Small-Ring Systems

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A Versatile and Stereoselective Synthesis of Functionalized Cyclobutenes**

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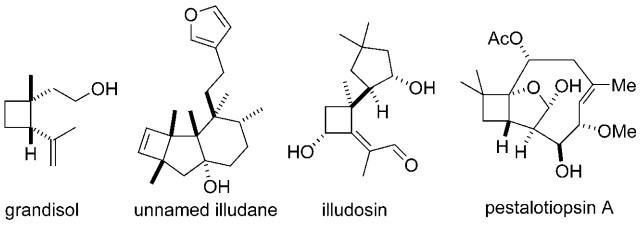
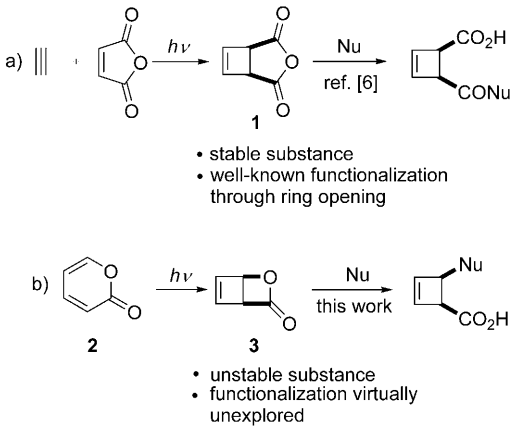
All-carbon four-membered rings are incorporated in a high number of naturally occurring and/or biologically active substances (Scheme 1),[1] and their preparation has been an ubiquitous topic in organic synthesis ever since chemists realized the potential associated with their inherent ring strain. Cyclobutanones and cyclobutenones are arguably the most readily available derivatives of cyclobutane, and the ones that have been most often studied.[2] In contrast, stereoselective and efficient methods for the preparation of cyclobutane and cyclobutene derivatives are comparatively scarce.[3] Indeed, cyclobutenes are especially attractive building blocks owing to the synthetic versatility associated with the presence of the additional carbon–carbon double bond in the four-membered ring.[3]



Scheme 1. Structures of selected natural products containing cyclobutane and cyclobutene units.[4]



Scheme 2. Photochemical approaches to the synthesis of cyclobutenes.

The photocycloaddition of maleic anhydride to acetylene is probably a benchmark of cyclobutene synthesis (Scheme 2a).[3a,5] In spite of the numerous advances reported in the desymmetrization of the adduct **1** (and analogues) through ring-opening reactions,[6] the somewhat low synthetic versatility of products bearing two carboxylic acid derivatives directly connected to the four-membered ring highlights a pressing need for more flexible and stereoselective routes to substituted cyclobutenes.

When we considered such routes, our interest was piqued by the 40-year-old, yet little explored, photoisomerization of 2-pyrone (**2**) reported to generate lactone **3** (Scheme 2b).[7a] Compound **3** is known to be a sensitive, unstable, and potentially explosive substance[7a,b] which, perhaps unsurprisingly remained overlooked as a potential starting material for further elaboration.[7] We were lured by its appeal as a promising, versatile starting material for a variety of chemical transformations. Herein we describe the first catalytic, stereoselective transformations of **3** that suggest a versatile synthesis of functionalized cyclobutenes in only two operations from 2-pyrone.

In our hands, the photochemical isomerization of readily available **2** to give **3** proceeded in quantitative yield. Stock solutions of **3** in diethyl ether with concentrations in the range of 0.1 to 0.2 M could be stored and routinely handled without special precautions.[8] Initial attempts at metal-promoted functionalization of **3** quickly revealed that its strained allylic lactone moiety responded productively to palladium catalysis.[9] After optimization,[10] we eventually found that treatment of **3** with sodium dimethylmalonate in the presence of 5 mol% $[Pd(PPh_3)_4]$ led to a nearly quantitative yield of the *cis*-cyclobutene carboxylic acid **4a** as a single diastereomer (Scheme 3).[11]

Encouraged by what essentially amounts to a stereoselective synthesis of a highly functionalized cyclobutene derivative in only two steps, we investigated further the range of nucleophiles that can be employed in this process (Table 1). For ease of purification and analytical purposes, most of the crude acids **4** were routinely converted into the

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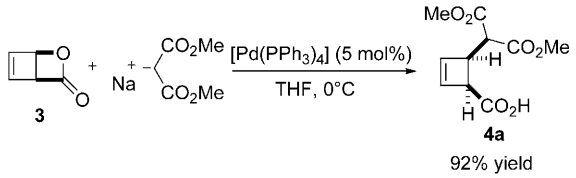
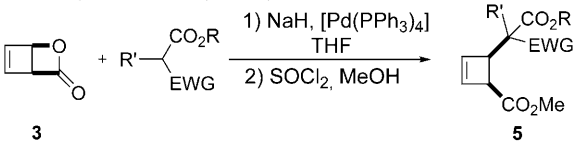


Scheme 3. First result on the catalytic functionalization of lactone **3**.

Table 1: Scope of the catalytic alkylation of lactone **3**.[a]



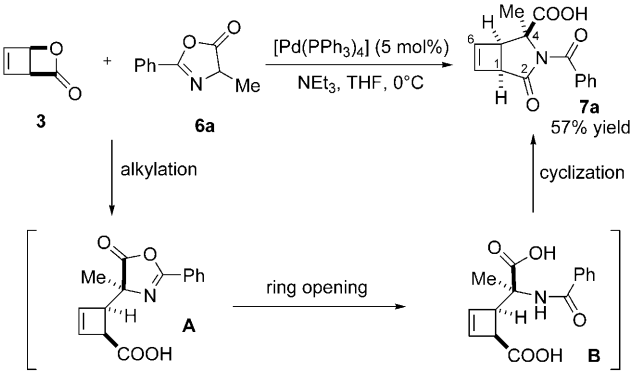
Entry	R	R′	EWG	Product	Yield [%][b]
1	Me	H	CO_2Me	**4a**	[92]
2	Bn	H	CO_2Bn	**4b**	[47]
3	*t*Bu	H	CO_2tBu	**4c**	[42]
4	Et	Me	CO_2Et	**5d**	80
5		Et		**4e**	[90]
6		*n*Bu		**5f**	74
7		Bn		**5g**	83
8		allyl		**5h**	76
9	Me	$CH_2C_6H_4(4\text{-}NO_2)$	CO_2Me	**5i**	59
10		$(CH_2)_2CH{\equiv}CH$		**5j**	88
11	Et	CH_2CO_2Et	CO_2Et	**5k**	51
12	Me	H	$CONPh_2$	**5l**	46[c]

[a] All reactions were conducted on a 0.1 or 0.2 mmol scale, with 5 mol% $[Pd(PPh_3)_4]$, 2.0 equiv NaH, and 2.2 equiv nucleophile at 0°C, unless noted otherwise. [b] Yields of pure isolated products. Yields in brackets correspond to analytically pure crude carboxylic acids **4**. [c] Compound **5l** was obtained as a single diastereoisomer after methylation.[8]

corresponding methyl esters **5** using thionyl chloride in methanol. As can be seen from Table 1, and in spite of the high instability of lactone **3**, a variety of active methylene derivatives perform competently as nucleophiles in this reaction. The electron-withdrawing substituents could be varied in this process (Table 1, entries 1–3 and 12), and substituted nucleophiles smoothly led to all-carbon quaternary centers (Table 1, entries 4–11). Importantly, alkyl, benzyl, acetate, allyl, and homopropargyl groups were well tolerated. Furthermore, high diastereoselectivity could be obtained when the carbonyl functionalities of the nucleophile were not identical (Table 1, entry 12).

The high atom economy of this reaction sequence (starting from 2-pyrone (**2**)) translates into a significant increase of molecular complexity employing only the simplest of starting materials, and stimulated us to seek additional opportunities. In line with our desire to target biologically relevant substructures, we became intrigued by the possibility of generating cyclobutene amino acid derivatives. Indeed, much interest has been recently devoted to the biological potential of constrained amino acids.[12] It appeared to us that the use of azlactones as nucleophiles in this process might lead to elaborated amino acid scaffolds with interesting properties.

In the event, exposure of lactone **3** to conditions analogous to those listed in Scheme 3, but in the presence of azlactone **6a** led to the formation of a new product which we surmised to be the alkylated acid **A**. However, single-crystal X-ray analysis of this compound showed it to be the rearranged azabicycle **7a**.[11] The putative product **A** appears to undergo rupture of the azlactone moiety followed by an unusually facile cyclization to the lactam **7a** (Scheme 4). To our knowledge, this type of rearrangement is unprecedented in the chemistry of azlactones.[13]

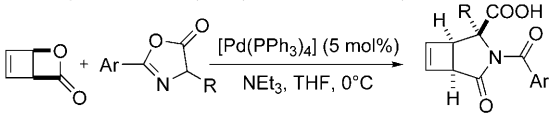


Scheme 4. Alkylation of lactone **3** with azlactone **6a** and unexpected rearrangement.

An additional intriguing aspect was the very high diastereoselectivity of this reaction. Careful analysis of crude reaction mixtures of **7a** revealed the presence of only small amounts (typically $\leq 10\%$) of the lactam epimeric at C4 (Scheme 4). Remarkably, this constitutes a rare case of high double diastereoselectivity using azlactones, in the absence of external chiral ligands (vide infra).[14]

A number of trends emerged upon inspection of the substrate scope (Table 2).[10] Interestingly, the aromatic portion of the incoming azlactone nucleophile played a significant role in this reaction (Table 2, entries 1 to 4); nearly 10%

Table 2: Scope of the catalytic synthesis of azabicycles **7**.[a]

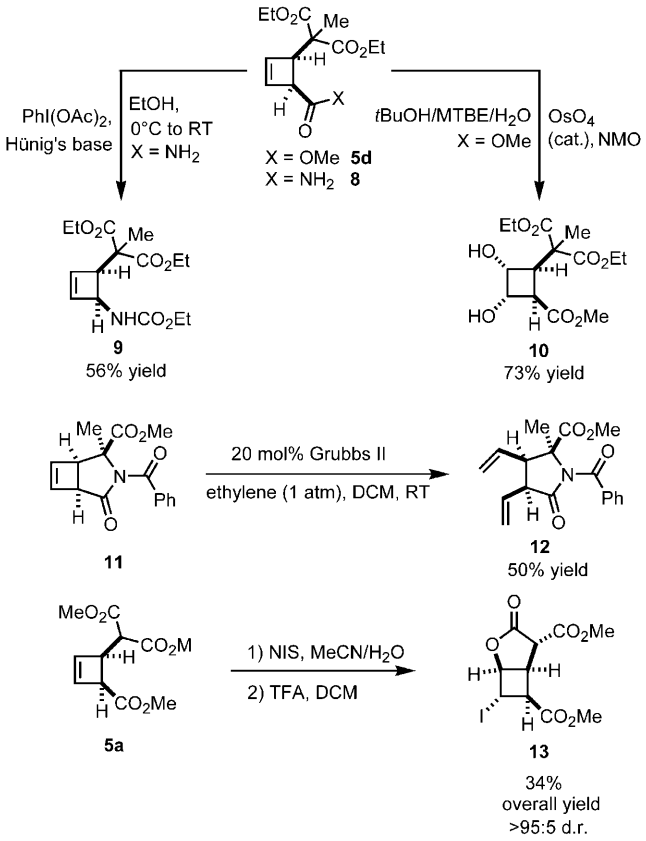


Entry	Azlactone	Ar	R	Product	Yield [%] (d.r.)[b]
1	**6a**	Ph	Me	**7a**	57 (90:10)
2	**6b**	$(4\text{-}OMe)\text{-}C_6H_4$		**7b**	37 (90:10)
3	**6c**	$(3,5\text{-}CF_3)\text{-}C_6H_3$		**7c**	45 (91:9)
4	**6d**	$(4\text{-}NO_2)\text{-}C_6H_4$		**7d**	68 (93:7)
5	**6e**	Ph	Bn	**7e**	26 (>95:5)
6	**6f**	$(4\text{-}NO_2)\text{-}C_6H_4$	Bn	**7f**	46 (95:5)
7	**6g**		Et	**7g**	54 (93:7)
8	**6h**		Bu	**7h**	57 (94:6)
9	**6i**		$(CH_2)_2Ph$	**7i**	47 (88:12)
10	**6j**		allyl	**7j**	56 (90:10)

[a] All reactions were conducted in a 0.2 mmol scale, with 5 mol% $[Pd(PPh_3)_4]$, 2.0 equiv NEt_3, and 2.25 equiv **6** at 0°C, unless noted otherwise. [b] Yields of isolated diastereomerically pure products; d.r. values refer to the crude reaction mixture.

increments in yield were observed when progressing from donating (*p*-OMe) to inductive withdrawing (*p*-CF_3), neutral (H), and strongly withdrawing (*p*-NO_2) substituents. That this was not simply a conversion effect could be seen by NMR analysis of the crude mixtures: considerably fewer by-products were observed when the *p*-nitroazlactone **6d** was employed. This effect[15] was also apparent in other substrates (cf. Table 2, entries 5 and 6, for example), and we opted for the nitrophenyl appendage in subsequent studies. Different alkyl, allyl, and benzyl moieties as the R group in **6** were compatible with this transformation (Table 2, entries 6–10).

The adducts formed through this simple reaction sequence proved amenable to a variety of transformations, which exploited the latent reactivity of the functional groups generated (Scheme 5). For instance, the strained double bond

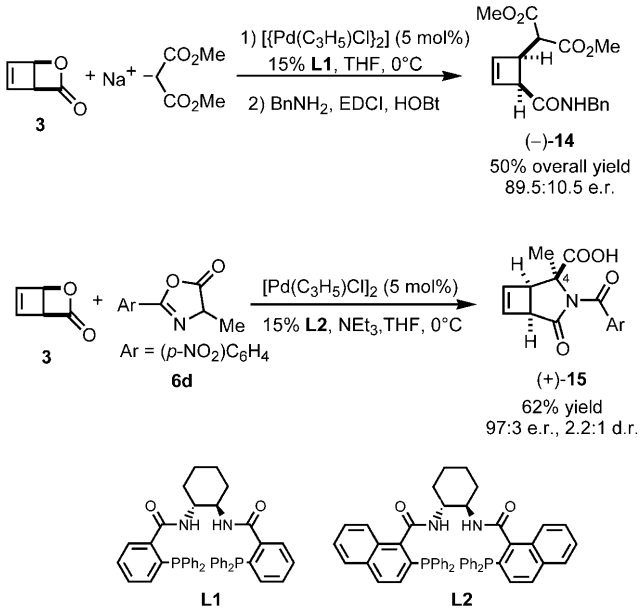


Scheme 5. Functionalization of the adducts obtained. DCM = dichloromethane, MTBE = methyl *tert*-butyl ether, NIS = *N*-iodosuccinimide, TFA = trifluoroacetic acid.

in cyclobutene **5d** could be easily dihydroxylated, affording the tetrasubstituted cyclobutane **10** in good yield with complete control of all four stereogenic centers. Aiming at biologically relevant scaffolds, the amide derivative **8** smoothly underwent Hofmann rearrangement to give the novel constrained, fully protected cyclobutene-γ-amino acid **9**.[16]

Other manipulations further showcase the synthetic advantage derived from the cyclobutene double bond and hint at potential applications of this method in total synthesis. Thus, ring-opening metathesis/cross-metathesis[17] of azabicycle **11** under an atmosphere of ethylene (1 atm) promoted by Grubbs' second-generation catalyst afforded the diastereomerially pure pyrrolidinone **12**, whose structure is reminiscent of kainic and domoic acid derivatives.[18] In another sequence, a two-step halolactonization of triester **5a** led to compound **13**, which embodies the core structure of pestalotiopsin A.[19] It is testament to the power of this approach that synthetically relevant compounds can be derived from 2-pyrone in only three straightforward synthetic manipulations.

Finally, initial studies aimed at developing an asymmetric variant provided encouraging results (Scheme 6). The simple replacement of the previously employed palladium catalyst



Scheme 6. Preliminary results on asymmetric alkylations of lactone **3**. The absolute configuration of the major enantiomer of (−)-**14** and (+)-**15** was not determined. EDCI = 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide.

system with a mixture of the dimeric [{$Pd(C_3H_5)Cl$}$_2$] and the Trost ligand (*R*,*R*)-**L1**, without any change in reaction conditions, led to product (−)-**14** (isolated as the benzamide derivative) in a 89.5:10.5 enantiomer ratio[20] (Scheme 6; the absolute configuration of the major enantiomer was not determined). Transposing this to the azlactone case using ligand (*R*,*R*)-**L2** led to azabicycle (+)-**15** in an impressive 97:3 enantiomer ratio. Interestingly, the powerful asymmetric induction of ligand **L2** strongly biased the inherently high diastereoselectivity of the racemic process (cf. Scheme 4 and Table 2), and a nearly 2:1 diastereomer ratio of epimers at C4 was obtained (Scheme 6, major diastereomer depicted; absolute configuration of the major enantiomer not determined). The origin of such an effect is not clear at present, but the prospect of weakening or even overriding the innate diastereopreference of the coupling between lactone **3** and nucleophiles through the choice of an appropriate ligand is particularly exciting and is being studied further.

In summary, we have developed a new and concise synthesis of functionalized cyclobutenes. To achieve this goal, palladium catalysis was decisive in taming the instability of lactone **3**. The overall process reported here combines the efficiency of clean, highly efficient photochemical reactions with the powerful selectivity that can be imparted by metal catalysis and should find broad applications in synthesis. That this sequence of events proceeds with excellent atom economy starting from cheap and readily available, achiral "flat" pyrones to produce versatile added-value products is perhaps the most striking consequence of such a combination. Further developments of this methodology and related sequences that harness the potential of lactone **3** and its derivatives, as well as applications to the total synthesis of biologically relevant targets are underway in our laboratories.

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[10] See the Supporting Information.

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