First example of intramolecular \([2\pi + 2\pi]\) alkene–arene photocyclization in the chromone series and its synthetic utility

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The Diels–Alder (D.–A.) adducts of 1,4-naphthoquinone with cyclic dienes were shown to undergo photoinduced \([2+2]\), or \([6+2]\), cycloaddition A → B, Scheme 1, disrupting the aromatic system and furnishing a facially stereo-differentiated cyclohexadiene moiety. The original discovery is attributed to Filipescu and Kushner. In the ensuing years the finding has sparked a flurry of research activity. Coxon and co-workers systematically studied facial selectivity in D.–A. reactions of B which primarily produced C (Scheme 1) as a result of an attack by a dienophile at the face decorated by the carbonyl groups, and several accounts of various acid- and base-catalyzed rearrangements involving either diene B or its D.–A. adducts have been published.

In a related development, \([2+2]\) intramolecular photocycloadditions in alkene–arene pairs or between two aromatic moieties were exploited by Prinzbach to access a spectacular array of polycyclic hydrocarbons, pagodanes.

Given the facile access to the starting materials and the potential benefits of synthetic developments around the basic sequence shown in Scheme 1, it was somewhat surprising for us to realize that 1,4-naphthoquinones are the only aromatic ketones that are reported to form polycyclic dienes of type B in intramolecular \([2+2]\) photo-cycloadditions.

It is conceivable that this limited variety has to do with the fact that very few benzo-fused aromatic ketones have been reported as good dienophiles for the first, that is, D.–A. step (→A). For example chromones (and even parent \(\gamma\)-pyrones) have received very little attention until about a decade ago, when Hsung reported the first stereoselective \([4+2]\) cycloaddition reactions of 3-cyanochromone derivatives with electron-rich dienes.

We have recently developed another high-yielding tandem ground state – excited state \([2\pi + 2\pi]\) alkene–arene photocyclization, leading to a versatile polycyclic diene, which is capable of dimerization or can be introduced into a high-yielding photoprotolytic oxametathetic sequence. This allows for an expeditious growth of molecular complexity over a few experimentally simple steps with stereochemistry being defined and locked at the very first Diels–Alder step. The overall reaction can potentially be utilized in diversity-oriented synthesis as it allows for three or more diversity inputs furnishing novel unique polycyclic scaffolds, which can readily be decorated with a variety of functionalities and aromatic/heterocyclic pendants.
The D.–A. adducts of substituted chromones and cyclic dienes undergo clean and quantitative photocyclization into dienes 2 upon irradiation in a Rayonet photoreactor with RPR-3500 lamps (a broadband UV source with \( \lambda = 350 \pm 50 \) nm). To the best of our knowledge this is the first example for a tandem D.–A. reaction followed by an aryl-alkene \([2\pi+2\pi]\) photocyclization involving an aromatic ketone other than a 1,4-naphthoquinone.

The 3-cyano-group certainly makes the chromone a much more reactive dienophile. While the unsubstituted chromone is not reactive at all, we found that its [formal] D.–A. adducts with cyclic dienes can nevertheless be obtained in moderate to good yields of 55–70% via the reactions of a better dienophile, chromone-3-carboxylic acid, because the immediate products of this cycloaddition, \( \beta \)-keto acids, undergo facile thermal decarboxylation into 1b,c.

Dienes 2 readily react with dienophiles such as vinyl phenyl ketone, generated in situ, or dibenzoyl ethylene to furnish D.–A. adducts 3. The facial selectivity of this second Diels–Alder step is the same as 1,4-naphthoquinone adducts, that is, the dienophile is approaching from the ‘ketone’ face. The regiochemistry of vinyl phenyl ketone addition was as shown in Scheme 2, that is, the position of endo-benzoyl group is proximal to the keto group of the chromone moiety.

A striking observation was that the chromone-based polycyclic dienes 2 undergo D.–A. cyclodimerization yielding a single diastereomeric product 4 (Scheme 3).

To better understand this ability of dienes 2 to dimerize diastereoselectively we employed a density functional theory study. Our calculations show that both the chromone and the 1,4-naphthoquinone-derived cyclodienes have similar HOMO and LUMO molecular orbitals, with HOMO dominated by the one-node butadiene MO and LUMO—by the two-node butadiene MO. The only significant difference is due to HOMO’s delocalization on the carbonyl’s oxygen, while very little of such interaction is involved with the ether oxygen, Figure 1. The calculated HOMO-LUMO gaps are also very similar, 4.68 eV for 2c and 4.46 eV for B.

It appears that the diastereoselectivity of dimerization is correlated with the relative stability of the D.–A. product. We have optimized the geometries of 16 possible anti dimers of 2b at a b3lyp/6-311+G(d,p) level of theory (the syn dimers were not considered, as the steric clash of the two polycyclic pendants in the syn structures is too severe). To assess the quality of computational predictions we also have computed the structure of 4a at the same level of DFT theory and superimposed it onto its experimental structure. A table of relative energies is presented in Table 1.

**Table 1**

<table>
<thead>
<tr>
<th>Group 1</th>
<th>Group 2</th>
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<tr>
<td>X(_i)/Y(_1)</td>
<td>X(_2)/Y(_2)</td>
</tr>
<tr>
<td>O/CO</td>
<td>O/CO</td>
</tr>
<tr>
<td>CO/O</td>
<td>0.3</td>
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<td>CO/O</td>
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\( a \) Relative energy, kcal/mol.

**Figure 1.** HOMOs of the diene B, derived from 1,4-naphthoquinone (left), and of 2b (right), viewed from the carbonyl face; B3LYP/6-311+G(d,p).
X-ray geometry. This gave an excellent RMSD of 0.046 for all heavy atoms, indicating that the b3lyp/6-311+G(d,p) is an adequate theory level for this large molecular system.

Table 1 lists computational results in four groups arranged by facial selectivity and sorted by the (global) relative energy, kcal/mol. As follows from Table 1, the observed dimer indeed has the lowest relative energy.

It appears that the most favorable regiochemistry for Group 1 and Group 3 is achieved when X₂ is oxygen and Y₂ is carbonyl. When X₂ is a carbonyl group, the steric destabilization can be attributed to the congestion created by this carbonyl's proximity to the double bond in the bicyclo[2.2.2] moiety. The positions of the X₁ and Y₁ groups (i.e., the –C(=O)– and –O– groups in the ‘diene component’) is predicted to have a lesser effect on the regiochemical outcome of the cyclodimerization.

The detrimental effect of the carbonyl group in the position X₂ can partially account for the reluctance of the 1,4-naphthoquinone-based caged dienes B to dimerize. Experimentally we did not observe any evidence for the dimerization of B. More revealing and relevant to this failure of B to dimerize is the comparative electronic population analysis in B and 2a. Figure 2 shows that atoms in the butadiene moiety of B are depleted of electronic density to a much greater extent—the cumulative positive charge of the moiety is 1.16 versus 0.405 in 2a—that is, almost threefold difference. The electronic density in the chromone-derived 2a is much less depleted and it is also appropriately polarized with the ‘dieneophilic’ bond becoming more electrophilic, Figure 2.

Conceivably, this polarization and lack of symmetry in 2a ensure that non-symmetric dienophiles, such as vinyl phenyl ketone, undergo a D.–A. addition to 2a in a highly regio- and stereo-selective fashion, yielding an endo-benzoyl bicyclo[2.2.2] structure 3a with syn-regiochemistry of carbonyl groups, Scheme 4. One notes that the regio- and stereochemistry of 3a are thus pre-defined at the first D.–A. step chromone→1a.

Endo-benzoyl polycycle 3a was then introduced into our photoprotolytic sequence. First, the Paternò–Büchi reaction, photoinduced with broadband 300–400 nm irradiation in benzene, yielded 85% of oxetane 5a. The oxetane, when treated with HCl–dioxane in DCM, undergoes cycloreversion to an alternative alkene-carbonyl pair, which amounts to alkene-carbonyl (oxa)-metathesis. Secondary electrophilic attack of H⁺ on the newly formed styrene moiety followed by nucleophilic participation of the transient enol results in the formation of cyclopropyl ring, as shown in Scheme 5.

It is worth noting that the regio- and stereochemical outcome of the overall synthetic sequence chromone→6 is not decided at the photoprotolytic oxametathesis step, as the configuration inherited in 3 is simply passed on to the rearranged 6. Given that the stereochemistry of 3 itself is effectively defined at the first D.–A. step (yielding 1), this observation is significant, as there exists a number of approaches to control the stereochemistry of the first D.–A. step. The endo/exo ratio for the cyanochromone cycloaddition is very high (>95:5), according to Hsung⁶ and our own observations. One expects that high enantioselectivity in the formation of 1 can also be achieved, as a number of suitable chiral auxiliaries, such as

![Figure 2. Calculated charges in the butadiene moiety of B and 2a (with hydrogen charges summed into heavy atoms) B3LYP/6-311+G(2d,2p).](image)

![Scheme 4. Photoprotolytic oxametathesis sequence. ORTEP drawings of the respective X-ray structures are shown at right.](image)

![Scheme 5. A plausible mechanism of the acid-catalyzed ring opening-ring closure step.](image)
Corey’s oxazaborolidines etc.,10 have been optimized for this task. The significance of this is hard to overestimate as the overall sequence chromone–6a produces a decorated polycycle possessing twelve stereogenic centers, five of which are quaternary.

In conclusion, we have demonstrated that the Diels–Alder adducts of chromones can be capable of photoinduced alkene–arene [2+2] cycloaddition furnishing a versatile diene, which can dimerize or can be introduced into a double-tandem [4+2][2+2] ring opening-ring closure, leading to expeditious growth of molecular complexity over a few experimentally simple steps. The appealing feature of this approach is that the first D–A step controls the stereochemical outcome of the entire sequence.

Acknowledgment

Support of this research by the NIH, GM093930, is gratefully acknowledged.

References and notes

9. General experimental procedures:
Alkene–arene [2+2] photo cycloaddition. Approximately 10 mM solution of an endo-precursor 1 in benzene was irradiated in a Pyrex vessel in the Rayonet reactor equipped with RFR–3500 UV lamps (broadband 300–450 nm UV source with peak emission at 350 nm) for 24–48 h. Irradiation resulted in a quantitative conversion to 2, which can be further purified by chromatography or used without purification.

Diene 2a: from 2.23 g of 1a (8.9 mmol) in 1.0 L of benzene, irradiation for 24 h (hexane/EtOAc gradient 15:1 to 5:1): 1.23 g (55%). \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 6.00 (dd, \(J = 9.6, 5.8\) Hz, 1H), 5.95 (ddd, \(J = 9.8, 5.8, 1.0\) Hz, 1H), 5.54 (d, \(J = 9.6\) Hz, 1H), 4.80 (m, 1H), 4.75 (d, \(J = 4.3\) Hz, 1H), 3.50 (ddd, \(J = 5.5, 3.5, 1.7\) Hz, 1H), 2.95–2.91 (m, 2H), 2.74 (ddd, \(J = 6.5, 1.8, 1.8\) Hz, 1H), 2.54 (dd, \(J = 7.6, 5.2\) Hz, 1H), 2.36 (m, 1H), 2.26 (m, 1H), 2.12 (dd, \(J = 6.2, 1.3\) Hz, 1H), 2.01–1.90 (m, 4H), 1.81 (dd, \(J = 13.2, 6.7\) Hz, 1H), 1.63–1.56 (m, 1H). \(^1\)C NMR (500 MHz, CDCl\(_3\)) \(\delta\) 202.03, 136.31, 129.11, 128.75, 127.15, 117.46, 110.10, 90.43, 81.47, 81.37, 56.84, 54.57, 53.16, 42.39, 63.89, 38.59, 37.05, 36.12, 35.43, 32.73, 92.12, 15.92, 14.11. HRMS (ESI) calcd for C\(_{25}\)H\(_{22}\)NO\(_3\) \(\text{[M} + \text{H}]^+\) 385.1594, found 385.1586.

HCl-catalyzed cyclotetras to aldehydes. A 10-fold excess of HCl (4.0 M solution in dioxane) was added to a solution of oxetane 5 in dichloromethane (D–A) and stirred overnight at room temperature, washed twice with 5% aqueous NaOH and water. The crude aldehyde 6 was purified by column chromatography.

Aldehyde 6a: from 200 mg (0.52 mmol) of 5a and 2.61 mL of HCl (4.0 M, 10.43 mmol) in DCM (hexane/EtOH 1:10, then DCM/MeOH 2:1) 278 mg (71%). \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 8.41 (s, 1H), 7.38–7.30 (m, 5H), 4.74 (dd, \(J = 4.1\) Hz, 1H), 3.16 (ddd, \(J = 7.8, 5.9, 1.3\) Hz, 1H), 2.89 (dd, \(J = 2.9\) Hz, 1H), 2.82 (m, 1H), 2.69 (dd, \(J = 7.9, 5.9\) Hz, 1H), 1.91 (m, 1H), 1.52 (m, 1H), 2.27–2.18 (m, 5H), 2.11–2.04 (m, 1H), 2.02–1.96 (m, 1.72–1.65 (m, 1H). \(^1\)C NMR (500 MHz, CDCl\(_3\)) \(\delta\) 200.43, 198.84, 137.60, 129.27, 128.99, 128.81, 117.41, 89.39, 82.69, 54.40, 52.37, 42.46, 40.09, 39.91, 37.74, 35.82, 35.73, 35.58, 34.57, 29.40, 28.18, 15.86, 14.31. HRMS (ESI) calcd for C\(_{22}\)H\(_{20}\)NO\(_3\) \(\text{[M} + \text{H}]^+\) 384.1594, found 384.1592.

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