



Cite this: *Chem. Commun.*, 2016, 52, 11539

Received 18th July 2016,
Accepted 24th August 2016

DOI: 10.1039/c6cc05904j

www.rsc.org/chemcomm

The role of steric hindrance in the intramolecular oxidative aromatic coupling of pyrrolo[3,2-*b*]pyrroles†

Maciej Krzeszewski,^a Paweł Świder,^a Łukasz Dobrzycki,^b Michał K. Cyrański,^b Witold Danikiewicz*^a and Daniel T. Gryko*^a

The presence of steric hindrance triggers different reaction pathways in the intramolecular oxidative aromatic coupling of tetraaryl-pyrrolo[3,2-*b*]pyrroles and leads to the formation of a fluorene moiety and a new cationic π -system linked together by a spiro carbon atom. Computational studies elegantly rationalized these results. These previously unknown functional dyes emit red light with reasonable efficiency.

Oxidative aromatic coupling and the Scholl reaction are often the methods of choice in the synthesis of large π -extended scaffolds.¹ Indeed, in some cases over 100 C–C bonds are formed from suitable precursors furnishing truly amazing polycyclic aromatic hydrocarbons in one synthetic operation.² Yet despite being known for almost 150 years, the oxidative aromatic coupling reaction continues to surprise chemists.³ The breakthrough works of various groups,⁴ most prominently Müllen⁵ and Durola,⁶ have proven that there is often no obvious relationship between steric hindrance and the output of this reaction. A general set of rules which would predict when and how this reaction occurs is still beyond our current reach. Additionally, the mechanistic aspects are still under discussion,^{1a,7} although Waldvogel and co-workers have recently made significant progress.⁸

The extraordinarily easy access to 1,2,4,5-tetraaryl-pyrrolo[3,2-*b*]pyrroles⁹ and their intrinsic electron-rich core make them ideal building blocks for the study on oxidative aromatic coupling.¹⁰ Our examination of the relationship between the structure of aromatic compounds and the results of oxidative aromatic coupling has provided key information for truly

understanding this system as well as the discovery of a new fluorophore. Herein we present the results of this study.

We began our investigation with the preparation of the corresponding 2-arylbenzaldehydes **1b–f** using Suzuki–Miyaura coupling. In order to obtain aldehydes **1b–c** and **1e–f**, respective bromides (iodides) were reacted with 2-formylphenylboronic acid. To synthesize derivative **1d**, 2-bromobenzaldehyde was reacted with 3,5-dimethylphenylboronic acid. Aldehydes **1b–f** were synthesized in 60–98% yields (see the ESI†), and they were subsequently used in the synthesis of tetraaryl-pyrrolo[3,2-*b*]pyrroles, a procedure developed and optimized in our laboratory (Scheme 1).^{9b} Desired products **4a–e** were smoothly obtained in yields ranging from 34% to 48% (Scheme 1 and Table 1). The only exception was the reaction of electron-rich aldehyde **3f**. The expected compound **4f** (based on ESI-MS of the crude reaction mixture) did not form and only tarry products were observed. The most plausible reason behind this result is the low intrinsic stability of hypothetical compound **4f** possessing an electron-rich pyrrolo[3,2-*b*]pyrrole core decorated with electron-donating substituents. Most likely, the oxidation potential of **4f** is low enough to facilitate its immediate transformation into polymeric materials in the presence of air.

In accordance with our previous results,¹⁰ we subjected **4b–4e** to FeCl₃ in MeNO₂/CH₂Cl₂. In the case of substrates **4b** and **4c**, ladder-type π -expanded pyrrolo[3,2-*b*]pyrroles **5b** and **5c** were formed according to our expectations *via* double intramolecular oxidative aromatic coupling (Scheme 1 and Table 1). On the other hand, unexpected results were observed for more congested compounds. Derivatives **4d** (R₁ = R₂ = Me) and **4e** (R₁ = R₂ = Br) were reacted with iron(III) chloride and produced very polar red products. Analysis of their NMR spectra led to inconclusive results and eventually the structure of compound **6e** was verified *via* X-ray crystallography. The single crystal structure of compound **6e** was established based on the procedures described in the references given in the ESI.† To our surprise the structure of compound **6e** contained a spiro carbon atom (Fig. 1).

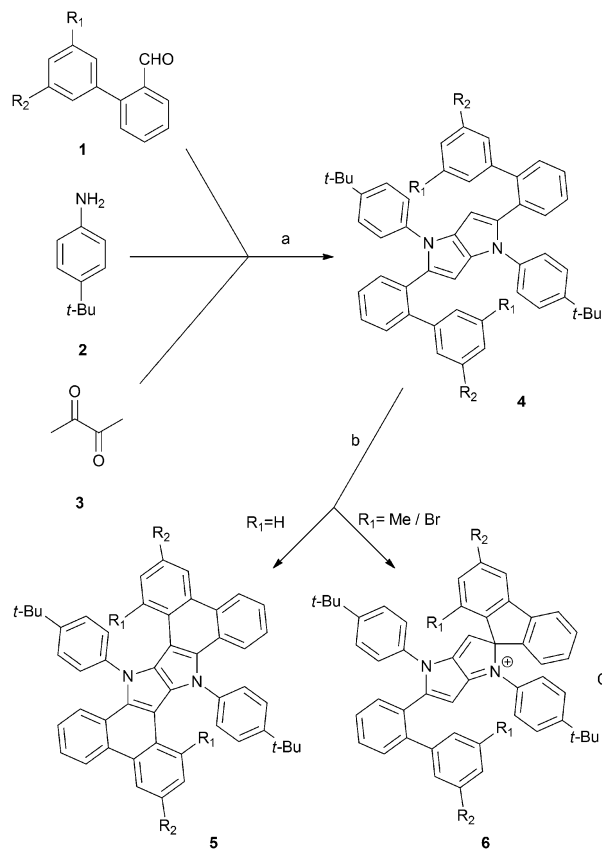
The structures of **4d** and **4e** differ from their analogues **4b** and **4c** in that they possess two substituents (Me or Br) adjacent

^a Institute of Organic Chemistry, Polish Academy of Sciences, Kasprzaka 44/52, 01-224 Warsaw, Poland. E-mail: dtgryko@icho.edu.pl, witold.danikiewicz@icho.edu.pl

^b Warsaw University, Chemistry Department, Pasteura 1, 01-224 Warsaw, Poland. E-mail: chamis@chem.uw.edu.pl

† Electronic supplementary information (ESI) available: Experimental details, ¹H NMR and ¹³C NMR spectra, UV-Vis absorption and emission spectra, details of DFT calculations and data on the crystal structure of compound (**6f**). CCDC 1487685. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c6cc05904j





Scheme 1 General method for the synthesis of π -expanded compounds **5** and spiro-derivatives **6**. Conditions: (a) TsOH, AcOH, 90 °C, 3 h, (b) FeCl₃, MeNO₂, DCM, r.t., 30 min.

Table 1 Synthesis of tetraaryl-pyrrolo[3,2-*b*]pyrroles and the products of their intramolecular oxidative aromatic coupling

Aldehyde	R ₁	R ₂	4 (yield)	5 (yield)	6 (yield)
1a ^a	H	H	4a (48%) ^a	5a (75%) ^a	—
1b	H	Br	4b (43%)	5b (50%)	—
1c	H	OMe	4c (34%)	5c (70%)	—
1d	Me	Me	4d (40%)	—	6d (90%)
1e	Br	Br	4e (39%)	—	6e (90%)
1f	OMe	OMe	4f (tar)	—	—

^a Data from ref. 10.

to the position of the expected C–C bond forming process (Scheme 1). The structures of salts **6d** and **6e** made it clear that the radical cation formed on the electron-rich pyrrolopyrrole moiety attacked the aryl substituent in a different way, forming a C–C bond on an already occupied position (rather than unoccupied position 3). Consequently, this led to the formation of a spiro system and the new chromophore (Scheme 1 and Fig. 1). The new core being effectively cation, in contrast to compounds **4**, is electron-deficient. Hence the reaction did not occur any further from the second site of the molecule. Interestingly, these unforeseen spiro derivatives **6d** and **6e** formed in almost quantitative yields (Table 1). It is noteworthy to add that recently Waldvogel and co-workers revealed the formation of spirocyclic compounds *via* intramolecular oxidative coupling of cinnamates.¹¹

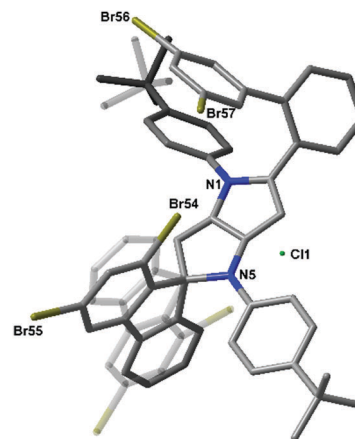
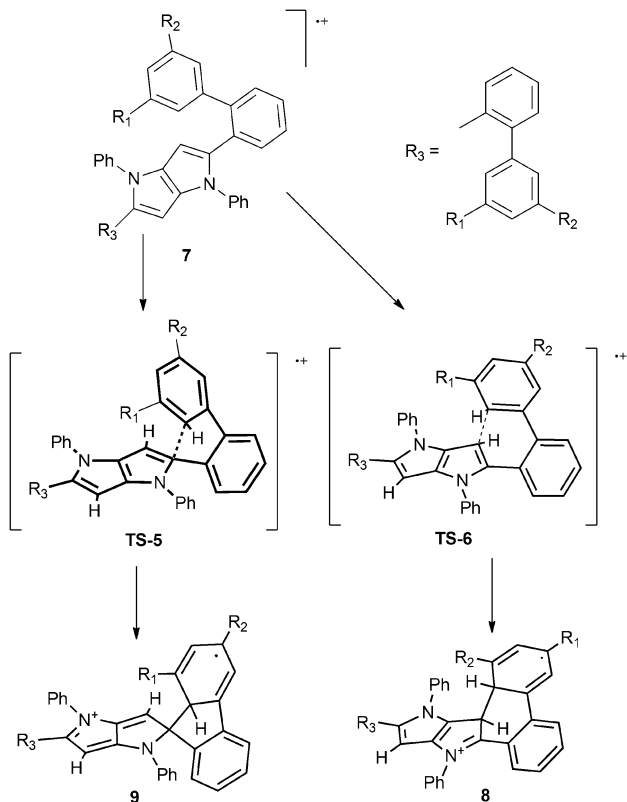


Fig. 1 Molecular structure of **6e**. Disordered fluorene and *t*-butyl fragments with lower occupancies are made transparent. H atoms and the disordered Et₂O molecule are omitted for clarity. CCDC 1487685.

To rationalize why the oxidation of compounds **4a–4c** results in the formation of six-membered rings while in the case of compounds **4d** and **4e** spiro five-membered rings are formed, we decided to model both reactions using quantum chemical calculations. Due to the relatively large size of the studied molecules Truhlar's unrestricted M05-2X DFT functional with the 6-31G(d) basis set has been selected as the method of choice.¹² Compounds **4a** and **4e** with removed *t*-butyl groups have been selected as the representative models. Calculations were performed using the Gaussian 09 rev. A.02 software package.¹³ Full computational details, including Cartesian coordinates of all calculated structures, are available in the ESI.†

As the starting point we assumed that the reaction starts with the formation of a radical cation of the substrate, which subsequently can undergo cyclization through different transition states (TS), resulting in the formation of either a 6-membered ring or a spiro-5-membered ring (Scheme 2). In the next step these intermediates are oxidized, yielding final products: a neutral molecule in the first case and a cation in the second one. The results of the calculations are summarized in Fig. 2. In the case of compound **7a** (an analogue of **4a** without *t*-butyl groups) both the activation energy barriers and the stability of the products favor the formation of a 6-membered ring. A different situation has been observed for tetrabromosubstituted compound **7e**. In this case the formation of a spiro-5-membered ring is preferred by both TS energy and the relative energy of the product. Both results are in full agreement with the experiments. These results also revealed that it is not possible to tell if the reaction is controlled kinetically or thermodynamically because in both cases the kinetic and thermodynamic products are the same. The main reason for the different reactivities of compounds **4a–c** and **4d–e** is the steric hindrance. Examination of the calculated structures of compounds **7a** and **7e** shows that in the case of the latter the formation of the transition state leading to the spiro 5-membered ring is less sterically demanding. A rather surprising observation is that the activation energy of the formation of both transition states for compound **7e** is lower than in the case of compound **7a**, which is obviously less





Scheme 2 Proposed reaction mechanism leading to the formation of the 6-membered ring (**8**) and the spiro-5-membered ring (**9**).

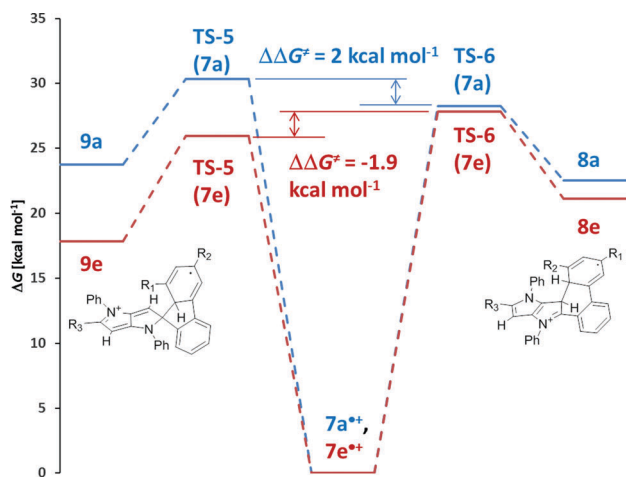


Fig. 2 Gibbs free energy diagrams of the reactions of radical cations of compounds **7a** (blue) and **7e** (red) in the gas phase leading to the formation of the 6-membered ring (right side) and the spiro-5-membered ring (left side).

sterically crowded. A plausible rationalization for this effect is that compound **7e** is already sterically crowded so the difference in steric hindrance between the starting molecule and TS is lower than for compound **7a**.

The optical properties of compounds **4b–e** and **5b–c** were analogous to previously described **4a** and **5a** (Fig. 3–5 and Table 2).¹⁰ The untypical direction of intramolecular oxidative coupling in the case of **4d** and **4e** led to the formation of not only a new heterocyclic

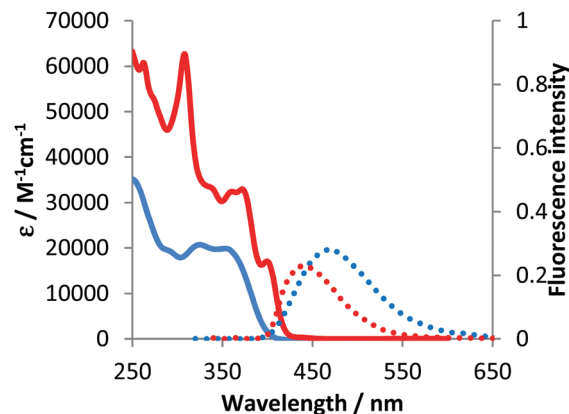


Fig. 3 Absorption (solid) and emission (dotted) spectra of **4b** (blue line) and **5b** (red line) measured in dichloromethane.

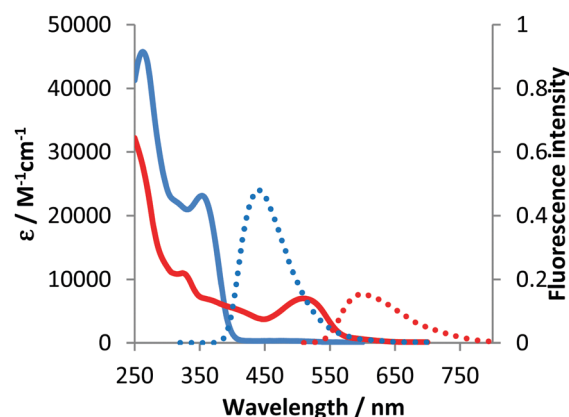


Fig. 4 Absorption (solid) and emission (dotted) spectra of **4d** (blue line) and **6d** (red line) measured in dichloromethane.

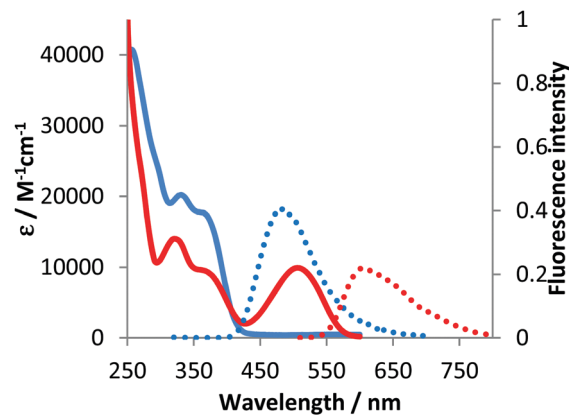


Fig. 5 Absorption (solid) and emission (dotted) spectra of **4e** (blue line) and **6e** (red line) measured in dichloromethane.

scaffold but also a new dye. Consequently, both absorption and emission of compounds **6d** and **6e** were entirely different from those of **5b–c** (Fig. 4 and 5 and Table 2). The absorption maxima were in the green region of the spectra. Both compounds emitted red light (λ_{em} 595–606 nm) with moderate intensity.



Table 2 Spectroscopic properties of synthesized dyes in dichloromethane

Cmpd.	λ_{abs} [nm]	λ_{em} [nm]	Stokes shift [cm ⁻¹]	ϵ_{max} [M ⁻¹ cm ⁻¹]	Φ_{fl}^a
4a ^b	350	452	6400	21 000	0.84
4b	353	461	6600	20 000	0.38
4c ^c	353	428	5000	22 000	0.37
4d	353	441	5600	23 000	0.62
4e	364	481	6700	18 000	0.13
5a ^b	372	428	3500	39 000	0.45
5b	399	444	2500	17 000	0.02
5c ^c	405	415	600	21 500	0.35
6d	508	595	2900	7000	0.34 ^d
6e	506	606	3300	10 000	0.22 ^d

^a Determined with quinine sulfate in H₂SO₄ (0.5 M) as a standard.

^b Ref. 10. ^c Spectra measured in toluene. ^d Determined with Rhodamine 6G in ethanol as a standard.

The Stokes shift for these new dyes was moderate, which probably stems from the difference in the geometry of these molecules between the ground and the excited state. The bathochromically shifted absorption and emission are not apparent in these cases since the novel chromophore is rather small. Due to the steric hindrance the conjugation of the phenyl substituent located at position 5 is most probably minimal (in the ground state).

In conclusion, we have proven that large substituents present at positions adjacent to the site of oxidative aromatic coupling can completely alter the expected reaction pathway. In particular, C–C bonds can form on the already occupied quaternary carbon atom leading to the formation of a five-membered ring and consequently the spiro-product possessing a novel π -conjugated core, the existence of which was unambiguously confirmed by X-ray crystallography. The difference in the course of these two reactions has been *post factum* rationalized by calculating the thermodynamic stabilization energies of the intermediate structures. As a result of a change of the π -electron system, the absorption and emission of these small dyes are significantly bathochromically shifted *versus* tetraarylpyrrolo[3,2-*b*]pyrroles or their π -expanded analogues. This unexpected result adds an important piece of information towards understanding the relationship between the structure of the polycyclic aromatic compound and the results of its interaction with oxidants.

We thank the Foundation for Polish Science (MISTRZ programme), the Polish National Research Center (PRELUDIUM 2015/19/N/ST5/00826) and the Global Research Laboratory Program (2014K1A1A2064569) through the National Research Foundation (NRF) funded by the Ministry of Science, ICT & Future Planning, Korea. M. K. thanks Yevgen Poronik for insightful consultations and Jillian Larsen (UC Riverside) for amending the manuscript.

Notes and references

- (a) M. Grzybowski, K. Skonieczny, H. Butenschön and D. T. Gryko, *Angew. Chem., Int. Ed.*, 2013, **52**, 9900; (b) A. Tsuda and A. Osuka, *Science*, 2001, **293**, 79; (c) J. He, S. Mathew, Z. J. Kinney, R. M. Warrell, J. S. Molina and C. S. Hartley, *Chem. Commun.*, 2015, **51**, 7245; (d) N. L. S. Davis, A. L. Thompson and H. L. Anderson, *J. Am. Chem. Soc.*, 2011, **133**, 30; (e) N. Ono, H. Yamada and T. Okujima, in *Handbook of Porphyrin Science*, ed. K. M. Kadish, K. M. Smith and R. Guilard, World Scientific, Singapore, 2009, vol. 2, pp. 1–102; (f) A. N. Lakshminarayana, J. Chang, J. Luo, B. Zheng, K.-W. Huang and C. Chi, *Chem. Commun.*, 2015, **51**, 3604; (g) H. Zhong, C.-H. Wu, C.-Z. Li, J. Carpenter, C.-C. Chueh, J.-Y. Chen, H. Ade and A. K.-Y. Jen, *Adv. Mater.*, 2016, **28**, 951; (h) J. Luo, X. Xu, R. Mao and Q. Miao, *J. Am. Chem. Soc.*, 2012, **134**, 13796; (i) C.-M. Chou, S. Saito and S. Yamaguchi, *Org. Lett.*, 2014, **16**, 2868; (j) J. He, D. M. Agra-Kooijman, G. Singh, C. Wang, C. Dugger, J. Zeng, L. Zang, S. Kumar and C. S. Hartley, *J. Mater. Chem. C*, 2013, **1**, 5833; (k) B. Kramer and S. R. Waldvogel, *Angew. Chem., Int. Ed.*, 2004, **43**, 2446; (l) B. Koszarna and D. T. Gryko, *Chem. Commun.*, 2007, 2994; (m) S. Ooi, T. Tanaka, K. H. Park, D. Kim and A. Osuka, *Angew. Chem., Int. Ed.*, 2016, **55**, 6535.
- (a) A. Narita, X. Feng, Y. Hernandez, S. A. Jensen, M. Bonn, H. Yang, I. A. Verzhbitskiy, C. Casiraghi, M. R. Hansen, A. H. R. Koch, G. Fytas, O. Ivasenko, B. Li, K. S. Mali, T. Balandina, S. Mahesh, S. De Feyter and K. Müllen, *Nat. Chem.*, 2014, **6**, 126; (b) K. Kawasumi, Q. Zhang, Y. Segawa, L. T. Scott and K. Itami, *Nat. Chem.*, 2013, **5**, 739.
- (a) N. Fukui, S.-K. Lee, K. Kato, D. Shimizu, T. Tanaka, S. Lee, H. Yorimitsu, D. Kim and A. Osuka, *Chem. Sci.*, 2016, **7**, 4059; (b) J. He, J. L. Crase, S. H. Wadumethrige, K. Thakur, L. Dai, S. Zou, R. Rathore and C. S. Hartley, *J. Am. Chem. Soc.*, 2010, **132**, 13848; (c) S. L. Skraba-Joiner, E. C. McLaughlin, A. Ajaz, R. Thamamam and R. P. Johnson, *J. Org. Chem.*, 2015, **80**, 9578.
- (a) M. Danz and G. Hilt, *Adv. Synth. Catal.*, 2011, **353**, 303; (b) B. T. King, J. Kroulik, C. R. Robertson, P. Rempala, C. L. Hilton, J. D. Korinek and L. M. Gortari, *J. Org. Chem.*, 2007, **72**, 2279.
- (a) J. Liu, A. Narita, S. Osella, W. Zhang, D. Schollmeyer, D. Beljonne, X. Feng and K. Müllen, *J. Am. Chem. Soc.*, 2016, **138**, 2602; (b) L. Dössel, L. Gherghel, X. Feng and K. Müllen, *Angew. Chem., Int. Ed.*, 2011, **50**, 2540.
- A. Pradhan, P. Dechambenoit, H. Bock and F. Durola, *Angew. Chem., Int. Ed.*, 2011, **50**, 12582.
- (a) P. Rempala, J. Kroulik and B. T. King, *J. Am. Chem. Soc.*, 2004, **126**, 15002; (b) N. Zhang, S. R. Samanta, B. M. Rosen and V. Percec, *Chem. Rev.*, 2014, **114**, 5848; (c) P. Rempala, J. Kroulik and B. T. King, *J. Org. Chem.*, 2006, **71**, 5067.
- (a) K. Wehming, M. Schubert, G. Schnakenburg and S. R. Waldvogel, *Chem. – Eur. J.*, 2014, **20**, 12463; (b) M. Schubert, S. Trosien, L. Schulz, C. Brandscheid, D. Schollmeyer and S. R. Waldvogel, *Eur. J. Org. Chem.*, 2014, 7091; (c) J. Leppin, M. Schubert, S. R. Waldvogel and K. Heinze, *Chem. – Eur. J.*, 2015, **21**, 4229; (d) M. Schubert, P. Franzmann, A. Wünsche von Leupoldt, K. Koszinowski, K. Heinze and S. R. Waldvogel, *Angew. Chem., Int. Ed.*, 2016, **55**, 1156.
- (a) A. Janiga, E. Głodkowska-Mrówka, T. Stokłosa and D. T. Gryko, *Asian J. Org. Chem.*, 2013, **2**, 411; (b) M. Krzeszewski, B. Thorsted, J. Brewer and D. T. Gryko, *J. Org. Chem.*, 2014, **79**, 3119; (c) A. Janiga, M. Krzeszewski and D. T. Gryko, *Chem. – Asian J.*, 2015, **10**, 212.
- M. Krzeszewski and D. T. Gryko, *J. Org. Chem.*, 2015, **80**, 2893.
- M. Schubert, K. Wehming, A. Kehl, M. Nieger, G. Schnakenburg, R. Frohlich, D. Schollmeyer and S. R. Waldvogel, *Eur. J. Org. Chem.*, 2016, 60.
- Y. Zhao, N. E. Schultz and D. G. Truhlar, *J. Chem. Theory Comput.*, 2006, **2**, 364.
- M. J. Frisch, *et al.*, *Gaussian 09, Revision D.01*, Gaussian, Inc., Wallingford CT, 2009, for full citation see the ESI†.

