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Intramolecular Paternò–Büchi reaction of atropisomeric α-oxoamides in solution and in the solid-state†

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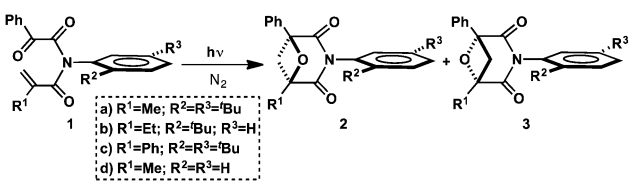
Atropisomeric α-oxoamides were synthesized and employed for intramolecular Paternò–Büchi reaction leading to very high enantio- and diastereoselectivity in the bicyclic oxetane photoproduct. A reversal of product selectivity was observed in solution and in the solid-state.

Light induced transformations are an important class of reactions in the field of organic synthesis that are often utilized to synthesize structurally important molecules.[1] While phototransformations are elegant, quite frequently it becomes challenging to control the excited state processes that often result in poor selectivity. In an attempt to address this bottleneck, photoreactions were done in confined media with capricious success.[2] This presents a distinct challenge to control photoreactions in solutions and achieve high stereoselectivity.[1a] In that regard, we have been successful in utilizing atropisomeric non-biaryl[3] photochromophores to perform various asymmetric photoreactions with good control over stereochemistry.[4] These include 6π-photocyclization,[4a] 4π-photocyclization,[4d] [2+2]-photocycloaddition[4e] and Norrish–Yang reactions.[4b,c] Now we wish to report the stereospecific Paternò–Büchi reaction of α-oxoamides in solution that results in a bicyclic oxetane photoproduct with very high stereoselectivity.

The [2+2]-photocycloaddition between a carbonyl group and an alkene termed as Paternò–Büchi reaction generates an oxetane ring that has interesting chemical properties and structural features.[5] The mechanism of cycloaddition is quite distinct depending on the interacting orbitals that initiate the reaction as well as the nature of alkenes (electron rich or electron poor alkenes).[6] In this report we present the stereospecific Paternò–Büchi reaction of atropisomeric α-oxoamides with a built-in photo-excitable ketone functionality and an electron deficient alkene unit.

Based on the structural parameters derived from crystals and the photoreactivity of benzoylformamides in the solid-state, Sakamoto and co-workers[7] detailed the importance of several structural features necessary to access the oxetane product. Their pioneering work revealed the key requirements concerning the role of N–CO bond orientation where the s-*trans*, s-*trans* conformer geometry was required for an efficient photochemical reaction (due to the optimal orientation of the excited ketone chromophore with the alkene) with the conformer geometry being dictated by steric and electronic factors on the N-aryl substituent.[7] They cleverly exploited the confinement offered by the crystalline matrix to freeze the molecular conformation to dictate the photochemical reactivity.[7,8] We were interested in biasing the photochemical reactivity in solution leading to an enhanced reaction specificity and product selectivity. One of the bottlenecks that had to be navigated for reactions done in solution was the presence of multiple conformations that caused differential reactivity leading to loss of specificity/selectivity.[9] This provided us the opportunity to examine the extent of axial chiral transfer from atropisomeric *o-tert*-butyl substituted α-oxoamides **1** to the oxetane in solution and compare their reactivities in the solid-state.

Atropisomeric *o-tert*-butyl substituted α-oxoamides (Scheme 1) were synthesized by a sequential acylation reaction from the corresponding aniline and were characterized by NMR spectroscopy, mass spectrometry and single crystal X-ray analysis.† The axial chirality arising due to the restricted rotation of N–C(aryl) substituents led to *P* and *M* isomers that were easily separated by HPLC on a chiral stationary phase. The purity of the individual *P* and *M* isomers of atropisomeric α-oxoamides was established by optical rotation and by analysis on a chiral stationary phase.†



Scheme 1 Intramolecular Paternò–Büchi reaction of **1a–d**.

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Table 1 Racemization parameters for optically pure **1a-b** at 50 °C[a]

Entry	Cpd	Solvent	k_{rac} (s^{-1})	$\tau_{1/2}$(days)	$\Delta G^{\ddagger}_{rac}$ (kcal mol^{-1})
1	**1a**	MeCN	1.26×10^{-6}	6.4	27.7
2		Benzene	2.11×10^{-6}	3.8	27.4
3	**1b**	MeCN	2.27×10^{-6}	3.5	27.3
4		Benzene	3.81×10^{-6}	2.1	27.0

[a] Values carry an error of ±5%. Kinetics followed by HPLC analysis, refer to ESI.

To employ atropisomeric α-oxoamides for stereospecific Paternò–Büchi reaction, it became critical to ascertain the barrier for racemization *i.e.*, N–C(aryl) rotation barrier in **1a-b**. Our kinetic studies established that **1a-b** racemize slowly at room temperature indicating a high barrier for N–C(aryl) bond rotation. Due to the slow racemization of optically pure **1a-b** at room temperature, racemization kinetics were performed at elevated temperatures in polar acetonitrile (MeCN) and non-polar benzene (Table 1). For example, in the case of **1a** at 50 °C, the activation barrier for racemization ($\Delta G^{\ddagger}_{rac}$) in MeCN was found to be ~27.7 kcal mol^{-1} with a racemization rate constant (k_{rac}) of 1.26×10^{-6} s^{-1} that corresponded to a half-life of racemization ($\tau_{1/2}$) of 6.4 days (Table 1; entry 1). Upon changing the solvent to benzene, the activation barrier for racemization ($\Delta G^{\ddagger}_{rac}$) at 50 °C was found to be ~27.4 kcal mol^{-1} with a racemization rate constant (k_{rac}) of 2.11×10^{-6} s^{-1} that corresponded to a half-life of racemization ($\tau_{1/2}$) of 3.8 days (Table 1; entry 2). We have already established that non-bonding interactions and solvent polarity affected the rates and half-life of racemization.[4d,e] The current results with the newly synthesized atropisomeric α-oxoamides **1a-b** indicated that they have a fairly high energy barrier for racemization even at higher temperatures (50 °C) and could be employed for desired photochemical transformations at room temperature without loss of their absolute configuration.

Irradiation of optically pure atropisomers of **1** was carried out at room temperature in benzene or acetonitrile using either a 450 W medium pressure Hg lamp placed inside a water-cooled jacket with a Pyrex cut off filter or a Rayonet reactor equipped with ~350 nm bulbs (24 Watts × 16 bulbs) under a constant flow of nitrogen.† After the consumption of reactants, the crude photoproduct was purified by chromatography and analysed by NMR spectroscopy, HRMS, optical rotation and single crystal XRD.[10]† The relative orientation of the oxygen atom in the oxetane ring was *syn* to the N-aryl *ortho-tert*-butyl substituent in photoproduct **2**, while it was *anti* in the case of photoproduct **3**. The dr between photoproducts **2** and **3** was ascertained using ^{1}H-NMR spectroscopy.‡ The enantiomeric relation in the individual photoproduct was established by its optical rotation values. HPLC analysis on a chiral stationary phase gave the ee values for the individual photoproduct **2** or **3**.

Table 2 reveals that Paternò–Büchi reaction of atropisomeric α-oxoamides are facile with 78–91% isolated yields of the oxetane photoproduct with excellent mass balance (even for large-scale irradiation). We believe that the presence of a bulky *ortho-tert*-butyl substituent on the N-phenyl ring influences the formation of the s-*trans*, s-*trans* conformer in solution, leading to enhanced reactivity in the atropisomeric substrates.[7] Control studies with **1d** that lacked the bulky *ortho-tert*-butyl substituent on the N-phenyl ring showed

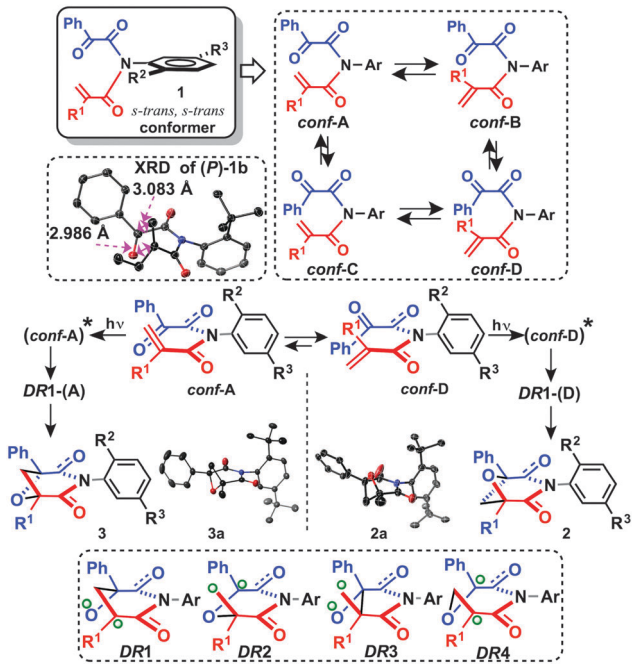
Table 2 Intramolecular Paternò–Büchi reaction of α-oxoamides **1a–d**[a]

Entry	Cpd[b]	Solvent	dr (**2** : **3**)[c]	% ee[d,e]	Yield[f]
1	(−)-**1a**	MeCN	71 : 29	98 (*R,R,M*)-**2a**	78
2	(+)-**1a**	MeCN		98 (*S,S,P*)-**2a**	
3	(−)-**1a**	Benzene	55 : 45	97 (*R,R,M*)-**2a**	90
4	(+)-**1a**	Benzene		97 (*S,S,P*)-**2a**	
5	(*M*)-**1b**	MeCN	82 : 18	99 (*R,R,M*)-**2b**	81
6	(*P*)-**1b**	MeCN		98 (*S,S,P*)-**2b**	
7	(*M*)-**1b**	Benzene	78 : 22	99 (*R,R,M*)-**2b**	78
8	(*P*)-**1b**	Benzene		98 (*S,S,P*)-**2b**	
9	(*M*)-**1b**	Crystal	15 : 85	98 (A)-**3b**	—
10	(*P*)-**1b**	Crystal	15 : 85	98 (B)-**3b**	—
11	**1c**	MeCN	95 : 05	—	91
12	**1c**	Benzene	89 : 11	—	90
13	**1d**	MeCN	—	—	30

[a] Reported values are an average of 3 runs with ±3% error. 2.5 h irradiation for **1a–c**, 12 h irradiation for **1d**. [b] (+) and (−) represent the sign of optical rotation, refer to ESI. [c] The diastereomeric ratio (dr) was determined using ^{1}H-NMR spectroscopy. [d] From HPLC analysis. A and B refer to the elution order for a given pair of enantiomers. Absolute configuration from single crystal XRD using Flack parameter. [e] Identical ee values for both **2** and **3**. [f] Isolated yield.

diminished reactivity.[7] The slow reactivity of **1d** likely reflected the conformational distribution where the s-*trans*, s-*trans* conformer was not preferred in solution. The diastereomeric ratio (dr) determined by NMR. The dr value in acetonitrile was higher than in benzene. For example, in the case of **1a**, the dr values were 71 : 29 in MeCN and 55 : 45 in benzene (Table 2; compare entries 1 and 3). Considerably higher dr values (82 : 18 in MeCN and 78 : 22 in benzene; Table 2; entries 5 and 7) were observed in the case of **1b**. To further improve the diastereoselectivity, we carried out the photoreaction in the solid-state as we were successful in crystallizing the individual atropisomers of **1b**. Irradiation of optically pure crystals of **1b** gave a dr value of 15 : 85. While the dr values in solution and in the solid-state were comparable, the enhanced diastereomer was different (Table 2; compare entries 5–8 with 9 and 10). Despite the reversal in dr values, analysis of the reaction mixture upon irradiation in solution and in the solid-state on a chiral stationary phase showed very high enantiomeric excess (ee values ~98%) in both **2** and **3** photoproducts (Table 2). A clear mechanistic rationale for the observed high selectivity is needed.

To understand the reactivity and selectivity during the Paternò–Büchi reaction of atropisomeric α-oxoamides, it is critical to appreciate not only the structural features (observed in single crystal X-ray analysis) but also the conformational influence arising from atropisomerism as well as the excited state reactivity of ketones with electron deficient alkenes. To understand the photochemical reactivity, we need to have a closer look at the excited state of the α-oxoamide chromophore. Based on the photochemical paradigm[6] of reactivity of excited ketones with electron deficient alkenes, it is likely that the half filled π* orbital triggered the reaction by charge transfer with the LUMO π* of the electron deficient alkene leading to oxetane formation.[11] The $\pi^*_{C=O} \rightarrow \pi^*_{C=C}$ charge transfer interaction has important consequences in the stereochemical features of the photoproduct as they will be dictated by the orbital overlap.[11] A good overlap between the $\pi^*_{C=O}$ and $\pi^*_{C=C}$ orbitals is necessary to initiate oxetane formation rather than the conventional radical stability that determines the reaction outcome of the photochemical transformations involving α-oxoamides.[11] Due to



Scheme 2 Mechanistic rationale for a stereospecific Paternò–Büchi reaction involving atropisomeric α-oxoamides.

the required $\pi^*_{C=O} \rightarrow \pi^*_{C=C}$ charge transfer interaction, the first bond that is likely formed during photochemical excitation of α-oxoamides will be the bond between the alkene CH_2 (unsubstituted β-alkene carbon) and the carbonyl carbon, as they will have the largest orbital coefficients.[11] This initial bond formation leading to a 1,4-diradical will dictate the stereochemical features of the oxetane product. The bulky *ortho-tert*-butyl substituent on the N-phenyl ring likely dictates the conformation responsible for the observed selectivity in solution and in the solid-state. Based on the stereochemistry of the photoproducts, it is clear that in addition to the s-*trans*, s-*trans* geometry at the CO–N bond, the conformation of the CO–CC bond is also critical. It is likely that the reactivity of the four s-*trans*, s-*trans* conformers *viz.*, *conf*-A, *conf*-B, *conf*-C and *conf*-D that arise due to the CO–CC and CO–CO bond rotations dictates the product ratio and selectivity (Scheme 2, top right inset). As observed in the case of oxetane **2** and **3**, the cycloaddition likely occurred from "*conf*-D" and "*conf*-A", respectively. Based on the orbital overlap between $\pi^*_{C=O}$ and $\pi^*_{C=C}$ orbitals, upon photoexcitation of α-oxoamide, formation of diradical *DR*1 is likely. Photoexcitation of "*conf*-A" and "*conf*-D" will lead to *DR*1-(A) and *DR*1-(D) respectively, that subsequently cyclize to the corresponding diastereomeric photoproducts **3** and **2**. The other diradicals (*DR*2, *DR*3 and *DR*4; Scheme 2, bottom inset) from individual conformers ("*conf*-A" and "*conf*-D") are feasible depending on the orbital coefficient in the excited chromophore, steric, electronic features present in the system as well as the substitution on the alkene double bond. The ratios of the conformers depend on the solvent polarity, the reaction media (solution *vs.* solid-state) as well as the steric and electronic features of the α-oxoamide. As **2** is observed as the major photoproduct in solution, it is likely that conformation "*conf*-D" is preferred in solution/reacts much faster upon photo-excitation than "*conf*-A". In the crystalline state, single crystal XRD analysis[10] ascertained that "*conf*-A" is preferred that leads to photoproduct **3** as the major isomer. A closer inspection of the crystal structure[10] of **1b** revealed that the distance between the keto carbonyl functionality and the alkene double bond is at an optimal distance *viz.*, OC···CH_2=C is ~3.083 Å and CO···C=CH_2 is 2.986 Å (Scheme 2) for undergoing photochemical transformation. As both "*conf*-A" and "*conf*-D" are atropisomeric, the axial chirality influences the formation of point chirality in the bicyclic oxetane with high stereospecificity that is reflected in the high ee value.

Our study has shown that atropisomeric chromophores can be employed for stereospecific Paternò–Büchi reaction both in solution and in the solid-state. The reactivity and selectivity are likely dictated by the degree of orbital overlap between the excited ketone and the electron deficient alkene. The stereospecificity is dependent on conformational aspects of the atropisomeric α-oxoamides. Our strategy opens up avenues for developing asymmetric phototransformations with a high degree of specificity to access molecules with unique stereochemical features.

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Notes and references

‡ We were not able to interconvert the **2** and **3** diastereomers at elevated temperatures (100 °C for 14 h), indicating a high-energy barrier for N–C(aryl) bond rotation in the photoproduct.

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