlet state reaction. In the case of anthraldehyde, both states could be responsible for the reaction.

In the reaction between acetone and (*E*)-1-methoxy-1-butene, an electron rich alkene, the ratio of **19/20** and **21/22** is found to be dependent on the initial concentration of the alkene (Scheme 6) [29]. Compounds **21** and **22** are removed from the reaction mixture through acid hydrolysis. The ratio of **19/20** extrapolated to zero concentration of the alkene is 1.06, whereas at high concentration of the alkene the ratio is *ca.* 2.5. At low concentration of the alkene, a mechanism involving a total loss of the configurational identity of the alkene seems to be operative, whereas at high concentration of the alkene, some preservation of the configuration is observed, probably indicating a different mechanism.



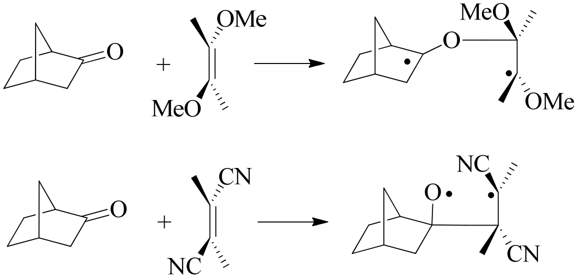
Scheme 6

The amounts of **19** and **20** are reduced in the presence of variable amounts of piperylene (quencher of triplet acetone), with the observation that quenching is not linearly related to concentration. Thus, the formation of **19** and **20** are not inhibited at the same rate. At high concentrations of piperylene, the only mechanistic pathway available is the addition from the singlet excited state of acetone.

These reactivity patterns can be explained by assuming that both the singlet and triplet state of acetone undergo the [2+2] cycloaddition. The formation of singlet and triplet biradical intermediates are proposed. The singlet biradical intermediates (a mechanism operative at high alkene concentration) retain the information of the configuration of the alkene (cyclizing rapidly to the oxetane). Triplet biradicals are expected to have a greater lifetime, allowing rotation of the carbon atom bearing the free-radical site.

Benzophenone phosphorescence is quenched by the addition of enol ethers [30]. The k_q and the energy of the HOMO of the enol ethers are correlated. Quenching data shows that the primary step in the quenching process is π-complex formation and not bond formation. Partial charge donation from the olefin to the ketone produces the initial exciplex. These results are relevant because they show that the formation of an exciplex is not limited to the processes involving the first excited singlet state, but also in those where triplet states are involved. Several articles have appeared on the kinetic behavior of the reaction [31].

A general way to rationalize the observed regioselectivity in the addition of (*E*)-1,2-dicyanoethene and (*E*)-1,2-dimethoxyethene to norbornanone derivatives has been proposed. In the case of electron-rich substrates, the reaction occurs through an attack of the carbonyl *n* orbital on the olefin in a perpendicular relationship. When using electron-poor alkenes, the attack occurs via a parallel conformation, allowing the formation of the corresponding C-C-C-O·biradical (Scheme 7) [32].



Scheme 7

Spectroscopic Studies. Spectroscopic studies of the Paternò-Büchi reactions allowed to determines evidences on the formation of the 1,4-biradical intermediate, when it is present. Furthermore, they can confirm the presence of radical ions due to the presence of an electron transfer mechanism. The mechanism of the reaction between quinones and quadricyclane or norbornadiene has also been studied using CIDNP measurements. The results are in agreement with the formation of a biradical intermediate [33]. CIDNP experiments were also performed to characterize the biradical intermediate in the reaction between acetylene and quinone [34].

Benzophenone shows a transient absorption due to the triplet at 525 nm. In the presence of dioxene, the transient triplet spectrum is quenched with $\tau_{½}$ = 175 ± 25 ps, and a new absorption appears at 535 nm [35]. This transient absorption has been identified as the triplet biradical. In fact, the triplet state of benzophenone is quenched by charge transfer to form a contact ion pair that rapidly collapses to give the biradical. The picosecond–resolved spectrum of the biradical intermediate has also been reported [36].

The triplet state of vinylformyl[2.2]paracyclophane derivatives has been studied using femtosecond time-resolved photoelectron spectroscopy [37]. Additionally, transient vibrational spectroscopy has been used to follow the decay of the biradical intermediate [38].

In the reaction between biacetyl and an electron-rich olefin, electron transfer accounts for the observed reactivity. The ESR spectra of the radical cation and the radical anion can be observed [39]. The radical ion arising from an electron transfer process has also been observed in another related study [40].

Calculations. A study on the Paternò–Büchi reaction has been performed with ab initio calculations at the STO-3G level using Gaussian 70 [41]. The alkene is assumed to approach the ketone in such a manner that its π orbitals lie in the plane defined by the ketone carbonyl group. In the reaction between formaldehyde and ethylene, the surface crossing is shown to occur at a CO bond distance of approximately 1.9 Å. Activation energies of 24 and 29 kcal mol^{-1} are required for the excited reactant to leave this well and reach the biradical product. The effects of substituents can be deduced by tracing the molecular energy level variations and orbital coefficient changes that are induced by the substituents. Substituents can be broadly grouped into electron-donating, electron-attracting, and conjugative categories. Electron-donating substituents raise the molecular energy levels. Electron attracting substituents lower all energy levels. The energy of the n-orbital [F(n)] is changed only by a second-order inductive effect. In general, conjugative substituents lead to a spreading of π energy levels, with the highest occupied π level raised, and the lowest vacant level being lowered in energy. In addition, a much lower electron density is found at the reactive sites in either the π or π* orbitals. In this way, an electron-donating group on the alkene favors the formation of a 1,4-biradical intermediate, whereas an electron-withdrawing group on the alkene favors a concerted mechanism [42].

Theoretical calculations show that in the reaction of benzoquinone with 2,3-dimethyl-2-butene to give the corresponding oxetane, an n→π* triplet state is involved [43]. In contrast, the tetramethyl derivative, duroquinone, gives the corresponding cyclobutane. In this case, calculations show the lowest triplet state is a π→π* triplet state. In the case of naphthoquinone, which gives both products, calculations show that both the n→π* triplet and the π→π* triplet are close in energy.

A description of the Paternò-Büchi reaction using the Woodward–Hofmann rules has been reported [44]. The effect of spin-orbit coupling in oxygen-containing biradicals was studied [45]. A conformational analysis of the biradical intermediate shows that the previously postulated conformational dependence of spin-orbit coupling in the biradical based on the "90-degree rule" is not satisfactory for quantitative estimates [46].

In the reaction between 1,4-dioxene and benzaldehyde, theoretical calculations indicate that the only transition able to give the observed transient absorption is that from the LSOMO to the LUMO (549 nm); the same result is obtained for the reaction between furan and benzaldehyde [16af].

The regioselectivity of the reaction can be explained invoking hard-soft acid and base theory, and this approach is in agreement with the experimental results [47]. Another way to explain the regiochemistry of the Paternò–Büchi reaction considers that atoms arrange themselves so that the obtained product reaches the minimum electrophilicity, that is considered the driving force in the reaction [48].

Another theoretical study of the Paternò–Büchi reaction shows that there are two conical intersection points located near the C-C and C-O bonded biradical regions of the ground state. These two conical intersections support a mechanism in which the decay from the excited state is accompanied by a geometric rotation of the terminal group, in the case of C-O attack, and by an orbital rotation at the oxygen center, in the case of C-C attack. Furthermore, for C-O attack, the triplet surface must cross the singlet to reach a biradicaloid minimum. For C-C attack, the triplet biradical minimum is located at the same geometry as the conical intersection between the two singlet states, and the efficiency of the intersystem crossing will be determined by the nature of the spin-orbit coupling. Thus, for the triplet, the reaction path can be predicted by the most stable biradical rule [49].

A CAS SCF geometry optimization using the TZV basis set of the intermediate biradicals shows that the biradical region corresponding to the C-C attack lies about 10 kcal mol^{-1} lower in energy than the C-O region [45]. This result, however, is not in agreement with reported experimental results. An AFIR method has been used to obtain a predictable model for the reaction between formaldehyde and ethene. The reaction product is obtained by minimizing the AFIR function. The O-C bond formation is more favorable than the C-C bond formation, and the oxygen atom forms a bond with the less bulky site of the alkene [50]. The same behavior has been observed by using the atomic zero steric potential (AZSP). AZSP can be considered as a measure of charge heterogeneity [51].

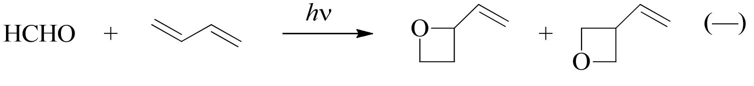
An electron transfer process can occur when the HOMO of the alkene is very near the LSOMO of the excited carbonyl compound [52].

Regioselectivity and Diastereoselectivity

The reaction of acetaldehyde with acrylonitrile is considered to be a concerted [2 + 2] cycloaddition in which the regioselectivity is controlled by the dipole-dipole orientation. Another hypothesis involves the formation of an oriented exciplex intermediate able to give only one possible constitutionally isomeric singlet biradical [31j].

The regioselectivity of the reaction of carbonyl compounds with furan derivatives is explained on the basis of the relative stability of the biradical intermediates [53]. The regioselectivity of the attack is postulated to depend on the frontier orbital coefficients [47].

The minimum electrophilicity principle $[\omega' \approx (\varepsilon_L - \varepsilon_H)^2/4(\varepsilon_L - \varepsilon_H)]$, wherein ω' is the electrophilicity, ε_L is the energy of LUMO, and ε_H is the energy of the HOMO, correctly predicts the most stable constitutional isomer formed in the reaction. This is based on the assumption that there is a tendency for atoms to arrange themselves such that the observed product reaches the minimum electrophilicity [48]. Thus, in the theorical reaction between formaldehyde and 1,3-butadiene, two possible constitutional isomers can be obtained (Scheme 8). The electrophilicity values are 0.21210 for the first oxetane product and 0.20269 for the second one. Finally, the electron density on the reactive carbon atoms is assumed to determine the regioselectivity of the reaction [54].

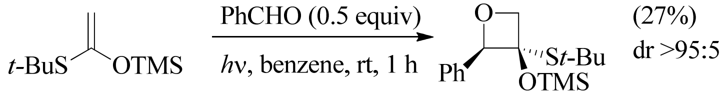


Scheme 8

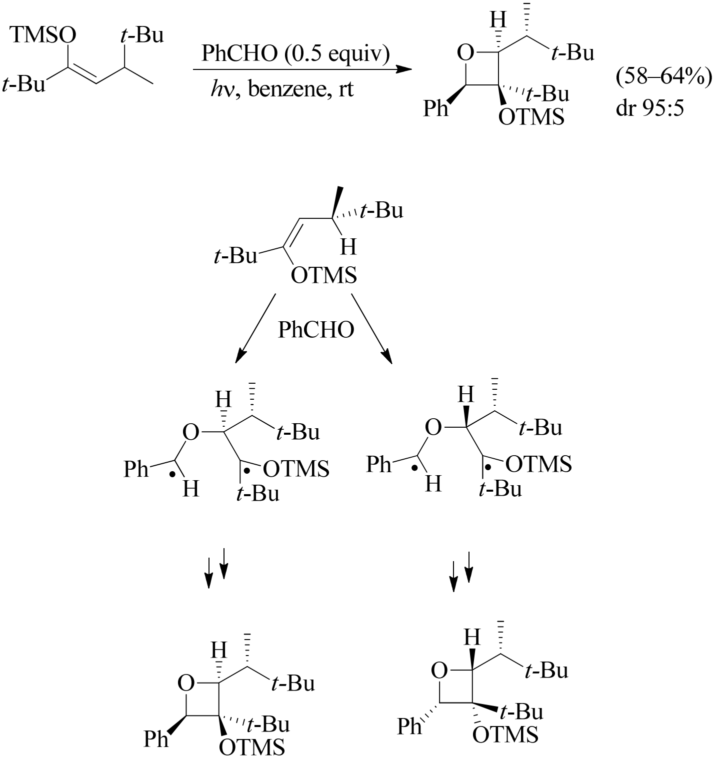
The stereoselectivity of the Paternò–Büchi reaction has attracted the attention of several researchers. Stereoselectivity in the alkenes bearing electron-withdrawing or electron-donating substituents are interpreted on the basis of the main interactions between the orbitals in the excited state [55].

3-(Silyloxy)oxetanes are successfully prepared from silyl enol ethers containing additional carbon-chlorine, carbon-silicon, or carbon-sulfur bonds (Scheme 9) [16ah, 56]. Ethers, esters, and simple alkenes are compatible with the reaction. When a β-alkyl-substituted silyl enol ether is used, a *trans* relationship between the C–2 and C-3 substituents in the oxetanes is observed.

This result does not depend on the geometry of the alkene. The products are obtained with high diastereoselectivity (dr 87:13 – 98:3) [57].



Scheme 9

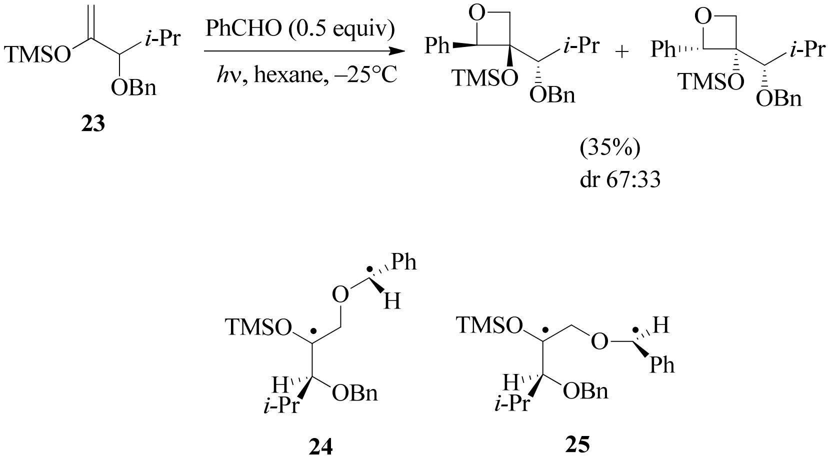


Scheme 10

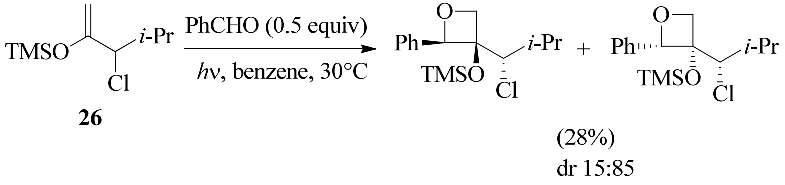
In the triplet biradical, free rotation leads to the sterically least congested conformation. A further reaction pathway of this species includes intersystem crossing (ISC) and an assumed selection step (cleavage vs. ring closure) at the singlet 1,4-biradical level, which accounts for the high diastereoselectivity at C-2/C-3.

The presence of a stereogenic center in the β-alkyl group induces facial diastereoselectivity. In some cases, high diastereoisomeric ratios are observed (Scheme 10) [58]. The observed diastereoselectivity probably arises because of a conformational preference represented in Scheme 10. This conformation allows the attack by benzaldehyde on the enol ether on the less shielded face [59].

Good diastereoselective results are obtained by using silyl enol ether **23**, which gives the corresponding adducts with a dr of 67:33 (Scheme 11), and compound **26**, giving the adducts with a dr of 15:85 (Scheme 12) [60]. In the former reaction, two conformers of the biradical intermediate can be obtained. Conformer **24** is calculated to be more stable than **25** by 3.11 kcal mol^{-1}) [61].

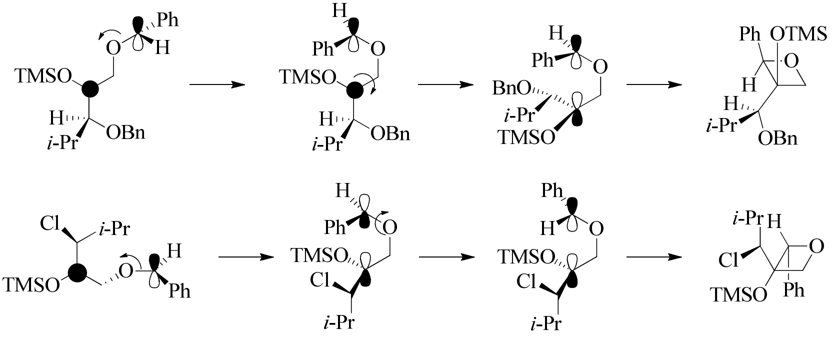


Scheme 11



Scheme 12

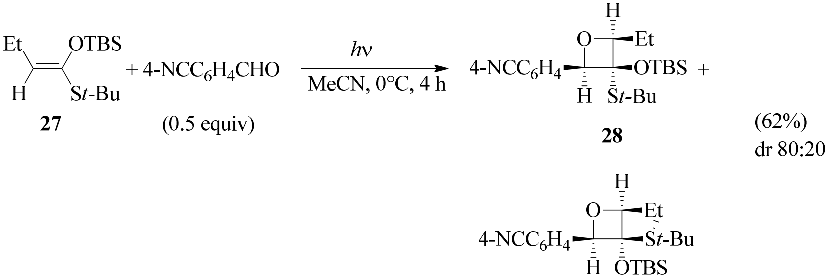
The LSOMO of the biradical **24** is at –0.077 H, while the HSOMO is at –0.073 H. The coupling of the radical carbon atoms gave two new orbitals in the product. The new orbitals are a σ orbital and a σ* one. To obtain the σ orbital, considering the atomic coefficients at the radical carbon atoms on the involved orbitals, the coupling of these carbon atoms can occur only as depicted in Scheme 13, where the in–phase superposition of the *p* orbitals allows the formation of only one stereoisomeric product.



Scheme 13

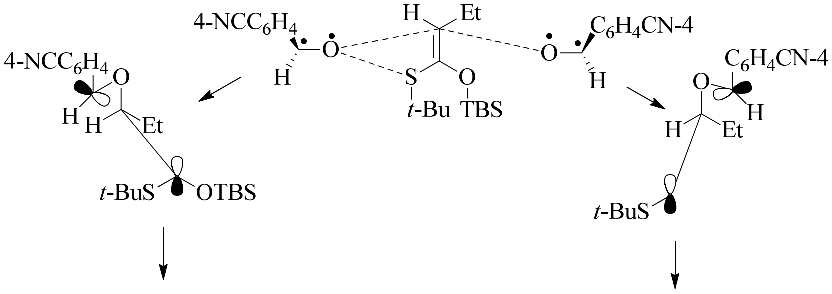
Conformer **24** gives the major stereoisomer observed in the reaction (Scheme 13). The calculations are in agreement with the experimental results, showing that the course of this reaction is strictly frontier orbital controlled. The other biradical conformer (**25**) gives the other diastereoisomer which is observed in the reaction. The observed diastereoisomer ratio (67:33) can be explained by the small difference between the energies of the conformers of the biradical intermediate (3.11 kcal mol^{-1}). To confirm this result, the behavior of **26** has been examined (Scheme 12). In this case, the authors observe an inverse diastereoselectivity [59b]. Also in this case, two conformers of the biradical intermediate are possible. The energy difference between these two conformers is 4.6 kcal mol^{-1}. The coupling between the carbon atoms, considering the atomic coefficients, allow the formation of the observed diastereoisomers, where the most stable conformer of the biradical intermediate is able to give the major observed diastereoisomeric product, while the other conformer of the biradical intermediate can give the minor observed diastereoisomeric product (Scheme 13). The larger diastereoisomeric ratio (85:15) observed in this case is in agreement with the larger energy difference between the conformers of the biradical intermediate.

When silyl O,S-ketene acetal (*E*)-**27**, is used, **28** is obtained as the main product (Scheme 14) [62].



Scheme 14

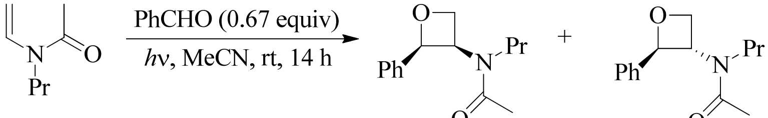
The stereochemical behavior of the reaction of **27** with aromatic carbonyl compounds is explained by considering the ability of the sulfur atom to coordinate the oxygen atom of the carbonyl compound [62]. The presence of such an interaction induces attack of the excited carbonyl compound on the side of the alkene bearing the sulfur atom (Scheme 15). The same regio- and stereoselectivity is observed when silyl O,Se-ketene acetals are used [63].



28

other diastereoisomer

Scheme 15

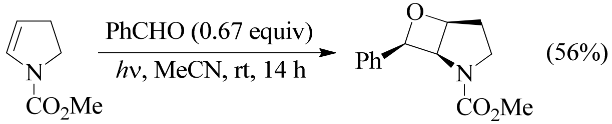


29

(70–71%)
dr 90:10

Scheme 16

Oxetanes are obtained in the Paternò–Büchi reaction of *N*-acyl enamines **29** and **30**. *N*-Acyl derivatives are used to reduce the electron density of enamines without changing the electronic properties of the double bond (σ_{para} of –NH$_2$ group is –0.66, while that of the –NHCOMe substituent is –0.15). These compounds give the corresponding adducts with high regio- and stereoselectivity (Schemes 16 [16o, 64] and 17 [65]). The main product in each case is the thermodynamically less stable isomer [66].

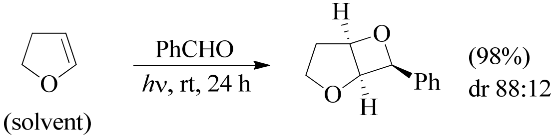


30

Scheme 17

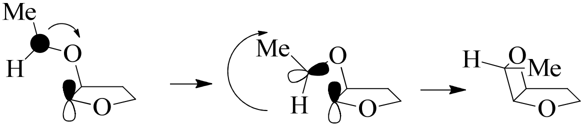
Sometimes, chiral enamine derivatives do not give the corresponding adduct with high diastereoselecti-vity [16r, 67]. For example, (*R*)-phenylethylamine reacts with acetaldehyde in the presence of acetic anhydride to give the corresponding *N*-acylenamine, that is irradiated in the presence of benzaldehyde to give the corresponding *cis*-oxetanes in 2:1 ratio [67].

The Paternò–Büchi reaction of 2,3-dihydrofuran with benzaldehyde shows a significant *endo* stereoselectivity (Scheme 18) [68].



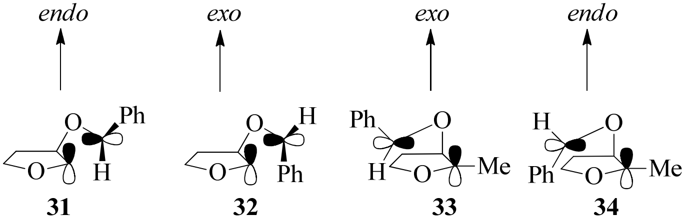
Scheme 18

When acetone is used as the carbonyl compound, the adduct with 2,3-dihydrofuran is obtained in 52% yield as a mixture of two constitutional isomers in a 200:1 isomeric ratio [69]. However, when acetaldehyde is used as the carbonyl compound, the adduct is obtained in 63% yield as a mixture of stereoisomers. The selectivity in this case depends on 2,3-dihydrofuran concentration, involving a switch from a triplet mechanism to a singlet mechanism at higher concentration [16u, 16v, 16z, 68e, 70]. The best interaction between the frontier orbitals is that from the LSOMO of acetaldehyde and the HOMO of 2,3-dihydrofuran [16am]. The atomic coefficients on the olefinic carbon atoms in 2,3-dihydrofuran are –0.26 at C-2 and –0.38 at C-3. The atomic coefficient on the oxygen atom in the LSOMO of singlet excited acetaldehyde is 0.48, while the atomic coefficient at the C-1 of acetaldehyde in the HSOMO is 0.49. The nature of the LUMO of 2,3-dihydrofuran excludes the possibility of a concerted mechanism. The reaction leads to the formation of an extremely reactive singlet biradical. In this case, the oxygen atom of acetaldehyde attacks the C-3 carbon atom in 2,3-dihydrofuran to give the more stable biradical intermediate. The reaction, in this case, allows the formation of only the *exo* isomer. This logical scheme explains the observed reactivity assuming that, when the reaction is performed in a concentrated solution, the excited singlet state will give the *exo* isomer, while the excited triplet state is responsible for the formation of the *endo* isomer. In the triplet state, the main interaction is that between the LSOMO of the triplet state acetaldehyde and the HOMO of the dihydrofuran. This interaction leads to the formation of the corresponding C-C 1,4-biradical intermediate (Scheme 19). The HSOMO on the biradical intermediate is mainly localized on the aromatic ring. The LSOMO is mainly localized on the dihydrofuran ring. Coupling between the radical carbons in these two orbitals to give the new σ orbital is possible only if the *endo* isomer is formed (Scheme 19).



Scheme 19

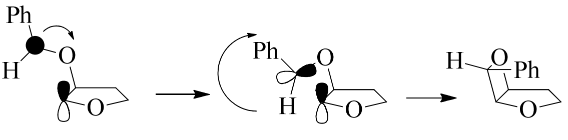
When benzaldehyde is used as the carbonyl component, the reaction with 2,3-dihydrofuran shows good regio- and stereoselectivity. The adducts are isolated with an overall yield of 98% as a >98:2 constitutional isomer mixture with the major isomer obtained as an 88:12 *endo/exo* mixture. The reaction of dihydrofuran with benzaldehyde is the first example where spin-controlled selectivity is observed [16v, 16ae]. In singlet photoreactions, stereoselectivity is often controlled by the optimal geometries for radical-radical combinations. By contrast, in triplet photoreactions, the optimal geometries are those able to favor the intersystem crossing from the triplet excited state to the singlet excited state. The singlet biradicals should be too short-lived to enable rotation about the endocyclic C-O or C-C bonds, and, therefore, conformational memory effects on the stereochemistry are expected. The geometries in the triplet state can be quite different from the former ones because of differences of the spin-orbit coupling (SOC) values. The lifetimes of many triplet biradical intermediates are definitely high enough to enable bond rotations. Therefore, the formation of the thermodynamically favored product can be expected because the radical-radical combination step should not be influenced by the approach geometry. "Memory effects" should be erased because of the relatively long biradical lifetimes. After transition from the triplet to the singlet potential energy surface, immediate product formation is expected. Thus, the intersystem crossing (ISC) proceeds in a concerted fashion with the formation of a new bond or by cleavage of the primarily formed single bond. As a consequence, the stereoselectivity of the Paternò–Büchi reaction is the result of a combination of several rate constants for cyclization versus cleavage reactions.



Scheme 20

Benzaldehyde reacts with 2,3-dihydrofuran in its triplet state and a triplet biradical intermediate is formed. To obtain the oxetane products, intersystem crossing into the singlet manifold is necessary. The most important factor influencing an intersystem crossing for flexible triplet biradicals is spin-orbit coupling. The angle between *p* orbitals at the radical centers is approximately 90° for maximum spin orbit coupling. For the pronounced *endo* selectivity in the reaction between aromatic aldehydes and 2,3-dihydrofuran, the two biradical conformers **31** and **32** can be considered to be responsible, **31** being more populated because of fewer steric interactions (Scheme 20).

When a methyl group at C-2 is present, the increasing *gauche* interactions with the β-alkyloxy substituent lead to a certain concentration of **33** and **34**, with **33** being preferred because of fewer steric interactions. Another explanation for the regio- and stereochemistry proposes that the HSOMO is mainly localized on the aromatic ring and the LSOMO is mainly localized on the dihydrofuran ring [71]. Coupling between the radical carbons in these two orbitals to form a new σ orbital is thus possible only if the *endo* isomer is formed (Scheme 21).



Scheme 21

α- and β-Naphthaldehydes, on the contrary, give high *exo* selectivity in the reaction with 2,3-dihydrofuran [72]. The cycloaddition occurs in the presence of triplet quenchers, while in the presence of 2,3-dihydrofuran fluorescence quenching is observed. In this case, the singlet excited state is responsible for the high *exo* selectivity [16z, 72], and the coefficients on the HSOMO and LSOMO allow coupling of the radical carbons to only give the *exo* isomer [61].

Furan and 2-methylfuran react with propanal and benzaldehyde [73]. In this case, the *exo* configuration at C-6 of the dioxabicyclo[3.2.0]heptene skeleton is observed [74]. Good regioselectivity is observed using silyl- and stannylfuran derivatives, and the reaction occurs on the less hindered side of the molecule [75]. When 2-silyloxyfuran is irradiated in the presence of aliphatic carbonyl compounds or with benzaldehyde, a 1:1 mixture of constitutionally isomeric products is formed. In contrast, when benzophenone is used, only the product derived from attack on the most hindered side of the molecule is formed. The same result is observed with acetone in a reaction where a low concentration of furan is used. In all these cases, *exo* selectivity is observed [76]. In contrast to the above reported data showing a good regioselectivity of the reaction of substituted furan derivatives with carbonyl compounds, 2-furylmethanol and the corresponding silyl ether give rise to low regioselectivity in the reaction with benzaldehyde [76, 77].

The high *exo* stereoselectivity of the reaction of furan with benzaldehyde has been extensively studied; the formation of the product occurs via a triplet 1,4-biradical which biradical must be converted (intersystem crossing) into a singlet biradical to give the product. To explain the pronounced *exo* stereoselectivity, a secondary orbital effect is postulated. Thus, an interaction