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Diels–Alder reactions between hexafluoro-2-butyne and bis-furyl dienes: kinetic *versus* thermodynamic control†

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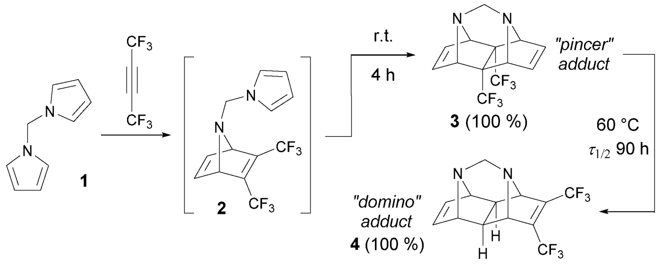
The tandem [4+2] cycloaddition between hexafluoro-2-butyne and bis-furyl dienes, like difurfuryl ester, at room temperature leads to the kinetically controlled "pincer"-adducts – annulated 4*a*,8*a*-bis(trifluoromethyl)hexahydro-1,4:5,8-diepoxynaphthalenes. On the other hand, if these reactions proceed at 140 °C, only the thermodynamically controlled "domino"-adducts – annulated 2,3-bis(trifluoromethyl)hexahydro-1,4:5,8-diepoxynaphthalenes – are formed. Therefore, a very rare and unexpected example of full kinetic and thermodynamic control in the Diels–Alder reaction is reported in this paper.

Domino and tandem intramolecular Diels–Alder reactions of furans (IMDAF reaction) are widely used in organic synthesis for different purposes due to their simplicity, reliability and controlled stereochemistry.[1] In particular, the products of the IMDAF reaction are often applied as starting materials for the synthesis of functionally substituted naphthalenes, indoles, isoindoles, quinolines and isoquinolines.[1c]

The products of the reaction between furans and alkynes have a 7-oxabicyclo[2.2.1]heptene scaffold. The structural motif has great potential as a tool for the design and synthesis of a broad diversity of substances with various practically useful properties. For example, recently these cycloadducts have been used for the construction of polycyclic aromatic hydrocarbons – fragments of graphene, which can serve as a model for new carbon based electronic materials.[2] The annulated 7-oxabicyclo[2.2.1]heptane moiety acts as a framework for molecular tweezers,[3] various supramolecular systems,[4] donor–bridge–acceptor molecules,[5] a wide range of bioactive and natural compounds,[6] high-molecular weight materials,[6e,7] *etc.*

Taking into account such widespread actual or potential applications of the IMDAF reaction products, design of new efficient molecular systems for these processes and the understanding of intimate mechanistic details and driving forces underlying these reactions are of obvious general importance.

Various alkynes were used in the tandem intramolecular [4+2] cycloaddition, but only limited information concerning the reactivity of fluorinated acetylenes is available.[8] In 1985, this journal published pioneering work by Visnick and Battiste,[9] who reported an unprecedented example of the total kinetic and thermodynamic control in the course of the domino [4+2] cycloaddition between hexafluorobut-2-yne and *N*,*N*′-dipyrrolylmethane (**1**, Scheme 1). When the reaction was carried out under kinetically controlled conditions (room temperature), only the pincer-type polycycle **3** was formed through the open intermediate **2**. Upon heating, however, the pincer adduct **3** underwent an intramolecular rearrangement into the domino-type adduct **4**. Both reactions proceeded in quantitative yields, unlike other known cycloadditions of this type,[10] which usually lead to a mixture of products of kinetic and thermodynamic control, regardless of the reaction temperature. For a long time,



Scheme 1 Example of the total temperature control in the tandem intramolecular Diels–Alder reaction.[9a]

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† Electronic supplementary information (ESI) available: Single-crystal X-ray descriptions for **7c**, **d**, and **g** and **8c**, **d**, and **g**; computational details and tables with energies and atomic coordinates; detailed synthetic procedures and spectral data for compounds **5**, **7**, and **8**. CCDC 1570123–1570128. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c7cc09466c

the transformation discussed in that paper had been attractive in synthetic[11] and theoretical[12] chemistry research, but it remained unique due to the limited accessibility of the suitable starting bis-dienes.

In 1997, the second example similar to system **1** appeared in a report by Lautens and Fillion who demonstrated that difuryl bis-dienes in a reaction with alkynes are able to give pincer-cycloadducts analogous to **3** under kinetically controlled conditions.[13]

Having obtained a significant insight from previous reports about the importance of kinetic and thermodynamic control in intra/intermolecular [4+2]-cycloaddition reactions, our main goal in this study was to expand the available classes of dienes and dienophiles for the implementation of the tandem Diels–Alder reaction under kinetic or thermodynamic control conditions. In this work, we focused on bis-furyldienes **5** that can be easily obtained in a two-step process,[10a,13a] and on hexafluorobutyne as a dienophile. The latter, apparently, is the most active known dienophile and usually ensures excellent yields of the cycloaddition products at low temperatures. However, the experimental treatment of this alkyne has some peculiarities due to its gaseous state under normal conditions.

Theoretical DFT calculations (IEFPCM-M06-2X/6-311++G**) of the reaction between $F_3CC{\equiv}CCF_3$ and three dienes (**5a**, **5c**, and **5g**) were carried out (for computational details, see the ESI†). The reaction starts with the cycloaddition of $F_3CC{\equiv}CCF_3$ at one of the furan moieties which occurs in a concerted fashion *via* **TS1** (Fig. 1) and represents the rate-limiting step of the whole process with the activation barrier of 23.1–26.8 kcal mol^{-1} (in terms of $\Delta G^{\neq}$).

Further, the reaction could proceed *via* two competing channels, *i.e.* either leading to the pincer-type products **7** *via* **TS2k** or resulting in the formation of the domino product **8** *via* **TS2t**. The calculations showed that the first channel is more kinetically favourable (by 5.7–5.9 kcal mol^{-1}), which is in agreement with the published experimental observations[9,13] on the exclusive formation of the pincer products at room temperature. Meanwhile, the domino products **8** are more thermodynamically stable than **7** by 4.2–4.7 kcal mol^{-1}, and this fact may cause the isomerization of **7** into **8** at elevated temperature. Indeed, the calculated activation barriers for the **7** → **8** isomerization *via* the retro-Diels–Alder reaction of **7** followed by the intramolecular [4+2]-cycloaddition in the chain intermediate **6** to give **8** are 34.0–34.4 kcal mol^{-1}. These values are reasonable to permit such a process at a sufficiently high temperature. Taking into account these predictions, the following experiments were performed.

Under kinetically controlled conditions, the reaction of bis-dienes **5** with hexafluorobutyne was carried out in sealed glass ampules at −70 °C, with subsequent increase of temperature to ~21–24 °C during 2–3 h. Toluene was chosen as a solvent due to its inertness, relatively low volatility and low melting point. Under these conditions, the reaction can occur within five days, but in order to reach a true equilibrium, all reactions were run for 10 days at r.t.

The ^{1}H NMR data of the crude reaction mixtures obtained after gentle evaporation of the solvent are given in Table 1. In most cases, the cycloaddition occurs chemospecifically leading to the kinetically controlled adducts **7a**, **d**, **g**, and **h** only in quantitative yields or proceeds with a high level of chemoselectivity; the ratio of pincer/domino adducts is **7**/**8** > 95/5 (entries **e**, **f**, and **i**). The ratio of diene/alkyne varied from 1/1 to 1/1.4, and in most cases did not significantly affect both the yield of the products and the composition of the reaction mixtures.

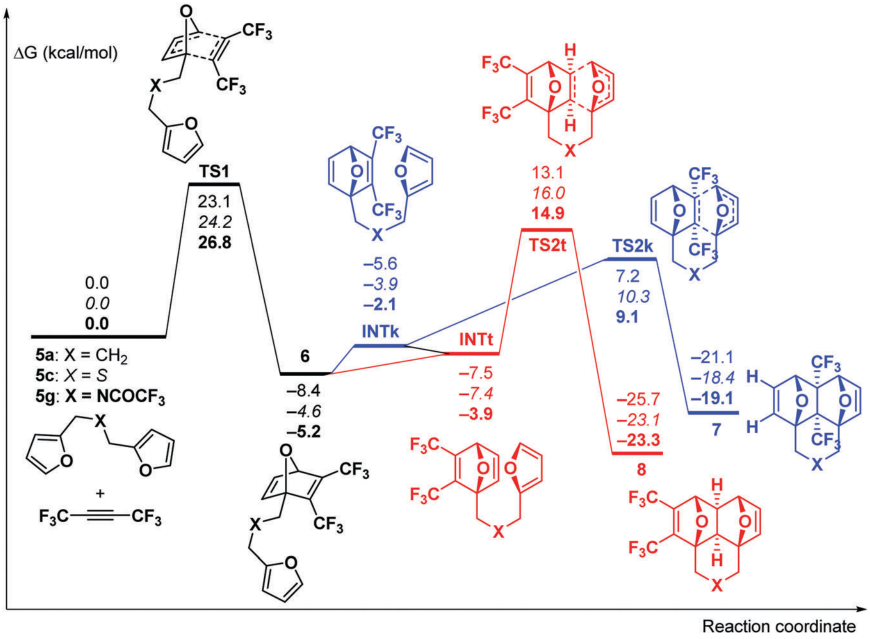


Fig. 1 Gibbs free energy profile for the reaction between bis-dienes **5a**, **c**, and **g** and $F_3CC{\equiv}CCF_3$. The relative energies are given in kcal mol^{-1} for X = CH_2 (plain text), S (*italic*) and NC(O)CF_3 (bold).

Table 1 Conditions of kinetic and thermodynamic control and yields of adducts **7** and **8**

Entry	X	Molar ratio of $5/C_4F_6$[a]	Ratio[b] of **7**/**8**	**7**[c] (%)	**8**[c,d] (%)
a	CH_2	1/1.1	100/0	69	62
b	O	1/1.1	—[e]	60	67
c	S	1/1.1	—[e]	76	76
d	N-Bn	1/1.4	100/0	71	66
e	N-Ac	1/1.1	>95/5	62	68
f	N-Bz	1/1.1	>96/4	70	76
g	$N\text{-}COCF_3$	1/1.4	100/0	56	77
h	$N\text{-}COCCl_3$	1/1	100/0	62	74
i	$N\text{-}CO_2Me$	1/1	>95/5	79	71

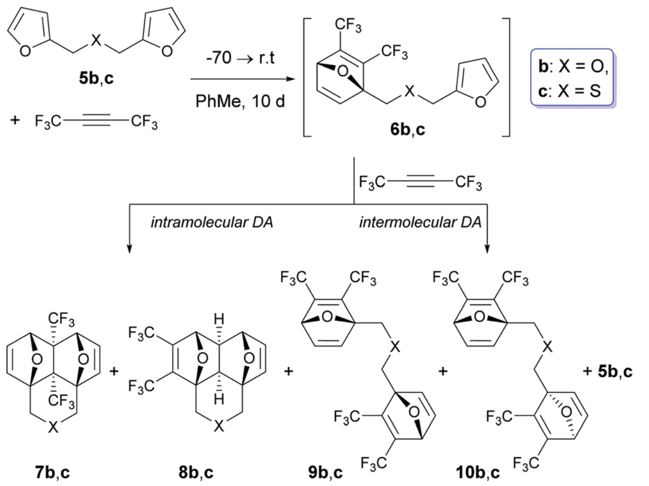
[a] All reactions were carried out in sealed ampules at r.t. for 10 days. [b] Ratio of **7**/**8** according to the ^1H NMR analysis of the reaction mixtures obtained after solvent evaporation. [c] Isolated yields after recrystallization. [d] Domino-adducts **8** were obtained by heating of pincer-adducts **7** in *o*-xylene for 2 h. [e] See Table 2.

However, two examples in Table 1 (rows **b**: X = O and **c**: X = S) drop out of the series and gave rise to a lower chemoselectivity (Scheme 2).

In these cases, in addition to the side domino-adducts **8b** and **c**, the products of the double cycloaddition **9b** and **c** and **10b** and **c** were formed as inseparable diastereomeric pairs with a practically equal ratio of components (Scheme 3 and Table 2).

The formation of bis-adducts **9** and **10** suggests that in these examples, the intermolecular Diels–Alder reaction involving a subsequent interaction of the second molecule of hexafluorobutyne with intermediates **6b** and **c** takes place. In other words, the intermolecular [4+2] cycloaddition between C_4F_6 and intermediate **6** starts to compete with the intramolecular Diels–Alder reaction in the chain intermediate.

Initially, the reactions of **5b** and **c** were carried out with 1.0 mol equivalent of C_4F_6 under similar conditions: 10 days at r.t. (rows **b** and **c** in Table 2). At the equimolar ratio of $5/C_4F_6$, the reaction mixtures contained 8–15% of unreacted starting bis-furans **5b** and **c**, therefore the molar ratio of $5/C_4F_6$ was changed by 1/1.1. Under these conditions (rows **b′** and **c′**), the percentage of the initial **5b** and **c** in the crude reaction mixtures was reduced to 4–5%. Simultaneously, a sharp increase (up to 28%) in the content of the double-adducts **9** and **10** was observed. Due to this, we did not perform further experiments with a larger excess of hexafluorobutyne. The data shown in Table 2 allow us to conclude that the excess of alkyne exerts a significant influence on the fraction of the double cycloaddition adducts **9** and **10**, but at the same time, the ratio of **7**/**8** remains virtually constant (it changes only from 96/4 to 93/7).



Scheme 3 Compositions of the reaction mixtures in the case of the [4+2] cycloaddition between $F_3CC{\equiv}CCF_3$ and bis-furans **5b** and **c**.

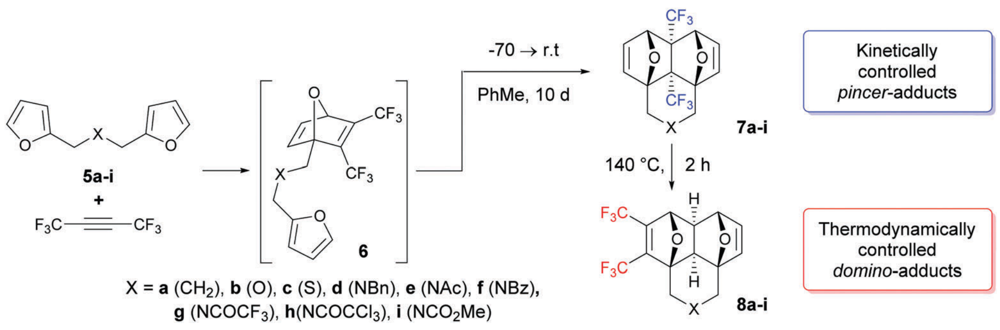
Table 2 Compositions of the crude reaction mixtures obtained after interaction of bis-dienes **5b** and **c** with $F_3CC{\equiv}CCF_3$ according to ^1H NMR analysis

Entry	X	Ratio of $5/C_4F_6$	**5** (%)	**7**[a] (%)	**8** (%)	**9** + **10**[b] (%)
b	O	1/1	14.9	64.9	5.1	15.1
b′	O	1/1.1	4.4	63.2	4.5	27.9
c	S	1/1	8.3	82.3	3.6	5.8
c′	S	1/1.1	5.2	78.0	2.9	13.9

[a] The isolated yield of pincer-adducts **7** after recrystallization is given in Table 1, rows **b** and **c**. [b] Ratio of **9**/**10** is ~50/50.

The rearrangement of the pincer-adducts **7** to the domino-products **8** is observed at temperatures higher than 110 °C (^1H NMR experiments with a temperature gradient were carried out) and proceeds rather quickly at 120 °C. According to NMR spectroscopic data in boiling *o*-xylene, the products of thermodynamic control **8** were formed in 100% yields at 1–2 h, but after recrystallization they were isolated in moderate yields (Table 1).

Since the last transformation **7** → **8** occurred in reasonable time without any by-products, the half-life and rate constant have been calculated using dynamic ^1H NMR spectroscopy assuming first-order kinetics. The reaction involving the



Scheme 2 Synthesis of pincer and domino adducts **7** and **8**.

rearrangements of **7b**, **c**, and **g** to **8b**, **c**, and **g** was carried out in an NMR tube in $CDCl_2$–$CDCl_2$ (for details, see the ESI†). At 120 °C, the half-life ($\tau_{1/2}$) was 37.5 min, 80 min, and 42.5 min (for X = O, S, and N–$COCF_3$, respectively), which corresponds to the first-order reaction rate constants of 0.0185 min^{-1}, 0.0087 min^{-1}, and 0.0163 min^{-1}. The transformation of **7b** to **8b** (X = O) is the quickest one along the series. As expected, at 140 °C in the same solvent, the reactions proceed even faster. For example, for the synthesis of compound **8b**, $\tau_{1/2}$ was ~4.6 min with the first-order reaction rate constants of 0.151 min^{-1}. The rearrangement is so quick at 140 °C that it is difficult to accurately measure the reaction rate by the NMR method.

Our attempts to carry out the analogical dynamic NMR experiment for the first step of the reaction under discussion (the cycloaddition of C_4F_6 to **5a**) in a sealed NMR tube failed due to its insufficient strength against the elevated pressure.

The spatial structures of the regioisomer pairs **7c**, **d**, and **g**/**8c**, **d**, and **g** have been determined by single-crystal X-ray diffraction using synchrotron radiation (see the ESI†).

In conclusion, a rare example of full kinetic and thermodynamic reaction control in the process of the tandem IMDAF reaction of bis-furyl dienes with hexafluoro-2-butyne has been discovered. At room temperature, the reaction occurs chemoselectively leading to adducts of the pincer-[4+2] cycloaddition. The exclusive formation of domino-adducts is observed at elevated temperatures. This reaction could be useful for the construction of natural product and supramolecular frameworks and can serve as an outstanding example of reaction reversibility to be used in physical chemistry courses.

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Conflicts of interest

There are no conflicts to declare.

Notes and references

1 For selected reviews on tandem intramolecular Diels–Alder cycloaddition in organic synthesis, see: (*a*) J. E. Sears and D. L. Boger, *Acc. Chem. Res.*, 2016, **49**, 241–251; (*b*) P. T. Parvatkar, H. K. Kadam and S. G. Tilve, *Tetrahedron*, 2014, **70**, 2857–2888; (*c*) A. Padwa and S. K. Bur, *Tetrahedron*, 2007, **63**, 5341–5378; (*d*) J. Wu, L. Sun and W.-M. Dai, *Tetrahedron*, 2006, **62**, 8360–8372; (*e*) K.-I. Takao, R. Munakata and K.-I. Tadano, *Chem. Rev.*, 2005, **105**, 4779–4807; (*f*) J. D. Winkler, *Chem. Rev.*, 1996, **96**, 167–176.

2 (*a*) S. Eda, F. Eguchi, H. Haneda and T. Hamura, *Chem. Commun.*, 2015, **51**, 5963–5966; (*b*) A. Criado, M. Vilas-Varela, A. Cobas, D. Peréz, D. Peña and E. Guitián, *J. Org. Chem.*, 2013, **78**, 12637–12649; (*c*) F. Furrer, A. Linden and M. C. Stuparu, *Chem. – Eur. J.*, 2013, **19**, 13199–13206.

3 (*a*) R. B. Murphy, R. E. Norman, J. M. White, M. V. Perkins and M. R. Johnston, *Org. Biomol. Chem.*, 2016, **14**, 8707–8720; (*b*) R. N. Warrener, D. Margetic, A. S. Amarasekara, D. N. Butler, I. B. Mahadevan and R. A. Russell, *Org. Lett.*, 1999, **1**, 199–202.

4 (*a*) T.-C. Chou and Y.-J. Li, *Tetrahedron*, 2015, **71**, 5620–5633; (*b*) C. H. Oh, H. J. Yi and K. H. Lee, *Bull. Korean Chem. Soc.*, 2010, **31**, 683–688; (*c*) M. Eckert-Maksić, D. Margetić, S. Kirin, D. Milić and D. Matković-Čalogović, *Eur. J. Org. Chem.*, 2005, 4612–4620.

5 S. Chakrabarti, M. Liu, D. H. Waldeck, A. M. Oliver and M. N. Paddon-Row, *J. Am. Chem. Soc.*, 2007, **129**, 3247–3256.

6 (*a*) S. Roscales and J. Plumet, *Nat. Prod. Commun.*, 2017, **12**, 713–732; (*b*) V. S. Enev, W. Felzmann, A. Gromov, S. Marchart and J. Mulzer, *Chem. – Eur. J.*, 2012, **18**, 9651–9668; (*c*) A. Gromov, V. Enev and J. Mulzer, *Org. Lett.*, 2009, **11**, 2884–2886; (*d*) C. S. Schindler and E. M. Carreira, *Chem. Soc. Rev.*, 2009, **38**, 3222–3241; (*e*) P. Vogel, *Tetrahedron*, 1999, **55**, 13521–13642.

7 (*a*) D. Margetić, M. Eckert-Maksić, P. Trošelj and Z. Marinić, *J. Fluorine Chem.*, 2010, **131**, 408–416; (*b*) R. N. Warrener, D. Margetić, P. J. Foley, D. N. Butler, A. Winling, K. A. Beales and R. A. Russell, *Tetrahedron*, 2001, **57**, 571–582.

8 For cycloaddition reactions between furans (pyrroles) and fluorinated alkynes, see: (*a*) D. Kozai, Y. Kabasawa, M. Ebert, S. Kiyonaka, Firman, Y. Otani, T. Numata, N. Takahashi, Y. Mori and T. Ohwada, *Mol. Pharmacol.*, 2014, **85**, 175–185; (*b*) A. A. Kislukhin, C. J. Higginson, V. P. Hong and M. G. Finn, *J. Am. Chem. Soc.*, 2012, **134**, 6491–6497; (*c*) K. M. Guckian, E. Y.-S. Lin, L. Silvian, J. E. Friedman, D. Chin and D. M. Scott, *Bioorg. Med. Chem. Lett.*, 2008, **18**, 5249–5251; (*d*) T. Yanagimoto, T. Toyota, N. Matsuki, Y. Makino, S. Uchiyama and T. Ohwada, *J. Am. Chem. Soc.*, 2007, **129**, 736–737; (*e*) G.-D. Zhu, M. A. Staeger and S. A. Boyd, *Chem. Lett.*, 2000, 3345–3348; (*f*) L. R. Domingo, M. T. Picher and M. J. Aurell, *J. Phys. Chem. A*, 1999, **103**, 11425–11430.

9 (*a*) M. Visnick and M. A. Battiste, *J. Chem. Soc., Chem. Commun.*, 1985, 1621–1622; (*b*) G. Sun, D. N. Butler, R. N. Warrener and D. Margetić, *J. Heterocycl. Chem.*, 2015, **52**, 1195–1200.

10 For selected reports on kinetic and thermodynamic control in the Diels–Alder reaction, see: (*a*) R. C. Boutelle and B. H. Northrop, *J. Org. Chem.*, 2011, **76**, 7994–8002; (*b*) C. Taffin, G. Kreutler, D. Bourgeois, E. Clot and C. Périgaud, *New J. Chem.*, 2010, **34**, 517–525; (*c*) J. D. White, F. W. J. Demnitz, H. Oda, C. Hassler and J. P. Snyder, *Org. Lett.*, 2000, **2**, 3313–3316; (*d*) A. P. Marchand, B. Ganguly, W. H. Watson and S. G. Bodige, *Tetrahedron*, 1998, **37**, 10967–10972; (*e*) M. Manoharan and P. Venuvanalingam, *J. Chem. Soc., Perkin Trans. 2*, 1997, 1799–1804; (*f*) S. G. Bott, A. P. Marchand and K. A. Kumar, *J. Chem. Crystallogr.*, 1996, **26**, 281–286; (*g*) D. Suarez, T. L. Sordo and J. A. Sordo, *J. Org. Chem.*, 1995, **60**, 2848–2852; (*h*) P. D. Bartlett and C. Wu, *J. Org. Chem.*, 1985, **50**, 4087–4092; (*i*) L. A. Paquette, M. J. Wyvratt, H. C. Berk and R. E. Moerck, *J. Am. Chem. Soc.*, 1978, **100**, 5845–5855.

11 L. F. Tietze, G. Brasche and K. M. Gericke, *in the book Domino reactions in organic synthesis*, Wiley-VCH Verlag GmbH & Co. KgaA, 2006, pp. 280–336.

12 For the density functional theory study of the reaction between hexafluorobut-2-yne and **1**, see: (*a*) L. R. Domingo, M. Arnó and J. Andrés, *J. Am. Chem. Soc.*, 1998, **120**, 1617–1618; (*b*) L. R. Domingo, M. T. Picher, M. Arnó, J. Andrés and V. S. Safont, *THEOCHEM*, 1998, **426**, 257–262.

13 (*a*) M. Lautens and E. Fillion, *J. Org. Chem.*, 1997, **62**, 4418–4427; (*b*) L. R. Domingo, M. T. Picher and J. Andrés, *J. Org. Chem.*, 2000, **65**, 3473–3477.