Cyclization

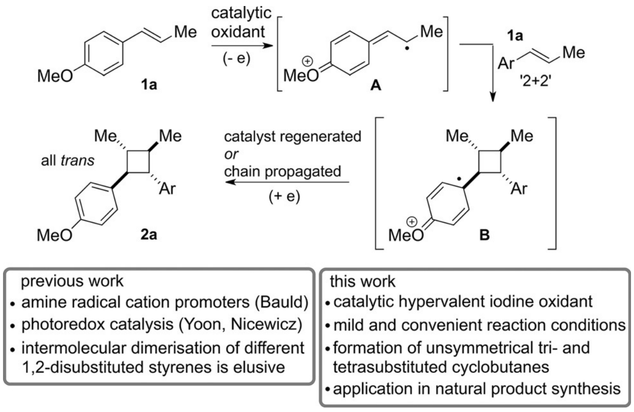
International Edition: DOI: 10.1002/anie.201511683
German Edition: DOI: 10.1002/ange.201511683

Catalytic Hypervalent Iodine Promoters Lead to Styrene Dimerization and the Formation of Tri- and Tetrasubstituted Cyclobutanes

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

***Abstract:** Reported herein is that the use of catalytic quantities of hypervalent iodine reagents (phenyliodine diacetate or Dess–Martin periodinane) allows the rapid and stereoselective formation of cyclobutanes under very mild reaction conditions. The presence of a fluorinated solvent is essential for the success of these reactions which form unsymmetrical tri- and tetrasubstituted cyclobutanes through a heterodimerization process involving two different alkenes.*

We have recently engaged in a program 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.[1] In particular, we wanted to explore hypervalent iodine reagents as promoters of single-electron transfer (SET)[2,3] 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[4,5] from electron-rich alkenes (notably styrenes).



previous work
- amine radical cation promoters (Bauld)
- photoredox catalysis (Yoon, Nicewicz)
- intermolecular dimerisation of different 1,2-disubstituted styrenes is elusive

this work
- catalytic hypervalent iodine oxidant
- mild and convenient reaction conditions
- formation of unsymmetrical tri- and tetrasubstituted cyclobutanes
- application in natural product synthesis

Scheme 1. Oxidation-promoted intermolecular styrene dimerization. The proposed reaction mechanism is shown.

The oxidation-promoted dimerization reaction of electron-rich alkenes was first reported by Ledwith and coworkers who used iron(III) and cerium(IV) to form a radical cation from an alkene.[6] Later work by Bauld et al. showed the effectiveness of triaryl amine radical cations to oxidize alkenes.[7] In general, the oxidized form of an alkene (exemplified with **1a**→**A**; Scheme 1) is proposed to react with another molecule of (unoxidized) alkene to form an oxidized cyclobutane intermediate (**B**) which then captures an electron to regain neutrality and form the product **2a**. The source of the electron for the final step may be either the reduced form of the catalyst (i.e., as produced in the first step), or alternatively another molecule of alkene, to propagate the chain.[8] Since these early reports, great progress has been made in developing this reaction using photoredox chemistry to promote the dimerization, and both the groups of Yoon[9] and Nicewicz[10] 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 heterodimerization processes. Herein, we report a simple and powerful catalytic method for styrene dimerization using hypervalent iodine reagents. It is especially notable in that it allows the rapid formation of unsymmetrical tetrasubstituted 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 the tetrasubstituted natural product[11] nigramide R.[12]

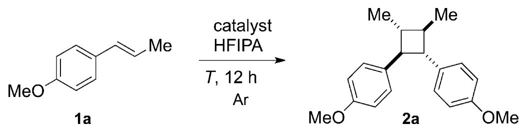
Our work began by screening hypervalent iodine reagents for the dimerization of **1a** to form **2a** (Table 1). Initially, we found that a wide range of standard solvents were not compatible with the reaction at all and only starting material was recovered. We noted that hypervalent iodine reagents are sometimes used in fluorinated solvents[3,13] 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 (entry 1). Other hypervalent catalysts were added and phenyliodine diacetate (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 room temperature after 2 h) gave 76% of **2a** (entry 8). A control experiment without a hypervalent iodine additive showed only starting material present, thus confirming the crucial role of the catalyst. Moreover, controls using 10 mol% of 2,6-bis(1,1-dimethylethyl)-4-methylphenol (BHT), added as a radical scavenger, meant that the yield for dimerization of **1a**→**2a** dropped from 76 to 7%; when using 1.0 equivalent of BHT additive the formation of cyclobutane **2a** was completely supressed. A

---

[*] Dr. I. Colomer, Dr. R. Coura Barcelos, Prof. T. J. Donohoe
Department of Chemistry, University of Oxford
Chemistry Research Laboratory
Mansfield Road, Oxford, OX1 3TA (UK)
E-mail: timothy.donohoe@chem.ox.ac.uk

Supporting information for this article can be found under http://dx.doi.org/10.1002/anie.201511683.

Table 1: Effect of hypervalent iodine reagent on head to head dimerization yields.

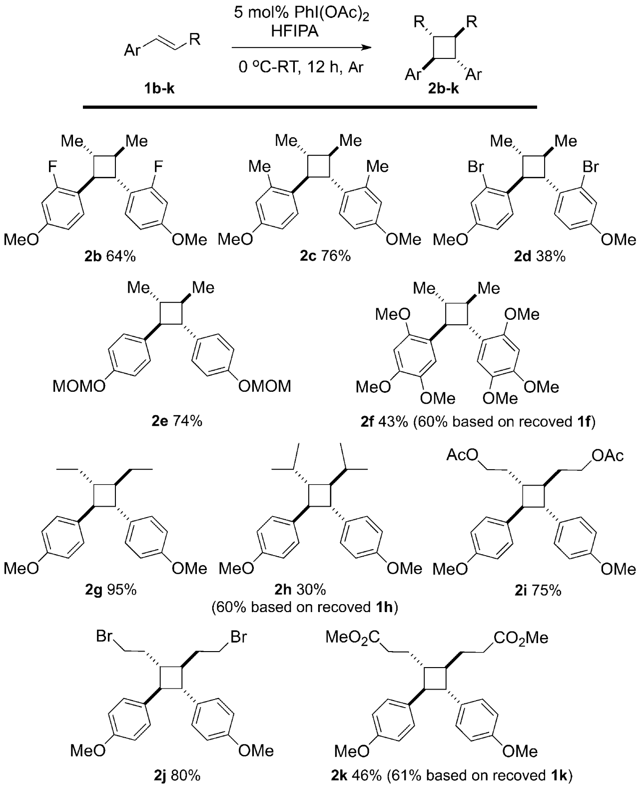


Entry	Catalyst	*T* [°C]	Yield of **2a** [%][a]
1	10 mol% IBX	RT	39
2	10 mol% DMP	RT	33
3	10 mol% $PhI(O_2CCF_3)_2$	RT	22
4	10 mol% $PhI(OAc)_2$	RT	51
5[b]	10 mol% $PhI(OAc)_2$	RT	34
6	5 mol% $PhI(OAc)_2$	RT	63
7	1 mol% $PhI(OAc)_2$	RT	39
8	5 mol% $PhI(OAc)_2$	0–RT	76
9	no catalyst	RT	0

[a] The product **2a** was isolated as a single (racemic)[14] diastereoisomer ($\geq$95:5 d.r.) according to NMR spectroscopy. [b] Reaction run in CF_3CH_2OH. DMP = Dess–Martin periodinane, IBX = *o*-iodoxybenzoic acid.

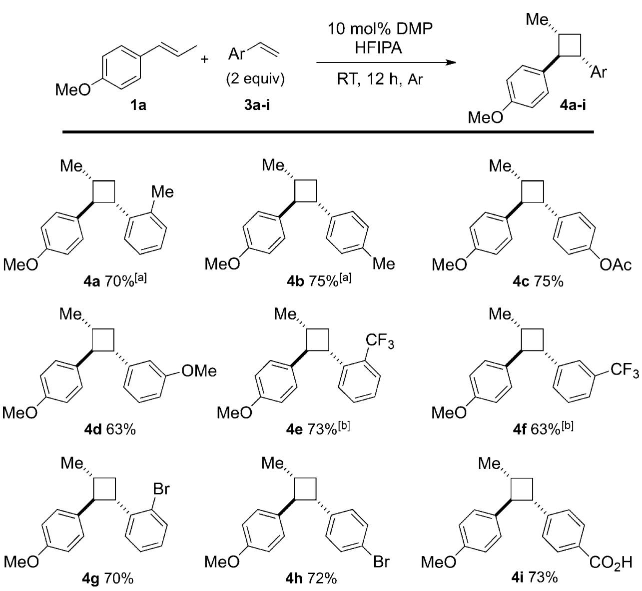
similar pattern of reactivity was observed when using TEMPO (10 mol% or 1.0 equiv).

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



Scheme 2. Homodimerization of electron-rich disubstituted styrenes using catalytic PIDA. The product was formed as a single diastereoisomer ($\geq$95:5 d.r.) according to NMR spectroscopy.

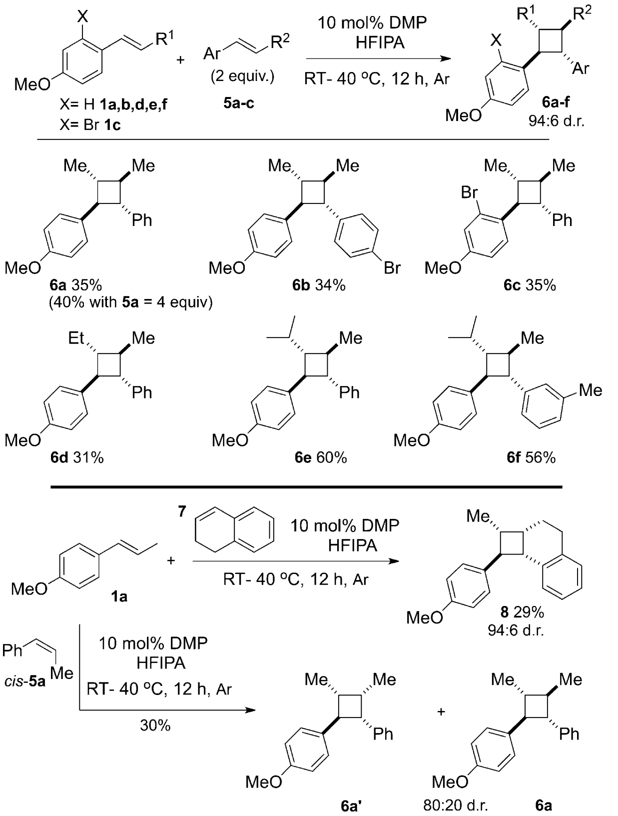
During this work, we noticed that several styrenes did not dimerize under the oxidative conditions (presumably this is a consequence of their inability to be oxidized by the hypervalent iodine reagent). However, this failure proved to be an advantage and allowed heterodimerization reactions to take place between these alkenes and electron-rich **1a**. Low concentrations of **1a** were necessary to avoid homodimerization, therefore, we added **1a** (dropwise) to a solution of an otherwise unreactive alkene (**3a—i**, 2 equiv; Scheme 3).



Scheme 3. Heterodimerization reactions of the electron-rich alkene **1a**. [a] CF_3CH_2OH used as solvent. [b] Reaction run at 40 °C.

Further optimization (not shown) of the heterodimerization revealed that catalytic Dess–Martin periodinane in HFIPA was the best set of conditions, with temperatures ranging from room temperature to 40 °C. Use of this protocol allowed us to form a range of heterodimerized cyclobutane products, where the unreactive (to homodimerization) alkene could contain either electron-donating (**3a**,**b**) or electron-withdrawing (**3d–i**) substituents.[15] In each case the cyclobutane product was isolated as a single diastereoisomer ($\geq$95:5 d.r.) according to NMR spectroscopy.

We could take this idea further and allow the formation of tetrasubstituted cyclobutanes by utilizing a 1,2-disubstituted styrene as a partner (Scheme 4). In this situation, we found that the cross-dimerization reaction was slower than those shown above with monosubstituted alkenes and consequently it was more difficult to prevent homodimerization of the *para*-

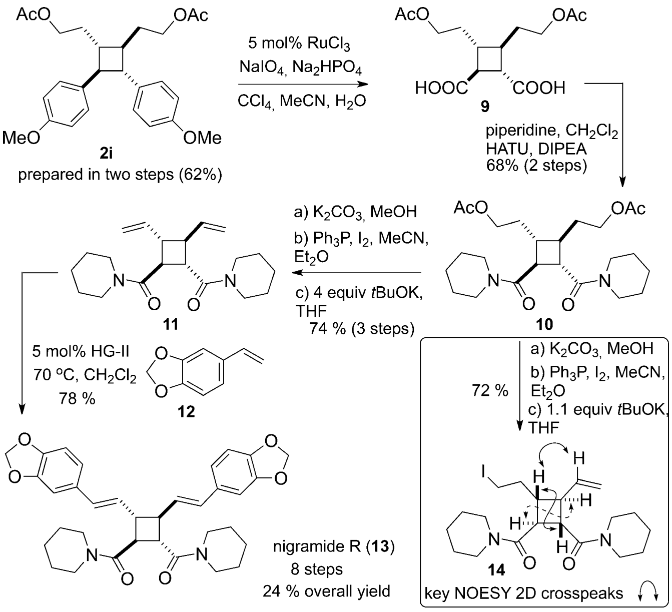


Scheme 4. Synthesis of unsymmetrical tetrasubstituted cyclobutanes. While the compounds **6** and **8** were formed with high selectivity ($\geq$94:6), minor traces of other cyclobutane compounds were observed in the NMR spectra.

methoxy styrene **1a**, thus resulting in lower yields (**6a**,**b**). In addition to the desired product, the reaction mixtures contained the unreacted alkene (**5**), traces of the homodimer of **1**, and baseline material (as determined by TLC) which could not be identified. We noted that the parent alkene **1h** bearing an isopropyl group gave low homodimerization yields (see Scheme 2; presumably because of a steric influence) and so this proved to be a good partner for crossed dimerizations with disubstituted alkenes, thus forming the tetrasubstituted cyclobutanes **6e** and **6f** in 56–60% yield (Scheme 4). The methodology reported here represents the only reaction conditions yet available for such a challenging oxidative-promoted heterodimerization reaction to form a 1,2,3,4-tetrasubstituted cyclobutane.[15]

We then examined the effect that differing alkene geometries had on this reaction (Scheme 4). This aspect is difficult to study because of the possibility of the starting alkenes isomerizing under the reaction conditions and leading to stereoisomeric products. Therefore, we began by reacting **1a** with the cyclic partner **7** in which isomerization was impossible, and the result was formation of the major stereoisomer **8** as shown.[15] Moreover, *cis*-methylstyrene (*cis*-**5a**) also participated in a heterodimerization process with **1a**, and gave the cyclobutane products **6a′** and **6a** in an 80:20 ratio. We note that *cis*-**5a** reacts more slowly in alkene dimerization than *trans*-**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.[9,10] Despite the modest yields reported, the results shown in Scheme 4 represent a unique way to synthesize cyclobutanes with four different substituents and with complementary stereochemical arrangements (e.g., all *trans* and *trans*, *cis*, *cis*).

Finally, we were keen to extend this methodology to encompass natural product synthesis, and chose the tetrasubstituted cyclobutane nigramide R (**13**) as our target (Scheme 5). This compound is isolated from the roots of *Piper nigrum* and exhibits inhibitory activity against cytochrome P450 2D6[16] and cytotoxicity against a mouse lymphoma cell line (L5178Y).[12b] Intriguingly, the natural product has a specific rotation of zero, which hints at biosynthesis by a non-enzymatically controlled process, and which could conceivably include an alkene dimerization.[12a] Starting with the cyclobutane **2i** (prepared in two steps using cross-metathesis and dimerization as shown in Scheme 2) we were able to oxidatively cleave both aromatic rings to carboxylic acids using catalytic ruthenium tetroxide.[17] The polar acid **9** was not purified but immediately coupled to piperidine to furnish the bis(amide) **10** in 68% yield over the two steps. Conversion of **10** into the vinyl compound **11** required three steps: 1) deacetylation (95%), 2) conversion into the bis(alkyliodide) (92%), and 3) finally double E_2 elimination (85%) to give **11** in 74% yield for the three steps combined. Finally, a double cross-metathesis with the terminal alkene **12** (excess) using a catalytic amount of the Hoveyda–Grubbs II catalyst allowed the formation of the symmetrical target nigramide R (**13**). The spectroscopic data for this compound was a very good match with that reported in the literature.[18] Given that this compound had not been prepared in



Scheme 5. Eight-step synthesis of nigramide R. DIPEA = diisopropylethylamine, HATU = 2-(1H-7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyl uronium hexafluorophosphate.

a laboratory, this eight-step synthesis also serves to confirm the structure of the natural product. Note that the intermediate diiodide derived from **10** could be subjected to a mono-elimination to furnish **14**. Extensive NMR (NOESY) analysis of this nonsymmetrical compound proved the all *trans* stereochemistry as shown.[18]

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

Acknowledgements

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.

Keywords: cyclizations · dimerization · hypervalent compounds · small ring systems · total synthesis

How to cite: *Angew. Chem. Int. Ed.* **2016**, *55*, 4748–4752
Angew. Chem. **2016**, *128*, 4826–4830

---

[1] For reviews on hypervalent iodine reagent chemistry, see: a) V. V. Zhdankin, *Hypervalent Iodine Chemistry*, Wiley, Hoboken, **2013**; b) V. V. Zhdankin, *J. Org. Chem.* **2011**, *76*, 1185; c) T. Dohi, Y. Kita, *Chem. Commun.* **2009**, 2073. For a general perspective of iodine chemistry, see: d) F. C. Küpper, M. C. Feiters, B. Olofsson, T. Kaiho, S. Yanagida, M. B. Zimmermann, L. J. Carpenter, G. W. Luther, Z. Lu, M. Jonsson, L. Kloo, *Angew. Chem. Int. Ed.* **2011**, *50*, 11598; *Angew. Chem.* **2011**, *123*, 11802.

[2] Hypervalent iodine reagents have been proposed to act as one-electron oxidants. For the generation of amidyl N-centered radicals using IBX, see: a) K. C. Nicolaou, P. S. Baran, Y.-L. Zhong, J. A. Vega, *Angew. Chem. Int. Ed.* **2000**, *39*, 2525; *Angew. Chem.* **2000**, *112*, 2625; b) K. C. Nicolaou, P. S. Baran, Y.-L. Zhong, S. Barluenga, K. W. Hunt, R. Kranich, J. A. Vega, *J. Am. Chem. Soc.* **2002**, *124*, 2233; c) B. Janza, A. Studer, *J. Org. Chem.* **2005**, *70*, 6991; d) K. C. Nicolaou, P. S. Baran, R. Kranich, Y.-L. Zhong, K. Sugita, N. Zou, *Angew. Chem. Int. Ed.* **2001**, *40*, 202; *Angew. Chem.* **2001**, *113*, 208. The combination of hypervalent iodine/I_2 under elevated temperatures or under irradiation has been used in radical pathways to generate oxygen or nitrogen radicals, such as the Suárez reaction: e) J. I. Concepción, C. G. Francisco, R. Hernández, J. A. Salazar, E. Suárez, *Tetrahedron Lett.* **1984**, *25*, 1953; f) C. Francisco, C. C. González, E. Suárez, *Tetrahedron Lett.* **1997**, *38*, 4141; g) A. Boto, R. Hernández, E. Suárez, *Tetrahedron Lett.* **2000**, *41*, 2899; h) A. Boto, R. Hernández, Y. de León, E. Suárez, *Tetrahedron Lett.* **2001**, *66*, 7796; i) D. Alvarez-Dorta, E. I. León, A. R. Kennedy, A. Martín, I. Pérez-Martín, E. Suárez, *Angew. Chem. Int. Ed.* **2015**, *54*, 3674; *Angew. Chem.* **2015**, *127*, 3745. For a review see: H. Togo, M. Katohgi, *Synlett* **2001**, 565, and references therein.

[3] a) Y. Kita, H. Tohma, M. Inagaki, K. Hatanaka, T. Yakura, *Tetrahedron Lett.* **1991**, *32*, 4321; b) Y. Kita, H. Tohma, K. Hatanaka, T. Takada, S. Fujita, S. Mitoh, H. Sakurai, S. Oka, *J. Am. Chem. Soc.* **1994**, *116*, 3684; c) H. Hamamoto, K. Hata, H. Nambu, Y. Shiozaki, H. Tohma, Y. Kita, *Tetrahedron Lett.* **2004**, *45*, 2293; d) T. Dohi, M. Ito, N. Yamaoka, K. Morimoto, H. Fujioka, Y. Kita, *Angew. Chem. Int. Ed.* **2010**, *49*, 3334; *Angew. Chem.* **2010**, *122*, 3406.

[4] Different reviews concerning aspects of cyclobutane chemistry have been published. For catalytic enantioselective [2+2] cycloaddition, see: a) Y. Xu, M. L. Conner, M. K. Brown, *Angew. Chem. Int. Ed.* **2015**, *54*, 11918; *Angew. Chem.* **2015**, *127*, 12086. For an update of thermal cyclobutane formation, see: b) B. Alcaide, C. Aragoncillo, P. Almendros, in *Comprehensive Organic Synthesis II*, 2nd ed. (Ed.: P. Knochel), Elsevier, Amsterdam, **2014**, pp. 66–84. For [2+2] photocycloaddition using α,β-unsaturated ketones, see: c) P. Margaretha, *Helv. Chim. Acta* **2014**, *97*, 1027. For the stereocontrolled synthesis of cyclobutanones, see: d) F. Secci, A. Frongia, P. Piras, *Molecules* **2013**, *18*, 15541. For the use of cyclobutanes in catalysis, see: e) T. Seiser, T. Saget, D. N. Tran, N. Cramer, *Angew. Chem. Int. Ed.* **2011**, *50*, 7740; *Angew. Chem.* **2011**, *123*, 7884. For allenes in [2+2] cycloaddition, see: f) B. Alcaide, P. Almendros, C. Aragoncillo, *Chem. Soc. Rev.* **2010**, *39*, 783.

[5] Alternative methods for the synthesis of cyclobutanes recently reported involve: iron-catalyzed [2+2] cycloaddition of unactivated alkenes: a) J. M. Hoyt, V. A. Schmidt, A. M. Tondreau, P. J. Chirik, *Science* **2015**, *349*, 960. Copper-catalyzed boration and cyclization of homoallylic sulfonates: b) H. Ito, T. Toyoda, M. Sawamura, *J. Am. Chem. Soc.* **2010**, *132*, 5990. Extensive work has been done on the metal-catalyzed intramolecular [2+2] of allenes. For nickel, see: c) N. N. Noucti, E. J. Alexanian, *Angew. Chem. Int. Ed.* **2015**, *54*, 5447; *Angew. Chem.* **2015**, *127*, 5537. For ruthenium, see: d) M. Gulías, A. Collado, B. Trillo, F. López, E. Oñate, M. A. Esteruelas, J. L. Mascareñas, *J. Am. Chem. Soc.* **2011**, *133*, 7660. For gold see: e) M. R. Luzung, P. Mauleón, F. D. Toste, *J. Am. Chem. Soc.* **2007**, *129*, 12402.

[6] For the first examples of cerium- and iron-catalyzed vinyl carbazole dimerization, see: a) A. Ledwith, *Acc. Chem. Res.* **1972**, *5*, 133; b) F. A. Bell, R. A. Crellin, H. Fujii, A. Ledwith, *J. Chem. Soc. D* **1969**, 251.

[7] a) N. L. Bauld, D. J. Bellville, B. Harirchian, K. T. Lorenz, R. A. Pabon, D. W. Reynolds, D. D. Wirth, H. S. Chiou, B. K. Marsh, *Acc. Chem. Res.* **1987**, *20*, 371; b) N. L. Bauld, D. J. Bellville, R. Pabon, R. Chelsky, G. Green, *J. Am. Chem. Soc.* **1983**, *105*, 2378; c) N. L. Bauld, R. Pabon, *J. Am. Chem. Soc.* **1983**, *105*, 633.

[8] A radical cation intermediate has been detected using extractive electrospray ionization mass spectrometry (EESI-MS). See: C. A. Marquez, H. Wang, F. Fabbretti, J. O. Metzger, *J. Am. Chem. Soc.* **2008**, *130*, 17208.

[9] For intramolecular styrene dimerization using a ruthenium-based catalyst, see: a) M. A. Ischay, Z. Lu, T. P. Yoon, *J. Am. Chem. Soc.* **2010**, *132*, 8572. For cross-dimerization of styrenes leading to trisubstitued cyclobutanes using ruthenium-based photoredox, see: b) M. A. Ischay, M. S. Ament, T. P. Yoon, *Chem. Sci.* **2012**, *3*, 2807.

[10] For homodimerization of styrenes using a combination of organic photoredox catalyst and electron relay, see: M. Riener, D. A. Nicewicz, *Chem. Sci.* **2013**, *4*, 2625.

[11] For recent reviews concerning cyclobutane-containing natural products, see: a) V. M. Dembitsky, *Phytomedicine* **2014**, *21*, 1559; b) A. Sergeiko, V. V. Poroikov, L. O. Hanuš, V. M.

Dembitsky, *Open Med. Chem. J.* **2008**, *2*, 26; c) V. Dembitsky, *J. Nat. Med.* **2008**, *62*, 1.

[12] Nigramide R was first isolated from *Piper Nigrum*: a) K. Wei, W. Li, K. Koike, Y. Chen, T. Nikaido, *J. Org. Chem.* **2005**, *70*, 1164. Nigramide R has also been isolated recently from *Piper retrofractum*: b) R. Muharini, Z. Liu, W. Lin, P. Proksch, *Tetrahedron Lett.* **2015**, *56*, 2521. For other members isolated from the genus *Piper*, see: c) S. Tsukamoto, B.-C. Cha, T. Ohta, *Tetrahedron* **2002**, *58*, 1667; d) S. Tsukamoto, K. Tomise, K. Miyakawa, B.-C. Cha, T. Abe, T. Hamada, H. Hirota, T. Ohta, *Bioorg. Med. Chem.* **2002**, *10*, 2981.

[13] The reason for the enhanced activity of PIDA towards alkene dimerization in HFIPA is not well understood, but we presume that it derives from its ability to stabilize charged intermediates, together with its low nucleophilic ability, which means that it does not readily trap reactive radical cation intermedates formed in situ. For a recent contribution, see: a) Y. Tian, X. Xu, L. Zhang, J. Qu, *Org. Lett.* **2015**, *18*, 268, and references therein. Alternatively, and based on DFT studies, HFIP has been proposed to stabilize a charged transition state through hydrogen-bonding interactions: b) M. C. DiPoto, R. P. Hughes, J. Wu, *J. Am. Chem. Soc.* **2015**, *137*, 14861.

[14] Examples of catalytic and enantioselective cyclobutane synthesis are rare. See: a) Y.-M. Wang, N. C. Bruno, Á. L. Placeres, S. Zhu, S. L. Buchwald, *J. Am. Chem. Soc.* **2015**, *137*, 10524; b) J. Du, K. L. Skubi, D. M. Schultz, T. P. Yoon, *Science* **2014**, *344*, 392; c) C. Müller, A. Bauer, M. M. Maturi, M. C. Cuquerella, M. A. Miranda, T. Bach, *J. Am. Chem. Soc.* **2011**, *133*, 16689; d) S. C. Coote, T. Bach, *J. Am. Chem. Soc.* **2013**, *135*, 14948; e) Ł. Albrecht, G. Dickmeiss, F. C. Acosta, C. Rodríguez-Escrich, R. L. Davis, K. A. Jørgensen, *J. Am. Chem. Soc.* **2012**, *134*, 2543.

[15] The stereochemistry of **4c**, **4d**, **4i**, **6e**, **8**, and **6a′** was assigned by NOESY studies (see the Supporting Information). Compounds **2a**, **2f**, and **4a–c** had spectroscopic data which matched that in the literature. The stereochemistry of all other cyclobutanes was assigned by analogy.

[16] For the inhibitory activity study of nigramide R, see: Subehan, T. Usia, S. Kadota, Y. Tezuka, *Planta Med.* **2006**, *72*, 527.

[17] P. H. J. Carlsen, T. Katsuki, V. S. Martin, K. B. Sharpless, *J. Org. Chem.* **1981**, *46*, 3936.

[18] For a table showing the comparison of the NMR data for the synthetic and natural nigramide R, and a complete NMR study of **14** see the Supporting Information.

Received: December 16, 2015
Revised: January 26, 2016