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Access to isoindole-derived BODIPYs by an aminopalladation cascade†

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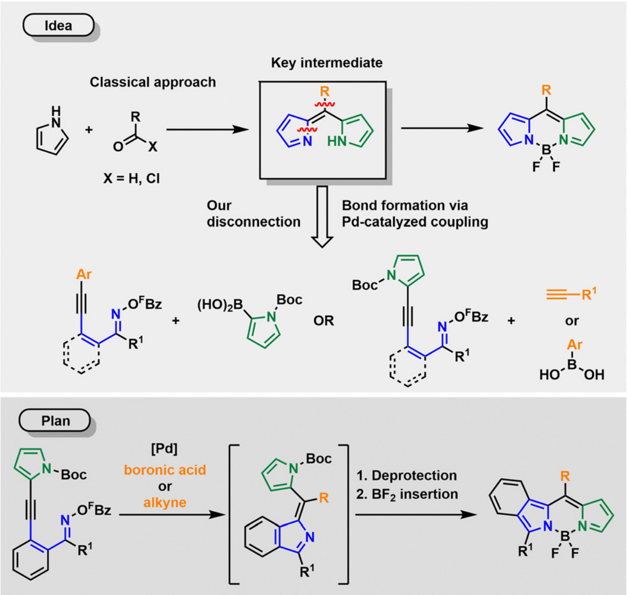
Here, we present a new route to dyes of the BODIPY family. We first built up a *N*-Boc-protected dipyrromethene scaffold *via* an aminopalladation cascade. Subsequentially, the pyrrole moiety was deprotected and the BF_2 unit inserted. Depending on the terminating reaction, BODIPYs with either aryl or alkynyl moieties were accessible.

Since their discovery in the 1960s by Treibs and Kreuzer, BODIPYs have become established in a wide range of different research areas.[1–7] They have been recognized as valuable fluorescent tags,[8,9] found application in bioimaging[5,10–13] and been investigated as part of photodynamic therapy.[14] Furthermore, they have been used as efficient photosensitizers,[15,16] photocatalysts[17,18] and photocages.[19–24] BODIPYs are also considered as potential candidates for circularly polarized luminescence.[25] Classically, dyes of the BODIPY family are built up by formation of a dipyrromethene through condensation and oxidation chemistry followed by the insertion of the chelating BF_2 unit *via* $BF_3{\cdot}OEt_2$. A broad pool of post-functionalization methods allows further decoration of the core structure, especially at the α- and β-positions, and therefore fine-tuning of the photophysical properties.[26] However, the residue in the *meso*-position of BODIPYs is mainly restricted to alkyl and aryl groups because of the nature of the condensation precursors (often aldehydes and acyl chlorides). To allow modification at this position, a functional group suitable for cross-coupling reactions has to be pre-installed and then addressed by palladium-catalyzed cross-coupling chemistry.[27–29] To complement classical textbook chemistry for assembling nitrogen-containing heterocycles, palladium-catalyzed reactions have also been developed that allow new modes of retrosynthesis and synthesis planning. This was achieved either in an aza-Wacker fashion with a Pd^{II} salt activating an alkene and allowing an amino group to attack,[30,31] by an internal Buchwald–Hartwig type coupling[32–35] or by oxidative addition of Pd^0 into an N–O bond and subsequent Heck reaction.[36] The latter strategy was first employed by Narasaka to synthesize pyrrole derivatives from *O*-pentafluorobenzoyloximes.[37] Thereafter, this aminopalladation strategy was applied to the synthesis of pyridine, isoquinoline, indole and imidazole derivatives.[38–42] Further mechanistic studies by Bower and co-workers revealed the electron-deficient $P(3,5\text{-}(CF_3)_2C_6H_3)_3$ ligand to be generally more efficient than PPh_3, whereas with electron-rich ligands such as $P(tBu)_3$ a single electron pathway is favored, leading to the iminyl radical



Scheme 1 Classical approach to BODIPYs and our new disconnection approach *via* aminopalladation.

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product instead of the aza-Heck product.[43] In further work Bower presented the successful synthesis of perhydroindoles,[44] dihydropyrroles,[45] pyrrolidines and piperidines.[46] Interception of the alkyl-Pd(II) intermediates by organometallic nucleophiles or alcohols was also demonstrated.[47] Besides the use of oxime esters, oxidative addition into the N–O bond of *N*-(pentafluorobenzoyloxy)-amides followed by a Heck reaction also afforded access to various N-heterocycles.[48,49] Our group employed *N*-(pentafluorobenzoyloxy)-amides to extend this concept to an aza-Heck reaction with internal alkynes, thereby obtaining tetrasubstituted enamines.[50]

Inspired by the scope of this alkyne aminopalladation/Heck cascade, we envisioned a synthesis of dipyrromethenes **2**, key intermediates in every BODIPY synthesis, *via* an aminopalladation cascade. Treating precursor **1** with Pd^0 should result in an oxidative addition of Pd into the N–O bond of the oxime ester, followed by an intramolecular aza-Heck reaction leading to the formation of an isoindole moiety. In the presence of a base and a boronic acid or a terminal alkyne, Suzuki- or Sonogashira cross-couplings, respectively, should terminate this cascade. The required pyrrole moiety, if not already present in the precursor, might be introduced *via* a boronic acid. In both cases protection of the N–H is mandatory. Deprotection of the aminopalladation product followed by the treatment with $BF_3{\cdot}OEt_2$ under basic conditions would then lead to the BODIPY scaffold (Scheme 1). To avoid β-hydride elimination after oxidative addition, R^1 of the oxime ester **1** must not be a hydrogen atom.[44]

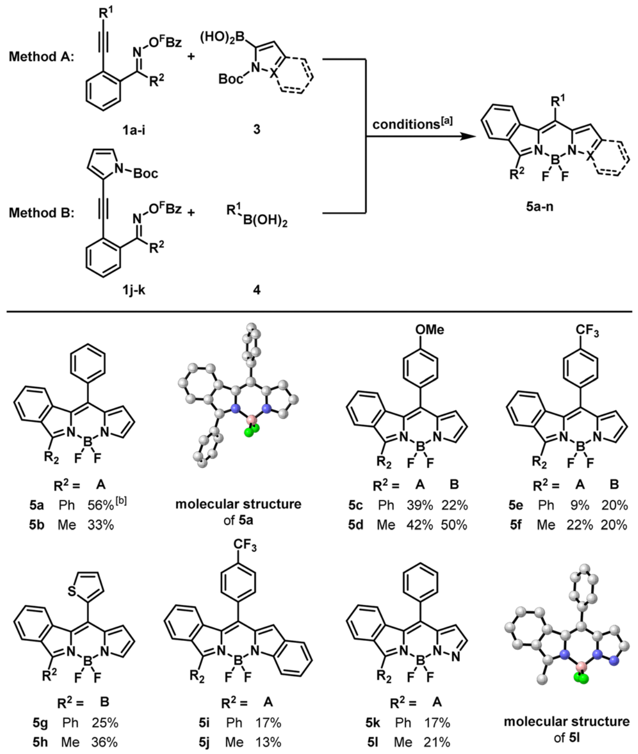
We started our investigations with precursor **1a** and *N*-Boc-protected pyrrole boronic acid and subjected them to Kitamura's conditions[51] to obtain the expected product in 56% yield. While DMF as a solvent halved the yield, 1,4-dioxane and toluene nearly shut down the reaction. Whereas triethylamine reduced the yield only slightly to 43%, inorganic bases (CsF, Cs_2CO_3) significantly decreased the yields. Additional ligands (JohnPhos, SPhos, dppe) had no beneficial effects on the yields, and the bidentate ligand dppe stopped the reaction completely. Even the ligand $P(3,5\text{-}(CF_3)_2C_6H_3)_3$ only gave the product in 32% yield. Nevertheless, when the equivalents of the boronic acid were increased from 1.5 to 3.0, the reaction time could be reduced to 1 h (Table S2, see ESI†).

After the successful formation of the dipyrromethene, we treated it with oxalyl chloride in methanol to remove the Boc-protecting group.[52] After aqueous work-up the crude product was reacted with $BF_3{\cdot}OEt_2$ under basic conditions (Et_3N) to insert the central BF_2-unit, providing BODIPY **5a** with a yield of 56% over three steps.

Since a mixture of (*E*)- and (*Z*)-isomers of intermediate **2a** was formed, slightly raised temperatures of 50 °C were employed during the BF_2 insertion step to allow isomerization. This synthesis was also performed on larger scale (1 mmol) to obtain BODIPY **5a** in a slightly decreased yield of 46% over three steps.

With this optimized reaction sequence in hand (for Method A), we explored the scope of the reaction. First, we varied the aryl group (R^1) that became the *meso*-substituent of the emerging BODIPY. When precursor **1c**, bearing a *p*-methoxyphenyl group at this position, was subjected to our conditions, BODIPY **5c** was obtained in 39%. A *p*-trifluoromethylphenyl group at the same position led to BODIPY **5e** with a yield of only 9%. Next, we started from the acetophenone-derived precursors (R^2 = Me). Employing the same residues for R^1, BODIPYs **5b**, **5d** and **5f** were formed with yields of 33%, 42% and 22%, respectively. Thereafter, we employed precursor **1g**, already substituted with a pyrrole at the triple bond, and reacted it under the same conditions with various aryl boronic acids that now deliver the *meso*-residue (Method B). *p*-Methoxy and *p*-trifluoromethyl phenyl boronic acids gave BODIPYs **5c** and **5e** in 22% and 20% yield, respectively. Thienyl, indolinyl and pyrazolyl boronic acids gave BODIPYs **5g**, **5i** and **5k** in 25%, 17% and 17% over 3 steps. The same boronic acids were also reacted with the acetophenone-derived precursor **1h**. The resulting BODIPYs **5d**, **5f**, **5h**, **5j** and **5l** were formed in improved yields of 50%, 20%, 36%, 13% and 21% (Scheme 2). It should be pointed out that, to the best of our knowledge, **5k** and **5l** are the first reported BODIPYs containing a pyrazole ring as part of their core structure. The structures of BODIPYs **5a**, **5b** and **5l** were also elucidated by X-ray diffraction analyses (see also ESI†).[55]

As a modification of the Pd-catalyzed cascade, we explored a Sonogashira reaction as the terminating step. Optimization studies of the reaction conditions revealed $Pd(P(3,5\text{-}(CF_3)_2C_6H_3)_3)_3$ to be the best catalyst together with triethylamine as base in THF. Both electron-richer (PPh_3, PCy_3) and also electron-poorer ($P(C_6F_5)_3$) ligands proved to decrease the yield. Furthermore, it



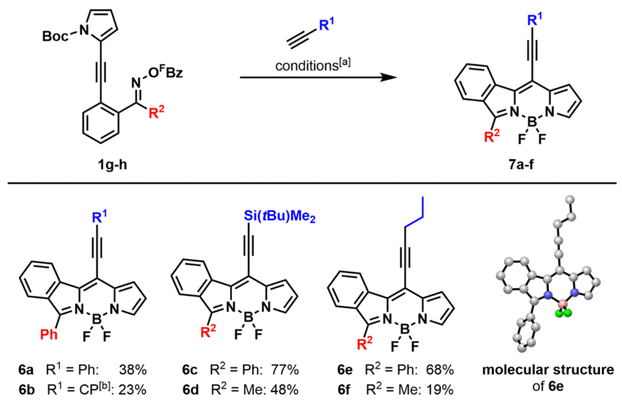
Scheme 2 Scope of the BODIPY formation *via* the Suzuki-terminated aminopalladation cascade. All yields are given over three steps. [a] (1) $Pd(PPh_3)_4$ (10 mol%), DIPEA (2.0 eq.), MeCN, 90 °C, 0.5–2.5 h; (2) $(COCl)_2$ (3.0 eq.), MeOH, r.t., 3–24 h; (3) Et_3N (10.0 eq.), $BF_3{\cdot}OEt_2$ (12.0 eq.), PhMe, 0 °C → 50 °C, 5–15 min. [b] 1 mmol scale 46% yield.

was shown that the presence of a copper co-catalyst is not beneficial to the reaction. Product formations also suffered from other organic and inorganic bases (Cs_2CO_3, Et_2NH, DIPEA). When other solvents (1,4-dioxane, MeCN, DMF) were tried, a significant drop in yield was observed (Table S3, see ESI†).

After having established the conditions for the amino-palladation-Sonogashira cascade, we found that deprotection attempts with oxalyl chloride led to decomposition of the substrate instead of cleavage of the Boc group. Therefore, we applied TFA/DCM (1 : 1) at r.t. to obtain the deprotected dipyrromethene smoothly,[53] into which then the BF_2 unit was inserted.

Next, we explored the scope of this cascade reaction. Generally, the benzophenone-derived precursor **1g** (R^2 = Ph) gave the corresponding BODIPY in better yields than the acetophenone-derived precursor **1h** (R^2 = Me). Using TBS-protected acetylene and pent-1-yne as alkynes gave BODIPYs **6c** and **6e** in 77% and 68% yield for the benzophenone derivatives and BODIPYs **6d** and **6f** in 48% and 19% yield for the acetophenone derivatives. However, when phenyl acetylene and cyclopropyl acetylene were used as coupling partners for precursor **1g** (R^2 = Ph), BODIPYs **6a** and **6b** were obtained only in mediocre yields of 38% and 23%, respectively (Scheme 3). Subjecting phenyl acetylene and cyclopropyl acetylene to the reaction conditions with precursor **1h** (R^2 = Me) led to the corresponding BODIPYs in poor yields and with stability problems that resulted in major purification issues. Attempts to use ethyl propiolate as an electron-poor alkyne under the optimized reaction conditions failed completely. The structure of BODIPY **6e** was also confirmed by X-ray diffraction analysis.[55]

The photophysical properties of a selection of our prepared BODIPYs are summarized in Table S1 (see ESI†) and Fig. 1. BODIPYs **5a–5l** absorbed and emitted light between 517 nm and 600 nm. Those bearing a phenyl group at the α-position showed a bathochromic shift compared to those having a methyl group at the same position. Compared to the effect of this substituent, the impact of the substituent at the *meso*-aryl group is low. In spite of high attenuation coefficients ($\sim 40 \times 10^3\ M^{-1}\ cm^{-1}$), only poor fluorescence was observed (quantum yields for **5a**, **5b**, **5e**, and **5f** between 1% and 4%). These values can be explained by an almost free rotation of the *meso*-aryl group, which allows non-radiative decay processes of the excited state.[54]



Scheme 3 Scope of the BODIPY formation *via* the Sonogashira-terminated aminopalladation cascade. All yields are given over three steps. [a] Alkyne (1.5 eq.) $Pd(P(3,5\text{-}(CF_3)_2C_6H_3)_3)_3$ (15 mol%), Et_3N (5.0 eq.), THF, 110 °C, 2–4 h; (2) TFA/CH_2Cl_2 (1 : 1), r.t., 2–3 h; (3) Et_3N (10.0 eq.), $BF_3{\cdot}OEt_2$ (12.0 eq.), PhMe, 0 °C → 60 °C, 5–15 min. [b] CP = cyclopropyl.

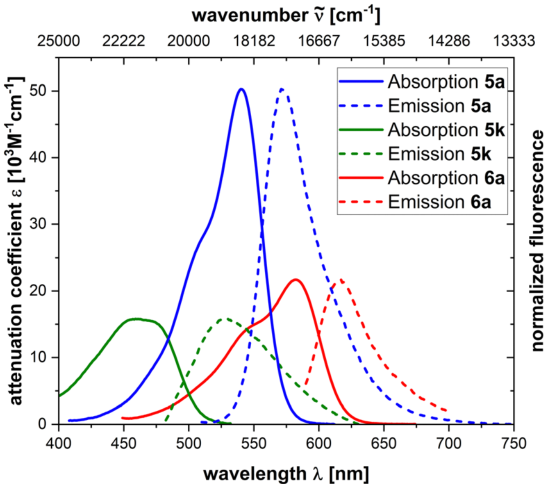


Fig. 1 Absorption and emission spectra of compounds of **5a**, **5k**, and **6a**.

BODIPYs **6a–6f** showed absorption and emission maxima in the range 544–617 nm. Again, α-phenyl substituted BODIPYs were bathochromically shifted compared to the α-methyl substituted BODIPYs. Stokes shifts lay between 961 cm^{-1} and 1119 cm^{-1}. In contrast to *meso*-aryl substituted BODIPYs, BODIPYs **6e** and **6f** exhibited a distinct fluorescence with quantum yields of 59% and 84%, nicely demonstrating the effect of the rigid alkynyl moiety.

A marked blue shift was observed for pyrazole-derived BODIPYs **5k** and **5l** with 459 and 434 nm, respectively, as absorption maxima and 530 and 507 nm as emission maxima. Furthermore, their Stokes shifts significantly increased to 2919 cm^{-1} and 3318 cm^{-1}, respectively. At the same time the attenuation also dropped to 15.8 and $16.2 \times 10^3\ M^{-1}\ cm^{-1}$, respectively. Additionally, quantum yields decreased below 1%, although we were still able to measure fluorescence spectra.

To conclude, we presented a novel approach to dipyrromethenes, key intermediates in the BODIPY synthesis, which employed an aminopalladation cascade starting from oxime esters. The oxidative addition of Pd into the N–O bond was followed by an intramolecular aza-Heck-reaction with an alkyne and was terminated by either a Suzuki or a Sonogashira cross-coupling reaction. The emerging *N*-Boc-protected diyprromethenes were deprotected and treated with $BF_3{\cdot}OEt_2$ under basic conditions to obtain unsymmetrical isoindole-derived BODIPYs. A broad range of boronic acids can be used for this transformation. For the Sonogashira-terminated cascade reaction, terminal alkynes were used. Investigation of the photophysical properties revealed that a pyrazole-derived BODIPY analogue shows a significant blue-shift compared to commonly used BODIPYs.

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Conflicts of interest

The authors declare no conflict of interest.

Notes and references

1 A. Treibs and F.-H. Kreuzer, *Justus Liebigs Ann. Chem.*, 1968, **718**, 208–223.
2 G. Ulrich, R. Ziessel and A. Harriman, *Angew. Chem., Int. Ed.*, 2008, **47**, 1184–1201.
3 A. Loudet and K. Burgess, *Chem. Rev.*, 2007, **107**, 4891–4932.
4 R. Ziessel, G. Ulrich and A. Harriman, *New J. Chem.*, 2007, **31**, 496–501.
5 L. J. Patalag, L. P. Ho, P. G. Jones and D. B. Werz, *J. Am. Chem. Soc.*, 2017, **139**, 15104–15113.
6 A. Patra, L. J. Patalag, P. G. Jones and D. B. Werz, *Angew. Chem., Int. Ed.*, 2021, **60**, 747–752.
7 L. J. Patalag, J. Hoche, M. Holzapfel, A. Schmiedel, R. Mitric, C. Lambert and D. B. Werz, *J. Am. Chem. Soc.*, 2021, **143**, 7414–7425.
8 L. Mendive-Tapia, L. Miret-Casals, N. D. Barth, J. Wang, A. de Bray, M. Beltramo, V. Robert, C. Ampe, D. J. Hodson, A. Madder and M. Vendrell, *Angew. Chem., Int. Ed.*, 2023, **62**, e202302688.
9 A. Barattucci, C. M. A. Gangemi, A. Santoro, S. Campagna, F. Puntoriero and P. Bonaccorsi, *Org. Biomol. Chem.*, 2022, **20**, 2742–2763.
10 T. Wang, Z. Jiang and Z. Liu, *Org. Lett.*, 2023, **25**, 1638–1642.
11 C. S. Wijesooriya, J. A. Peterson, P. Shrestha, E. J. Gehrmann, A. H. Winter and E. A. Smith, *Angew. Chem., Int. Ed.*, 2018, **57**, 12685–12689.
12 T. Kowada, H. Maeda and K. Kikuchi, *Chem. Soc. Rev.*, 2015, **44**, 4953–4972.
13 L. J. Patalag, S. Ahadi, O. Lashchuk, P. G. Jones, S. Ebbinghaus and D. B. Werz, *Angew. Chem., Int. Ed.*, 2021, **60**, 8766–8771.
14 L. Schneider, M. Kalt, S. Koch, S. Sithamparanathan, V. Villiger, J. Mattiat, F. Kradolfer, E. Slyshkina, S. Luber, M. Bonmarin, C. Maake and B. Spingler, *J. Am. Chem. Soc.*, 2023, **145**, 4534–4544.
15 T. Yogo, Y. Urano, Y. Ishitsuka, F. Maniwa and T. Nagano, *J. Am. Chem. Soc.*, 2005, **127**, 12162–12163.
16 R. Prieto-Montero, R. Sola-Llano, R. Montero, A. Longarte, T. Arbeloa, I. López-Arbeloa, V. Martínez-Martínez and S. Lacombe, *Phys. Chem. Chem. Phys.*, 2019, **21**, 20403–20414.
17 M. A. Filatov, *Org. Biomol. Chem.*, 2019, **18**, 10–27.
18 P. de Bonfils, L. Péault, P. Nun and V. Coeffard, *Eur. J. Org. Chem.*, 2021, 1809–1824.
19 R. Weber, K. Chok, S. Junek, C. Glaubitz and A. Heckel, *Chem. – Eur. J.*, 2023, **29**, e202300149.
20 P. Shrestha, A. Mukhopadhyay, K. C. Dissanayake and A. H. Winter, *J. Org. Chem.*, 2022, **87**, 14334–14341.
21 J. A. Peterson, C. Wijesooriya, E. J. Gehrmann, K. M. Mahoney, P. P. Goswami, T. R. Albright, A. Syed, A. S. Dutton, E. A. Smith and A. H. Winter, *J. Am. Chem. Soc.*, 2018, **140**, 7343–7346.
22 D. Kand, P. Liu, M. X. Navarro, L. J. Fischer, L. Rousso-Noori, D. Friedmann-Morvinski, A. H. Winter, E. W. Miller and R. Weinstain, *J. Am. Chem. Soc.*, 2020, **142**, 4970–4974.
23 A. Poryvai, M. Galkin, V. Shvadchak and T. Slanina, *Angew. Chem., Int. Ed.*, 2022, **61**, e202205855.
24 P. Shrestha, D. Kand, R. Weinstain and A. H. Winter, *J. Am. Chem. Soc.*, 2023, 145, asap.
25 T. Mori, *Circularly Polarized Luminescence of Isolated Small Organic Molecules*, Springer Singapore, Singapore, 2020.
26 R. G. Clarke and M. J. Hall, *Adv. Heterocycl. Chem.*, 2019, **128**, 181–261.
27 T. V. Goud, A. Tutar and J.-F. Biellmann, *Tetrahedron*, 2006, **62**, 5084–5091.
28 E. Lager, J. Liu, A. Aguilar-Aguilar, B. Z. Tang and E. Peña-Cabrera, *J. Org. Chem.*, 2009, **74**, 2053–2058.
29 V. Leen, P. Yuan, L. Wang, N. Boens and W. Dehaen, *Org. Lett.*, 2012, **14**, 6150–6153.
30 B. Åkermark, J. E. Bäckvall, L. S. Hegedus, K. Zetterberg, K. Siirala-Hansén and K. Sjöberg, *J. Organomet. Chem.*, 1974, **72**, 127–138.
31 L. S. Hegedus, G. F. Allen, J. J. Bozell and E. L. Waterman, *J. Am. Chem. Soc.*, 1978, **100**, 5800–5807.
32 A. S. Guram, R. A. Rennels and S. L. Buchwald, *Angew. Chem., Int. Ed. Engl.*, 1995, **34**, 1348–1350.
33 J. P. Wolfe, R. A. Rennels and S. L. Buchwald, *Tetrahedron*, 1996, **52**, 7525–7546.
34 J. P. Wolfe, S. Wagaw, J.-F. Marcoux and S. L. Buchwald, *Acc. Chem. Res.*, 1998, **31**, 805–818.
35 A. J. Peat and S. L. Buchwald, *J. Am. Chem. Soc.*, 1996, **118**, 1028–1030.
36 A. Minatti and K. Muñiz, *Chem. Soc. Rev.*, 2007, **36**, 1142–1152.
37 H. Tsutsui and K. Narasaka, *Chem. Lett.*, 1999, 45–46.
38 H. Tsutsui and K. Narasaka, *Chem. Lett.*, 2001, 526–527.
39 M. Kitamura, S. Chiba, O. Saku and K. Narasaka, *Chem. Lett.*, 2002, 606–607.
40 M. Kitamura and K. Narasaka, *Chem. Rec.*, 2002, **2**, 268–277.
41 S. Chiba, M. Kitamura, O. Saku and K. Narasaka, *Bull. Chem. Soc. Jpn.*, 2004, **77**, 785–796.
42 S. Zaman, K. Mitsuru and A. D. Abell, *Org. Lett.*, 2005, **7**, 609–611.
43 N. J. Race, A. Faulkner, M. H. Shaw and J. F. Bower, *Chem. Sci.*, 2016, **7**, 1508–1513.
44 A. Faulkner and J. F. Bower, *Angew. Chem., Int. Ed.*, 2012, **51**, 1675–1679.
45 N. J. Race and J. F. Bower, *Org. Lett.*, 2013, **15**, 4616–4619.
46 I. R. Hazelden, R. C. Carmona, T. Langer, P. G. Pringle and J. F. Bower, *Angew. Chem., Int. Ed.*, 2018, **57**, 5124–5128.
47 A. Faulkner, J. S. Scott and J. F. Bower, *J. Am. Chem. Soc.*, 2015, **137**, 7224–7230.
48 I. R. Hazelden, X. Ma, T. Langer and J. F. Bower, *Angew. Chem., Int. Ed.*, 2016, **55**, 11198–11202.
49 C. Jing, B. T. Jones, R. J. Adams and J. F. Bower, *J. Am. Chem. Soc.*, 2022, **144**, 16749–16754.
50 F. J. Geffers, F. R. Kurth, P. G. Jones and D. B. Werz, *Chem. – Eur. J.*, 2021, **27**, 14846–14850.
51 M. Kitamura, Y. Moriyasu and T. Okauchi, *Synlett*, 2011, 643–646.
52 N. George, S. Ofori, S. Parkin and S. G. Awuah, *RSC Adv.*, 2020, **10**, 24017–24026.
53 D. M. Shendage, R. Fröhlich and G. Haufe, *Org. Lett.*, 2004, **6**, 3675–3678.
54 A. B. Zaitsev, R. Méallet-Renault, E. Y. Schmidt, A. I. Mikhaleva, S. Badré, C. Dumas, A. M. Vasil'tsov, N. V. Zorina and R. B. Pansu, *Tetrahedron*, 2005, **61**, 2683–2688.
55 Deposition Numbers 2298671–2298673, and 2284407 contain the supplementary crystallographic data for this paper†.