Hypervalent iodine initiated intramolecular alkene dimerisation: a stereodivergent entry to cyclobutanes

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The emergence of new methods for the stereoselective synthesis of strained carbocycles is a challenging but worthwhile endeavour. Cyclobutanes, in particular, have attracted the attention of both medicinal chemists and material scientists for their unique properties. Herein, we present a new method that allows access to highly functionalized cyclobutanes with complementary *all-trans* and *trans-cis-trans* relative stereochemistry, that could not be accessed before. This approach consists of an intramolecular dimerisation of non-conjugated dienes using an oxidative single electron transfer (SET) process, and is initiated by catalytic amounts of hypervalent iodine reagents. The potential uses of these cyclobutanes is demonstrated with selective functionalization, including the formation of diols and carboxylic acids.

Developing new routes for the stereoselective synthesis of substituted cyclobutanes is of great interest and represents a challenging topic in organic chemistry.¹ Despite the appearance of the cyclobutane ring in different natural products with antifungal, anticancer and many other biological activities,² the absence of reliable, efficient and benign methods for the synthesis and incorporation of this strained carbocycle into complex molecules has hindered its widespread use.

Among the different methods reported for preparing cyclobutanes,³ the oxidative dimerisation of olefins represents a promising approach that was firstly developed by Ledwith⁴ and Bauld.⁵ However, the method was not fully exploited and this strategy, which involves the formation of an active radical cation, has recently attracted the attention of different groups

using metal complexes⁶ and organic⁷ photoredox catalysis to promote cyclisation.

We have also contributed to this field by using catalytic amounts of hypervalent iodine reagents⁸ in hexafluoroisopropanol (HFIP)⁹ for the stereoselective functionalization of alkenes; our methods include a metal-free *syn*-dihydroxylation¹⁰ and a formal [2+2]-cycloaddition of alkenes. This latter method proceeds via a single electron oxidation of styrene **I** to a radical cation and subsequent dimerisation with another molecule of styrene **I** (homodimerization) or with a different alkene **II** (heterodimerization) to give (after the re-addition of an electron to the product) the *all-trans* cyclobutane product **III** (Scheme 1a).¹¹ Moreover, mechanistic studies, using electrochemical and NMR experiments, revealed the formation of a hydrogen-bond between HFIP and the hypervalent iodine reagent as the physical origin of an enhanced oxidative strength of the iodine reagent in HFIP solvent (Scheme 1a).¹²

Aiming to exploit this selective and powerful method, we sought to investigate an intramolecular version¹³ whereby the dimerisation of two alkenes linked with an appropriate tether **IV** would allow access to cyclobutanes with complementary relative stereochemistry, depending on the length of the tether.

Scheme 1. Inter- and intramolecular alkene cycloaddition

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Moreover, developing a tethered variant whereby both olefins are easily attached and the tether is readily cleaved afterward might offer reactivity advantages (Scheme 1b).¹⁴

We began our investigation by examining the reactivity of symmetrical dienes **1a-c** (obtained from the corresponding homoallyl alcohol bearing a 4-methoxyphenyl (PMP) group, and different silyl-dichlorides or ditriflates, see ESI for details). Reaction of isopropyl derivative **1a** under the two sets of optimal conditions reported for the intermolecular version, with 10 mol% of hypervalent iodine reagent in HFIP at room temperature, revealed that phenyl iodonium diacetate (PIDA) was the best initiator (Table 1, entries 1 and 2). Product **2a**, with a [7.2.0] fused bicyclic core, was obtained as a single all-*trans* diastereoisomer in a respectable 55% isolated yield. However, efforts to optimise these conditions were not productive; see the use of alternative fluorinated solvents (Table 1, entry 3), lowering the PIDA loading (Table 1, entry 4) or using different temperatures, 0 °C or 40 °C (Table 1, entry 5,6). Higher concentrations of the reagents (Table 1, entry 7) was detrimental, while dilution (Table 1, entry 8) showed no effect. Finally, modifying the silicon tether, introducing bulkier substituents, **1b** (Table 1, entry 9) or changing the electronic properties, **1c** (Table 1, entry 10) were satisfactory in producing the all-*trans* isomer, but gave no improvement in yield.

Entry	[s.m.]	Oxidant	Temperature	Yield (%)
1	0.1M of 1a	10 mol% DMP	RT	26
2	0.1M of 1a	10 mol% PIDA	RT	55
3 ^a	0.1M of 1a	10 mol% PIDA	RT	12
4	0.1M of 1a	5 mol% PIDA	RT	37
5	0.1M of 1a	10 mol% PIDA	0 °C	35
6	0.1M of 1a	10 mol% PIDA	40 °C	37
7	0.2M of 1a	10 mol% PIDA	RT	26
8	0.02M of 1a	10 mol% PIDA	RT	50
9	0.1M of 1b	10 mol% PIDA	RT	42
10	0.1M of 1c	10 mol% PIDA	RT	21

^a Reaction run in CF₃CH₂OH

Table 1. Optimization for the silicon tethered dimerisation.

Using the best conditions (Table 1 entry 2) we turned our attention to explore the scope, paying particular attention to challenging unsymmetrical dimerization processes and varying the size of the ring and position of the heteroatom in the tether. When changing one of the PMP aryl groups to a less electron rich *p*-methyl the reaction proceeded with all-*trans* stereoselectivity, although with slightly diminished yield (Table 2, **2d**).¹⁵ One of the limitations of the intermolecular version of this reaction was the unproductive reaction of allylic alcohols,

where no desired product was observed.¹¹ However, the intramolecular cycloaddition that we report herein allows us to overcome this limitation. Using allylic alcohols and a bis-silyloxy tether to keep the size of the fused [7.2.0] bicycle fixed, **2e** was obtained in good yields and respectable stereocontrol. Encouraged by this result, we sought to dimerise an allylic and a homoallylic alcohol using the same bis-silyloxy tether, leading in this case to the fused [8.2.0] bicycle **2f** with high all-*trans* stereocontrol and good yield. This example is of special relevance, because it pushes the boundary of our previous method, and encompasses the formation of a tetrasubstituted cyclobutane bearing four different substituents, using allylic alcohol derivatives as reactants.

Following the same strategy incorporating both allylic and homoallylic alcohols, but turning back to the original silicon tether used in the optimization, the smaller fused [6.2.0] bicycle **3g** was obtained in good yield and modest diastereoselectivity, although this does represent a reversal in the stereocontrol. For instance, starting with the same allylic and homoallylic alcohols building blocks, simply by changing the silicon tether complementary all-*trans* **2f** or *trans-cis-trans* **3g** can be accessed. Different aromatic substitution (Table 2, **3h**) and swapping the allylic/homoallylic moiety (Table 2, **3i** vs. **3g**) were also tolerated, giving similar results. Finally, using two allylic alcohols as precursors allowed us to access even smaller fused [5.2.0] bicycles, both symmetric, **3j-m** and unsymmetric, **3n**, with better stereocontrol for the *trans-cis-trans* isomers (dr of up to 3:1, Table 2, **3l**).¹⁶

Table 2. Silicon tethered alkene dimerisation.

Encouraged by the promising results using shorter silicon tethered examples, where the stereoselectivity is constrained to form *trans-cis-trans* **3** within a smaller ring, we sought to investigate another intramolecular version, with an even shorter tether by using symmetrical and unsymmetrical ethers **4**, derived from allylic alcohols (see ESI for details).¹⁷ Under the optimal experimental conditions *trans-cis-trans* fused [3.2.0] cyclobutyl tetrahydrofurans **5** were formed, as had been observed by Yoon under photoredox catalysis¹³ (Table 3). Keeping one PMP substituent fixed on one of the alkenes, both aromatic and aliphatic substitution in the remaining alkene was well tolerated, although better results were obtained with aromatic substitution. Electron rich aromatic rings, such as PMP (Table 3, **5a**), neutral non-substituted phenyl (Table 3, **5b**) or electron withdrawing, for example bromo- and trifluoromethyl derivatives (Table 3, **5c** and **5d**) performed extremely well, with up to 80% isolated yields. Challenging unsymmetrically substituted examples bearing *ortho* substituents on the aromatic ring were sluggish partners in our previous intermolecular approach. However, this limitation is, once again, solved in the intramolecular approach. For example, *ortho*-methyl derivative **5e** was obtained in 64% yield as a single diastereoisomer (Table 3). Aliphatic substitution was briefly explored, and we are delighted to observe that cyclobutanes bearing gem-dialkyl groups can be obtained, although in modest yield (Table 3, **5f-g**).

Table 3. Intramolecular bis-allylether dimerisation.

One of the advantages of the new silicon tethered approach is the opportunity to functionalise the products by cleaving the silicon tether. Treating cyclobutanes from Table 2 with TBAF in THF furnished the corresponding diols in excellent yields (Table 4). Therefore, 1,4-diols, incorporating either an *all-trans* (**6b**) or *trans-cis-trans* (**7a**) cyclobutyl motif can be obtained straightforwardly in high yields.

Table 4. Silicon tether cleavage leads to 1,6- and 1,4-diols.

Finally, selective functionalization of the cyclobutane products offers an opportunity to install a variety of groups that can be used to manipulate these strained carbocycles. For example, selective oxidation of the electron rich aromatic ring PMP to a carboxylic acid was carried out in the presence of other functionalities; the silicon tether resists oxidative conditions using catalytic RuCl_3 and NaIO_4 affording carboxylic acid **8a**.¹⁸ Pleasingly, neutral (Table 5, **8b**) electron deficient (Table 5, **8c**) and electron rich (Table 5, **8d**) aromatic rings are also compatible with this oxidation.

Table 5. Carboxylic acids via oxidation of the PMP group.

In conclusion, we have developed a new approach for the synthesis of highly substituted and stereodefined cyclobutanes via intramolecular dimerisation of two alkenes in an oxidative process, initiated by hypervalent iodine reagents in HFIP. Longer tethering gave rise to all *trans* stereochemistry, while shorter tethers favoured the formation of the *trans-cis-trans* isomers. We have also demonstrated the utility of the fused bicyclic products. Cleavage of the tether affords 1,4- and 1,6-diols, while oxidation of the aromatic ring installs a valuable carboxylic acid; both functionalities could be used as a handle to further manipulate these structures.

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