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Conformationally Driven Two- and Three-Photon Cascade Processes in the Stereoselective Photorearrangement of Pyrroles

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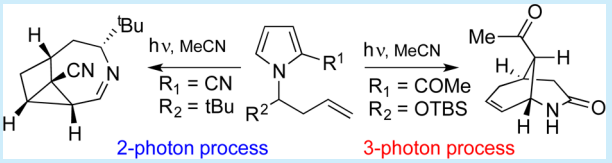
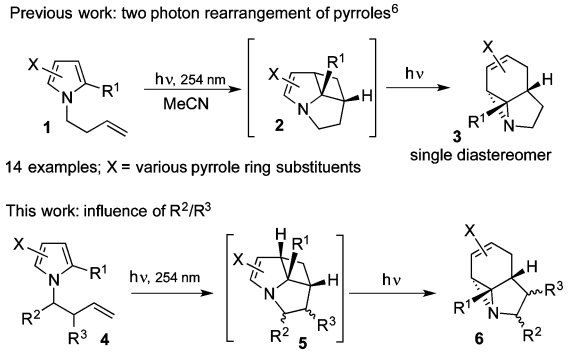
Supporting Information

ABSTRACT: A TBSO group has been shown to exert a high degree of stereocontrol during the two-photon photocycloaddition/rearrangement of *N*-butenylpyrroles to complex tricyclic aziridines. Moreover, this and other bulky groups have been shown to change the outcome of the reaction, promoting a new two-photon sequence to tricyclic imines and an unprecedented stereoselective three-photon sequence to azabicyclo[3.3.1]-nonanes.



Photochemistry is largely unrivaled in its ability to access complex molecular structures from simple starting materials. Part of this is due to reaction types specific to the photochemical excited state such as alkene−alkene [2 + 2],[1] arene *m*-photocycloaddition,[2] di-π-methine rearrangements,[3] and various Norrish−Yang[4]-type hydrogen abstraction−recombination sequences to name but a few. Useful sequences involving a second photon-mediated step are rare[5] but do offer the promise of large increases in molecular complexity due to massive reorganization of the original starting material structure. We recently[6] described an example of a general two-photon cascade sequence of pyrroles **1** to give structurally complex aziridines **3** via a second photon-mediated rearrangement step of the initially formed cyclobutane **2** (Scheme 1).

Scheme 1. Photocycloaddition−Rearrangement Reactions of Pyrroles



Herein, we describe the unusually high diastereoselectivity observed in the photocycloaddition/rearrangement of *N*-butenylpyrroles bearing bulky groups and how these groups change the course of the reaction to uncover unprecedented two- and three-photon-mediated processes.

Unlike thermal chemistry, and outside of photoredox catalysis, asymmetric bond formation from photochemically excited states remains highly challenging due to the very short lifetimes involved. Only recently have effective organocatalysts for asymmetric photochemistry been developed as exemplified by the very elegant host−guest sensitizer work of Bach et al.[7] Successful enantioselective photochemical reactions induced by chiral auxiliaries have been reported. However, despite notable successes, diastereomeric ratios (dr) in these auxiliary-controlled reactions can often be lower than ideal[8] as the rapid reaction of excited-state intermediates can thwart the establishment of key auxiliary-controlled transition states.

Against this backdrop, we wished to explore whether functional groups (R^2/R^3) on the butenyl side chain of pyrrole **4** would influence the outcome of this complex photochemical sequence and lead to single diastereomers of sp^3-rich aziridines as reactive scaffolds[9] for use in drug discovery. Initially, we focused on synthesizing a range of 2-substituted pyrroles (R^1 = CO-Aux) bearing common chiral auxiliaries such as (+)-menthol, Evans' auxiliary, camphor sultam, borneol, and various chiral amines. All attempts gave aziridines (R^1 = CO-Aux; R^2/R^3 = H) with very little or no observed diastereoselection. This result was surprising given the likely proximity of the butenyl double bond to the 2-acyl unit bearing the chiral auxiliary during the initial [2 + 2] cycloaddition. Moving to substituents on the butenyl side chain, we initially studied the β-methylpyrrole **4** (R^1 = CONHEt, R^2 = H, R^3 = Me). Although the aziridine **6** (R^1 = CONHEt, R^2 = H, R^3 = Me) was obtained in 56% yield, the *exo*/*endo* diastereoselectivity was low at 4:1, although still better than the R^1 auxiliary approach (Scheme 1).

We therefore decided to study a range of α-substituted pyrrole examples **7**. Moving the methyl group to the α-position (Table 1, entry 1) gave excellent diastereoselectivity (≥98:2 dr) during the two-photon process. Pleasingly, this high level of stereocontrol was maintained for a range of α-substituted examples bearing even more bulky alkyl groups (entries 2−5).

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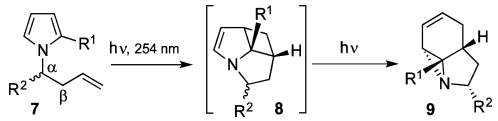
Table 1. Exploring the Effects of Stereocontrol with Various α-Substituents during the Photochemical Rearrangement of Pyrroles[a,b]



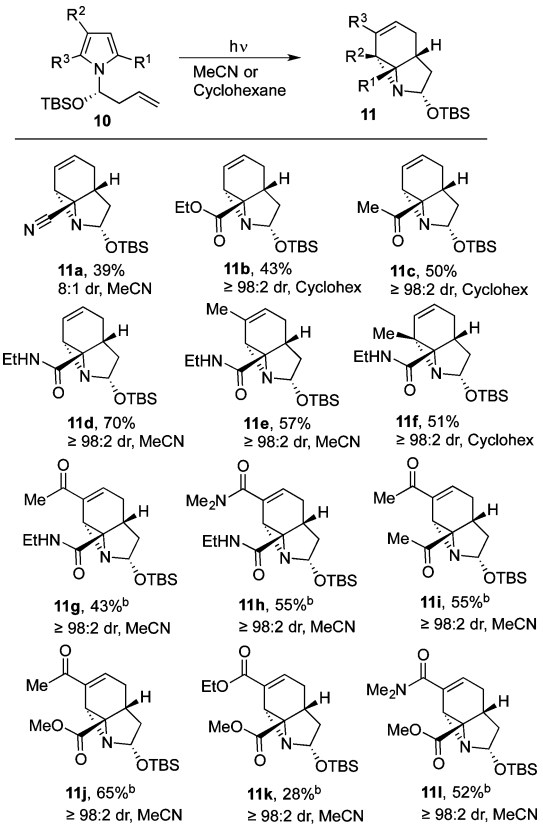
entry	R^1	R^2	**9** (%)	dr
1	CONHEt	Me	39	≥98:2
2	CONHEt	Et	51	≥98:2
3	CONHEt	Pr	46	≥98:2
4	CONHEt	iBu	60	≥98:2
5	CONHEt	iPr	38	≥98:2
6	CN	Me	37	5:1
7	CN	Pr	40	5:1
8	CN	OAc	50	2:1
9	CN	OTBS	39	8:1
10	CONHEt	OTBS	70	≥98:2

[a]Reactions performed in MeCN. [b]All products are racemic.

Interestingly, however, on switching from an amide activating group (R^1) to nitrile a significant drop in diastereocontrol was observed that was not improved by switching from Me to Pr (entries 6 and 7). Use of more functionally useful groups led to interesting results. Although R^2 = OAc (entry 8) gave very poor dr, the use of R^2 = OTBS gave high selectivity (8:1). The lower yields obtained with the nitrile activating group are a reflection of the known competing 2- to 3-cyano photorearrangement[10] of pyrroles. In all of these examples, NMR and X-ray experiments indicated that the *endo* product (**9**) was the major diastereomer formed, where the R^2 group was placed in the concave face of the "bowl" generated by the three new rings (vide infra).

We were keen to exploit this unusually high level of stereoselectivity observed by the OTBS group, especially since the aziridine products would possess a useful functional group (R^2) for further elaboration. The requisite pyrrole carbinols (**7**, R^2 = OH) have been described by Evans as remarkably stable and have been frequently used as masked aldehydes.[11] Using this methodology, we synthesized a range of substituted pyrroles containing OTBS ethers at the α-substituted carbon and investigated their two-photon rearrangement (Scheme 2). All 12 examples gave excellent levels of selectivity, with essentially the *endo*-isomer of the aziridines **11a–l** being formed as the single product in each case. In examples possessing two electron-withdrawing groups (**11g–l**), better yields were obtained with a dual lamp system at 254 and 312 nm, where the longer wavelength was a better match for the now conjugated cyclobutane intermediates. Only the nitrile example **11a** showed less than optimal selectivity at 8:1 dr. With the exception of **11k**, the yields of these rearrangements can be considered moderate to good; i.e., this is a complex cascade process involving two photons of very high energy (254 nm), generating very strained tricyclic products of high reactivity.[9,12] As the stereogenic center bearing the OTBS group had such a profound and consistent level of stereocontrol during rearrangement, we were keen to prove that an asymmetric synthesis of **11** could be achieved in high ee from enantiopure **10**. Synthesis of *S*-**10d** (R^1 = CONHEt, R^2 = OTBS) gave enantioenriched **11d** (98% ee) with no erosion of chirality observed during the photochemical process (see the Supporting Information).

Scheme 2. Scope of the OTBS as a Chiral Auxiliary in the Diasteresoselective Photochemical Rearrangement of Pyrroles[a]

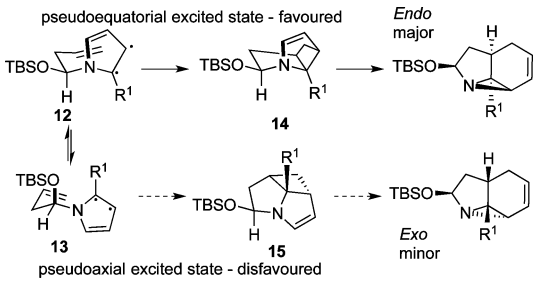


[a]All products except **11d** were synthesized as racemates; [b]Concurrent irradiation at 312 nm was employed using a dual lamp system (see the SI).

Initially, we found it curious that the products were formed as the most hindered isomers; i.e., the large OTBS group was placed on the concave face of the tricyclic aziridine ring system. The origin of this high selectivity is very likely to arise during the first step in the formation of the cyclobutane ring.[13] If a simple diradical-like mechanism is considered, then after initial excitation a Beckwith radical cyclization transition-state model[14] could be adopted (Scheme 3).

Here, the diradical could adopt one of two equilibrating chairlike transition states **12** and **13**, where the former, pseudoequatorial disposition of the OTBS group would be greatly favored. On cyclization of **12**, the cyclobutane **14** would result, which in turn would lead to the *endo*-isomer of **11**. This

Scheme 3. Stereochemical Model To Explain *Endo*-Selectivity during Cycloaddition/Rearrangement of Pyrroles



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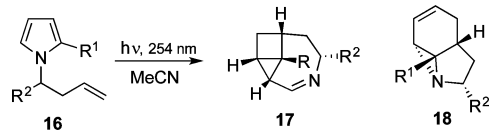
well-documented Beckwith model for stereoselective cyclization neatly explains why in our case the more sterically congested *endo*-isomers of the aziridines are obtained in every case (Scheme 2). This also explains the *exo* selectivity obtained for *β*-substituted methyl isomer **6** (R^1 = CONHEt, R^2 = H, R^3 = Me).

While attempting to increase the dr of the 2-cyano-substituted pyrroles (Table 1, entries 6–9), we explored a range of alkyl substituents of increasing steric bulk. During the course of this, we uncovered a novel mode of reactivity that we had not previously observed. For example, irradiation of the *i*Bu substrate **16** (Table 2, entry 1, R^1 = CN, R^2 = *i*Bu) gave the

Table 2. Discovery of a New Conformationally Controlled Two-Photon Cycloaddition–Rearrangement Sequence[c]



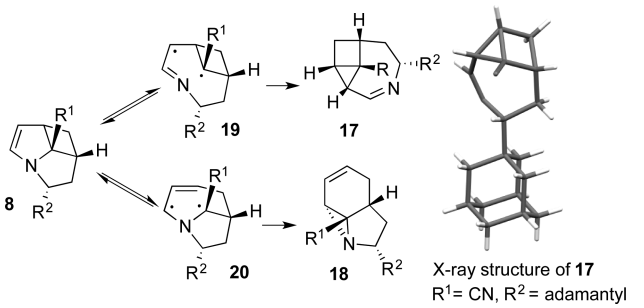
entry	R^1	R^2	**17** (%)	**18** (%)	dr[a] (**18**)
1	CN	^{i}Bu	19	35	11:1
2	CN	Cy	8	27	>98:2
3	CN	iPr	22	7	>98:2
4	CN	^{t}Bu	52	13	>98:2
5	CN	Ad	47	10	>98:2
6[b]	CO_2Et	^{t}Bu	23	29	>98:2

[a]Determined by ^{1}H NMR. [b]Reaction performed in cyclohexane. [c]All products are racemic.

aziridine **18** (R^1 = CN, R^2 = *i*Bu) with an improved dr of 11:1. However, along with this we isolated the remarkable tricyclic imine **17** (R^1 = CN, R^2 = *i*Bu) as a single isomer. We then synthesized a variety of pyrroles with more sterically demanding R^1 groups. In all cases, this unusual tricyclic product was observed, and indeed, with very bulky groups this was the main product (entries 3–5). It is also interesting to note that that as the steric bulk of R^2 increased so too did the dr, to the point that no other isomers of the aziridine **18** were detected.

It is likely that this is a two-photon process proceeding via the initial cyclobutane **8** as a common intermediate. As previously discussed, aziridine formation (**18**) is thought to proceed from rearrangement of **8** via the diradical species **20**. Clearly, the large R^2 group is exerting a degree of conformational control that favors fragmentation of **8** to the imine diradical **19**, which then cyclizes to **17** (Scheme 4). In our previous work, we proved that irradiation of intermediate

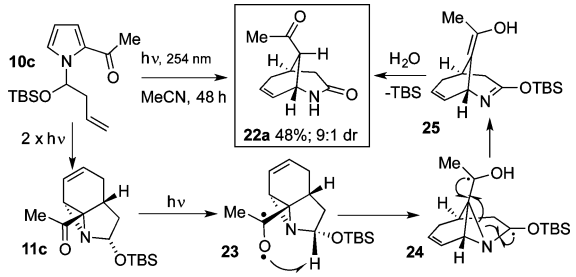
Scheme 4. Mechanism of Tricyclic Imine Formation



cyclobutanes (**8**) led to aziridine formation and small amounts of the starting pyrrole. However, irradiation of the aziridines showed no sign of the reverse rearrangement to the cyclobutanes. We believe that the formation of **19** likely occurs directly from an excited state of **8**, which influenced by R^2, adopts a conformation that favors fragmentation to **19**. It is also possible that in **20** the large R^2 now dictates a conformation that disfavors radical recombination to **18** and so equilibrates back to **8**. This 3,4,7-fused ring system is novel and stable, and the X-ray structure of the crystalline adamantyl derivative **17** (R^1 = CN, R^2 = Ad) shows the interesting fusion of 3-, 4-, and 7-membered rings. The two-photon process represents an entirely novel photochemical reaction, and further studies are ongoing to determine its generality. In particular, the ability to influence very complicated two-photon pathways by choice of R^2 group size introduces the exciting prospect of control of short-lived reactive species.

During the extensive work with the TBSO derivatives (Scheme 2), we became aware that traces of a new product were being formed in addition to the aziridine. Prolonged irradiation of **10c** showed the appearance of the aziridine **11c**, which over time was consumed to give a new product, the lactam **22a**, in 50% yield as essentially a single diastereomer. This remarkable product would appear to be a *three-photon* process involving pyrrole → cyclobutane → aziridine → lactam. Further excitation of the ketone in the initially formed aziridine **11c** leads to a Norrish Type II hydrogen atom abstraction sequence **23** to **24**. The resulting biradical **24** then undergoes fragmentation to **25** and upon protonation and desilylation yields **22a** (Scheme 5). This is the first time that we have

Scheme 5. Novel Three-Photon Conversion of Pyrroles to Bicyclic Lactams and Proposed Mechanism



observed fragmentation of this particular aziridine bond; reactions with nucleophiles, organometallics, and internal H atom-transfer processes have all proceeded with cleavage of the alternative N–C bond. We believe that the OTBS group performs two crucial roles in directing this alternative pathway. First, the *endo* stereochemistry places the key H atom in close proximity to the excited ketone in **23**. Second, the radical center resulting from abstraction is additionally stabilized by virtue of the *α*-oxygen atom, explaining why this mode has not been observed in other 2-acylpyrrole systems.

It was interesting to note that enol–keto tautomerization of **25** would appear to proceed by protonation from the amide/OTBS side of the molecule to give predominantly one diastereoisomer. As the resulting ketone proved stable to epimerization during isolation and purification by flash chromatography, this is likely a kinetic protonation to the stereoisomer observed. Although we were never able to observe the silyloxy imine motif in **25**, such species are very labile[15] and

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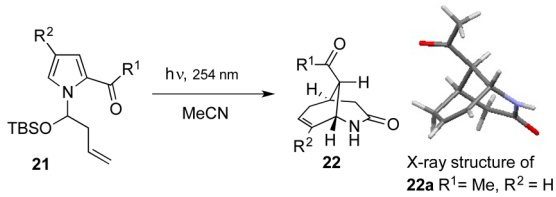
would likely undergo rapid hydrolysis to the amide in the hygroscopic MeCN solvent used.

An optimization study showed that a ketone in the 2-position of the pyrrole was essential to enable lactam formation (Table 3, entries 1−5) and that a second ketone was actually deleterious to the process (entry 6). Although yields averaged around 50%, this in itself is quite remarkable as intense, high energy 254 nm UV light is used and the successful formation of **22** relies on three successive and independent photon-mediated events. Unfortunately, three sequential photochemical reactions make for a very low overall quantum yield and thus proved to be a scalability issue in batch. However, we were keen to make gram quantities of these compounds and were pleased to be able to produce 1.83 g of **22c** (R^1 = Cy, R^2 = H) in a 13 h run in our 3 × 36W 254 nm FEP flow reactor. This highlights once again the value of flow photochemistry for scaling up very unproductive batch reactions.[16]

Table 3. Discovery of a Novel Three-Photon Rearrangement Cascade Sequence of 2-Acylpyrroles to 2-Azabicyclo[3.3.1]nonanes[b]



entry	product	R^1	R^2	**22** (%)	dr[a]
1	**22a**	Me	H	43	9:1
2	**22b**	Et	H	53	97:3
3	**22c**	Cy	H	57 (54)[c]	98:2
4	**22d**	*t*Bu	H	39	98:2
5	**22e**	$CH_2C(Me)_2Ph$	H	41	92:8
6	**22f**	Me	Ac	31	97:3

[a]Determined by ^{1}H NMR. [b]Products are racemic. [c]Flow reaction yield.

It has been demonstrated that in the photocycloaddition rearrangement of simple pyrroles OTBS substitution of the *N*-butenyl side chain exerts powerful stereocontrol during subsequent tricyclic aziridine formation. Further investigation of 2-cyanopyrroles bearing other bulky groups led to the discovery of a novel two-photon pathway for the formation of highly unusual 3,4,7-fused imine ring systems. In the case of 2-acylpyrroles, OTBS substitution facilitates an unprecedented and highly stereoselective three-photon cascade sequence leading to azabicyclo[3.3.1]nonanes. Overall, this further underlines the versatility of photochemistry for the synthesis of highly complex molecules from simple starting materials. The ability to select a desired reaction manifold through substituent choice allows access to broad areas of molecular space from a common structural starting point, potentially making it of considerable value in drug discovery.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02829.

Synthesis procedures; additional spectral and characterization data, including ^{1}H and ^{13}C NMR (PDF)
X-ray data for **17** (CIF)
X-ray data for **22a** (CIF)

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Notes

The authors declare no competing financial interest.

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