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## Catalytic hypervalent iodine promoters allow styrene dimerisation and the formation of tri- and tetrasubstituted cyclobutanes

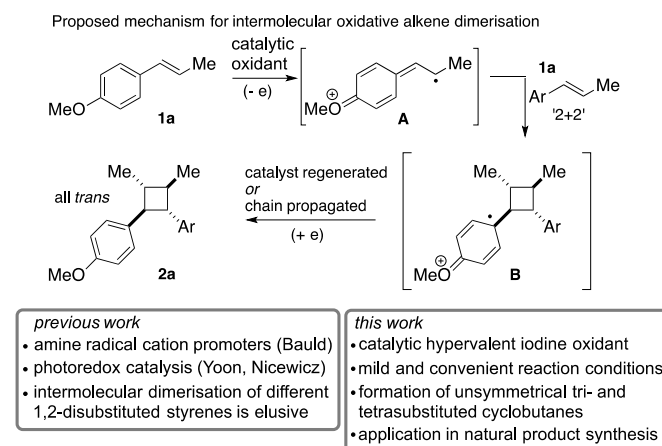
Ignacio Colomer, Rosimeire Coura Barcelos and Timothy J. Donohoe\*

**Abstract:** We report that the use of catalytic quantities of hypervalent iodine reagents (PIDA or Dess Martin Periodinane) allows the rapid and stereoselective formation of cyclobutanes under very mild conditions. The presence of a fluorinated solvent is essential for the success of these reactions which are able to form unsymmetrical tri- and tetrasubstituted cyclobutanes *via* a heterodimerisation process involving two different alkenes.

We have recently engaged in a programme of research aimed at exploring metal-free conditions for the oxidation of organic compounds. One of our objectives is the study of hypervalent iodine reagents and the contributions that they can make to organic synthesis.<sup>[1]</sup> In particular, we wanted to explore hypervalent iodine reagents as promoters of single electron transfer (SET)<sup>[2,3]</sup> processes, because we think it is an underdeveloped and underutilized area with significant potential for reaction discovery. One interesting SET promoted reaction that captured our attention involves the formation of cyclobutanes<sup>[4,5]</sup> from electron rich alkenes (notably styrenes).

The oxidation-promoted dimerisation reaction of electron-rich alkenes was first reported by Ledwith who used Fe(III) and Ce(IV) to form a radical cation from an alkene.<sup>[6]</sup> Later work by Bauld showed the effectiveness of triaryl amine radical cations to oxidise alkenes.<sup>[7]</sup> In general, the oxidised form of an alkene (exemplified with **1a**→**A**, Scheme 1) is proposed to react with another molecule of (unoxidised) alkene to form an oxidised cyclobutane intermediate (**B**) which then captures an electron to regain neutrality and form the product **2a**, Scheme 1. The source of the electron for the final step may be either the reduced form of the catalyst (ie as produced in the

first step), or alternatively another molecule of alkene, to propagate the chain.<sup>[8]</sup> Since these early reports, great progress has been made in developing this reaction using photoredox chemistry to promote the dimerisation, and both Yoon<sup>[9]</sup> and Nicewicz<sup>[10]</sup> have explored the role of different photoredox catalysts in cyclobutane formation. However, problems still remain with the generality of this reaction especially in the formation of more substituted cyclobutane rings from intermolecular heterodimerisation processes. Herein, we report a simple and powerful catalytic method for styrene dimerisation using hypervalent iodine reagents. It is especially notable in that it allows the rapid formation of unsymmetrical tetra-substituted cyclobutanes, and we are not aware of any examples of this motif being prepared by such an oxidative pathway. The products are formed with high diastereoselectivity (all *trans*) by a reliable head to head coupling process. Moreover, we also illustrate the power of this methodology with a short synthesis of a tetrasubstituted natural product,<sup>[11]</sup> nigramide R.<sup>[12]</sup>



**Scheme 1.** Oxidation promoted intermolecular styrene dimerisation.

Our work began by screening hypervalent iodine reagents for the dimerisation of **1a** to form **2a**, Table 1. Initially, we found that a wide range of standard solvents were not compatible with the reaction at all and only starting material was recovered. We noted that hypervalent iodine reagents are sometimes used in fluorinated solvents<sup>[3,13]</sup> and therefore we screened hexafluoroisopropanol (HFIPA) for the dimerization. Pleasingly, the reaction began to work well, and the addition of 10 mol% IBX formed **2a** in 39% yield (Table 1, entry 1). Other hypervalent catalysts were added and PIDA (entry 4) showed the most promise. Surprisingly, lowering the catalyst loading to 5 mol% increased the yield of **2a** to 63% (entry 6), and finally, performing the reaction at 0 °C (with warming to RT after 2h) gave 76% of dimer **2a** (entry 8). A control experiment without hypervalent iodine additive showed only starting material present, confirming the crucial role of the catalyst. Moreover, controls using 10 mol% of BHT, added as radical scavenger, meant that the yield for dimerization of **1a**→**2a** dropped from 76% to 7%; when using 1.0 equiv. of BHT additive the formation of cyclobutane **2a** was completely suppressed. A similar pattern of reactivity was observed when using TEMPO (10 mol% or 1.0 equiv.).

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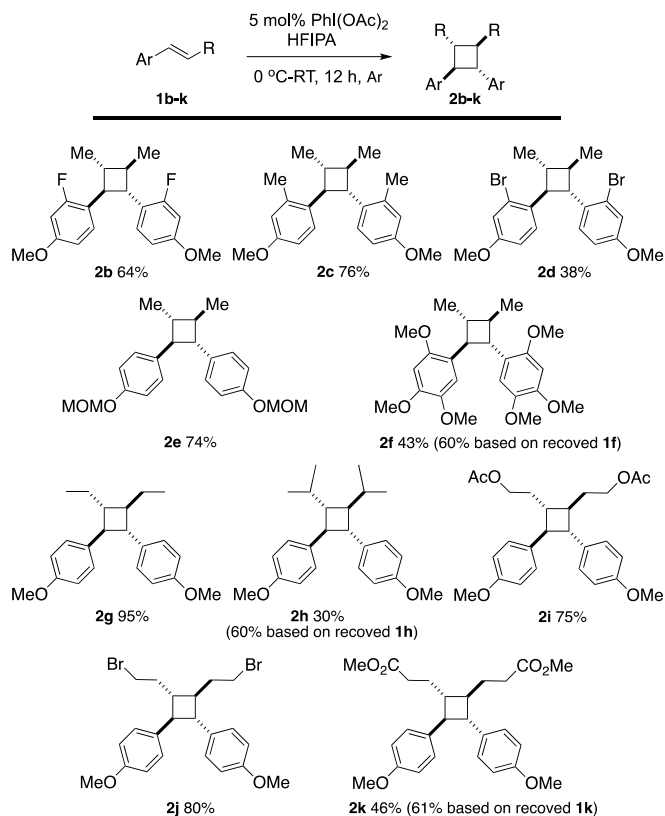
[\*\*] We thank the European Union and the European Commission for financial support: the research leading to these results has received funding from the People Programme (Marie Curie Actions) of the European Union's Seventh Framework Programme (FP7/2007-2013). RCB thanks FAPESP (Award No. 2014/16516-9) for scholarship funding.

Entry	Catalyst	Temperature	Yield <b>2a</b> (%)
1	10 mol% IBX	RT	39
2	10 mol% DMP	RT	33
3	10 mol% PhI(O <sub>2</sub> CCF <sub>3</sub> ) <sub>2</sub>	RT	22
4	10 mol% PhI(OAc) <sub>2</sub>	RT	51
5 <sup>a</sup>	10 mol% PhI(OAc) <sub>2</sub>	RT	34
6	5 mol% PhI(OAc) <sub>2</sub>	RT	63
7	1 mol% PhI(OAc) <sub>2</sub>	RT	39
8	5 mol% PhI(OAc) <sub>2</sub>	0 °C - RT	76
9	No catalyst	RT	0

<sup>a</sup> Reaction run in CF<sub>3</sub>CH<sub>2</sub>OH

**Table 1.** Effect of hypervalent iodine reagent on head to head dimerisation yields. **2a** was isolated as a single (racemic<sup>[14]</sup>) diastereoisomer (≥95:5 dr) according to NMR spectroscopy.

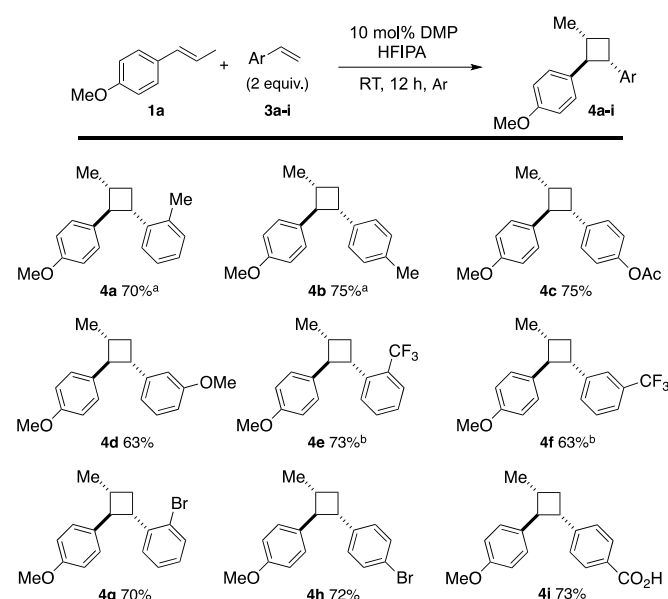
We then examined the dimerisation of a wider range of alkenes using the optimized conditions, Scheme 2. These studies revealed that there is significant variation possible in the aromatic ring, but that it must remain electron-rich in order to facilitate dimerisation (compare the yields of **2d** with both **2b** and **2c**). The natural product magnosalin **2f** was prepared by dimerization in 43% yield.<sup>[10]</sup> It was also possible to dimerise a variety of alkenes whereby the methyl group had been replaced by a longer chain (**2g**) and/or a more functionalized group (**2i-k**). Steric hinderance retarded cyclisation, as evidenced by the slow (and lower yielding) formation of cyclobutane **2h** bearing two isopropyl groups.<sup>[15]</sup>



**Scheme 2.** Homodimerisation of electron-rich disubstituted styrenes using catalytic PIDA. The product was formed as a single diastereoisomer (≥95:5 dr) according to NMR spectroscopy.

During this work, we noticed that several styrenes did not dimerise under the oxidative conditions (presumably this is a consequence of their inability to be oxidized by the hypervalent iodine reagent). However, this failure proved to be an advantage and allowed heterodimerisation reactions to take place between these alkenes and electron rich **1a**. Low concentrations of **1a** were necessary to avoid homodimerisation; therefore, we added **1a** (dropwise) to a solution of an otherwise unreactive alkene **3a-i** (2 equivalents). Further optimization (not shown) of the heterodimerisation revealed that catalytic Dess-Martin Periodinane in HFIPA was the best set of conditions, with temperatures ranging from RT to 40 °C.

Use of this protocol allowed us to form a range of heterodimerised cyclobutane products, where the unreactive (to homodimerisation) alkene could contain either electron donating (**3a,b**) or electron withdrawing (**3d-i**) substituents, Scheme 3.<sup>[15]</sup> In each case the cyclobutane product was isolated as a single diastereoisomer (≥95:5 dr) according to NMR spectroscopy.

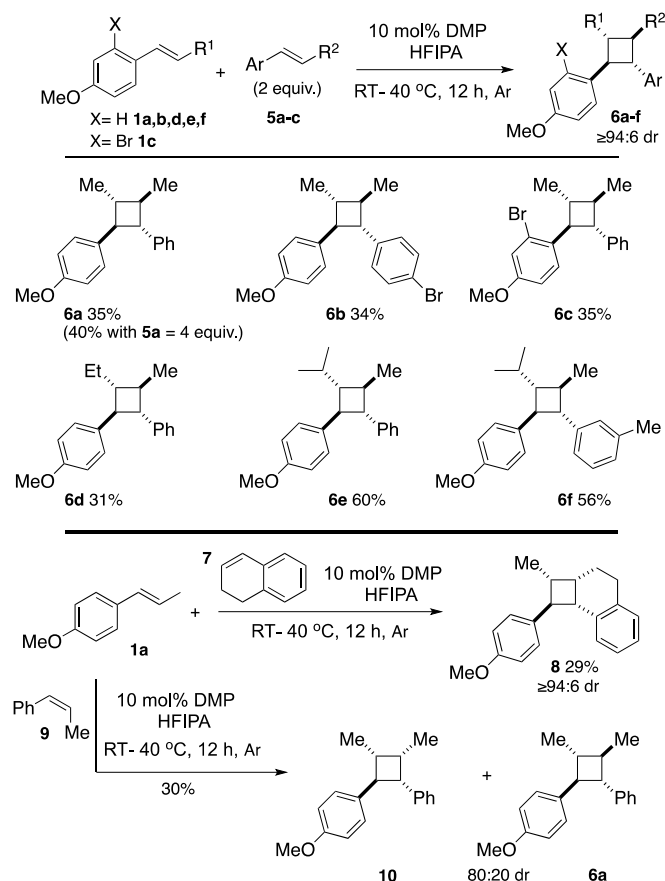


<sup>a</sup> CF<sub>3</sub>CH<sub>2</sub>OH used as solvent; <sup>b</sup> reaction run at 40 °C

**Scheme 3.** Heterodimerisation reactions of electron-rich alkene **1a**.

We could take this idea further and allow the formation of tetra-substituted cyclobutanes by utilizing a 1,2-disubstituted styrene as a partner, Scheme 4. In this situation, we found that the cross dimerisation reaction was slower than those shown above with mono-substituted alkenes and consequently it was more difficult to prevent homodimerisation of the *para*-methoxy styrene **1a**, resulting in lower yields (see **6a,b**). In addition to the desired product, the reaction mixtures contained unreacted alkene **5**, traces of the homodimer of **1** and baseline material (tlc) which could not be identified.

We noted that the parent alkene **1h** bearing an isopropyl group gave low homodimerisation yields (see **2h**, Scheme 2, presumably because of a steric influence) and so this proved to be a good partner for crossed dimerisations with disubstituted alkenes, forming tetrasubstituted cyclobutanes **6e** and **6f** in 56-60% yield. The methodology reported here represents the only conditions yet available for such a challenging oxidative promoted heterodimerisation reaction to form a 1,2,3,4-tetra-substituted cyclobutane.<sup>[15]</sup>



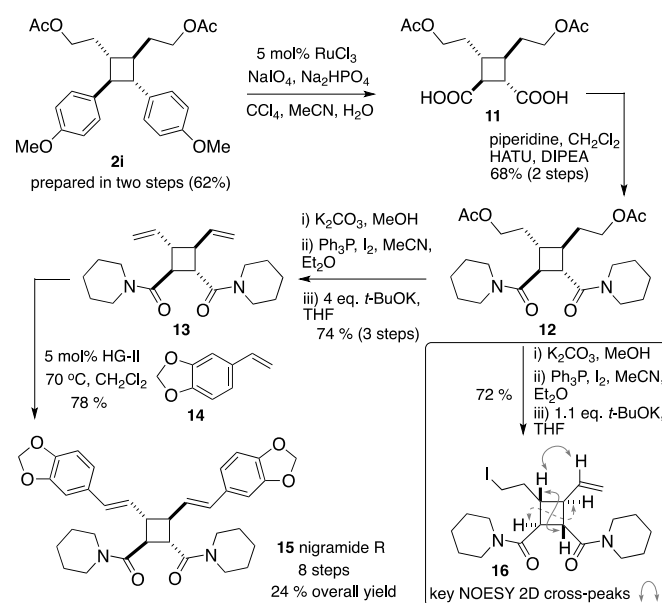
**Scheme 4.** Synthesis of unsymmetrical tetrasubstituted cyclobutanes. While compounds **6** and **8** were formed with high selectivity ( $\geq 94:6$ ), minor traces of other cyclobutane compounds were observed in the NMR spectra.

We then examined the role that differing alkene geometry played on this reaction, Scheme 4. This is a difficult aspect to study because of the possibility of the starting alkenes becoming isomerized under the reaction conditions, leading to stereoisomeric products being formed. Therefore, we began by reacting alkene **1a** with a cyclic partner **7** in which isomerisation was impossible; the result was formation of the major stereoisomer **8** as shown.<sup>[15]</sup> Moreover, *cis*-methylstyrene **9** also participated in a heterodimerisation process with **1a**, and gave cyclobutane products **10** and **6a** in an 80:20 ratio. We note that the *cis* isomer **9** reacts more slowly in alkene dimerization than its *trans* counterpart **5a**.

Although we do not wish to comment on the stereoselectivity and stereospecificity of the process with respect to each partner at this point, there is clearly some transfer of stereochemical information from the starting materials to the products.<sup>[9,10]</sup> Despite the modest yields reported, the results shown in Scheme 4 represent a unique way to synthesise cyclobutanes with four different substituents and with complementary stereochemical arrangements (eg all *trans* and *trans, cis, cis*).

Finally, we were keen to extend this methodology to encompass natural product synthesis, and chose the tetra-substituted cyclobutane nigramide R as our target, Scheme 5. This compound is isolated from the roots of *Piper nigrum* and exhibits inhibitory activity against cytochrome P450 2D6<sup>[16]</sup> and cytotoxicity against a mouse lymphoma cell line (L5178Y).<sup>[12b]</sup> Intriguingly, the natural product has a specific rotation of zero, which hints at biosynthesis via a non-enzymatically controlled process, and which could conceivably include an alkene dimerization.<sup>[12a]</sup> Starting with cyclobutane **2i** (prepared in two steps using cross metathesis and

dimerisation as shown in Scheme 2) we were able to oxidatively cleave both aromatic rings to carboxylic acids using catalytic ruthenium tetroxide;<sup>[17]</sup> the polar acid **11** was not purified but immediately coupled to piperidine to furnish bis-amide **12** in 68% yield over the two steps. Conversion of bis acetate **12** into the vinyl compound **13** followed three steps (i) deacetylation (95%), conversion to the bis alkyl iodide (92%) and finally double E<sub>2</sub> elimination (85%) to give alkene **13** in 74% yield for the three steps combined. Finally, double cross metathesis with terminal alkene **14** (excess) using catalytic Hoveyda-Grubbs II allowed the formation of the symmetrical target nigramide R **15**; the spectroscopic data for this compound was a very good match with that reported in the literature.<sup>[18]</sup> Given that this compound had not been prepared in a laboratory, this eight step synthesis also serves to confirm the structure of the natural product. Note that the intermediate diiodide derived from **12** could be subjected to a mono-elimination to furnish **16**; extensive NMR (NOESY) analysis of this non-symmetrical compound proved the all *trans* stereochemistry as shown.<sup>[18]</sup>



**Scheme 5.** Eight step synthesis of nigramide R.

To conclude, we have shown that hypervalent iodine reagents are excellent catalysts for the dimerisation of electron-rich styrenes, with the use of hexafluoroisopropanol being essential. Both symmetrical and unsymmetrical cyclobutanes were prepared by promoting both homo- and heterodimerisation processes. The formation of unsymmetrical 1,2,3,4-tetra-substituted cyclobutanes from the intermolecular heterodimerisation of styrenes is now possible, and this is particularly significant. Finally, this method was used to synthesise the natural product nigramide R in an efficient eight step protocol, thus confirming the identity of this natural product.

**Keywords** · hypervalent iodine · cyclobutane · hexafluoroisopropanol · nigramide R · heterodimerisation

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**Homo- and heterodimerisation of styrenes to functionalised cyclobutanes**

**Catalytic hypervalent iodine promoters allow styrene dimerisation and the formation of tri- and tetrasubstituted cyclobutanes**

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The use of catalytic quantities of hypervalent iodine reagents (PIDA or Dess Martin Periodinane) allows the rapid and stereoselective formation of cyclobutanes under very mild conditions. The presence of a fluorinated solvent is essential for the success of these reactions which are able to form unsymmetrical tri- and tetrasubstituted cyclobutanes *via* a heterodimerisation process involving two different alkenes.

