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Cu-catalyzed C(sp²)-N-bond coupling of boronic acids and cyclic imides†

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A general Cu-catalyzed strategy for coupling cyclic imides and alkenyl-boronic acids by forming C(sp²)-N-bonds is reported. The method enables the practical and mild preparation of (*E*)-enimides. A large range of cyclic imides are allowed, and di- and tri-substituted alkenylboronic acids can be used. Full retention was observed in the configuration of the alkene double bond in the coupled products. The method is also applicable for preparing *N*-arylimides, using arylboronic acids as coupling partners. The usefulness of this strategy is exemplified by the convenient derivatization of the chemotherapy medication 5-fluorouracil, the nucleoside uridine and the anti-epileptic drug phenytoin.

Enimides (Fig. 1) are functional groups found in *N*-sulfonylurea isosteres,¹ biologically active structures,^{2,3} functional materials,⁴ and natural products such as the parazoanthines A-E.⁵ They are also building blocks in synthesis of complex structures,⁶ polycyclic architecture,⁷ and β-2-amino acid derivatives.⁸

The growing interest in the enamide moiety has catalyzed a recent spurt of attention for methodology appropriate for its construction (Fig. 2).⁹ In reactions where the enamide C(sp²)-N-bond is formed, only a few strategies are known. The main access point is the Ru-catalyzed hydroimidation strategy, wherein imides and alkynes are condensed (Fig. 2, strategy 1).¹⁰ Drawbacks include the use of an expensive Ru-catalysts, and the structural limitations imposed. A second approach involves the Cu-mediated coupling of imides and vinylic halides (Fig. 2, strategy 2).¹¹ This strategy is only applicable to phthalimide, and therefore specialized. Other examples are substrate specific.^{12,13}

The Chan-Lam¹⁴ inspired Cu-catalyzed process using alkenyl boron coupling partners, is an attractive route to enimes for several reasons: (i) the availability of alkenylboronic reagents¹⁵ provide synthetic flexibility, (ii) the use of an inexpensive Cu-catalyst is attractive, and (iii) a potentially larger structural diversity

of enimes is conceivable, compared to Ru-methods currently used. Thus far, only highly substrate dependent examples are known,¹⁶ but a general method has not been reported before now.

Our endeavors were initiated as shown in Table 1. Due to our ongoing interest¹⁷ in the pharmaceutically relevant hydantoin framework,¹⁸ hydantoin **1a** was used as a model substrate, with styrylboronic acid **2a** as reagent. The optimal conditions (entry #1) involved the use of excess reagent **2a** (3.0 equiv.) with copper(II)triflate and pyridine in ethanol at 25 °C. Less expensive Cu-salts may also be effective (#2 and 3). The process was also effective using 2.0 equiv. of the reagent (entry #4), so less reagent can be employed if a slight reduction in yield is acceptable. Our investigations uncovered that the process was inefficient in aprotic solvents such as DMF and toluene (entries #6 and 7), and that the use of base/ligand was of paramount importance. Surprisingly, triethylamine (entry #8) performed poorly compared to pyridine. Strong, non-nucleophilic bases (entries #9 and 11) were also ineffective. The complete optimization study can be found in the ESI.†

We next investigated the scope and limitations of the method, Scheme 1. Complete retention of the configuration

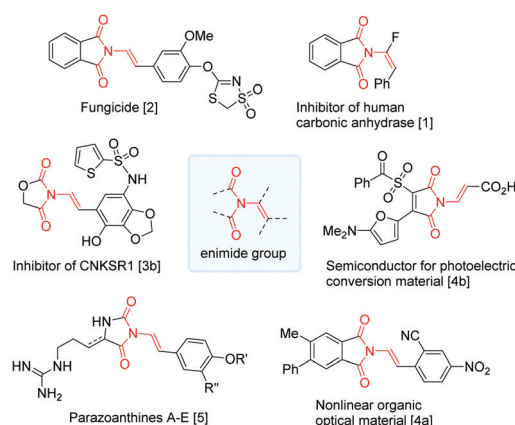


Fig. 1 Some examples of cyclic enimes.

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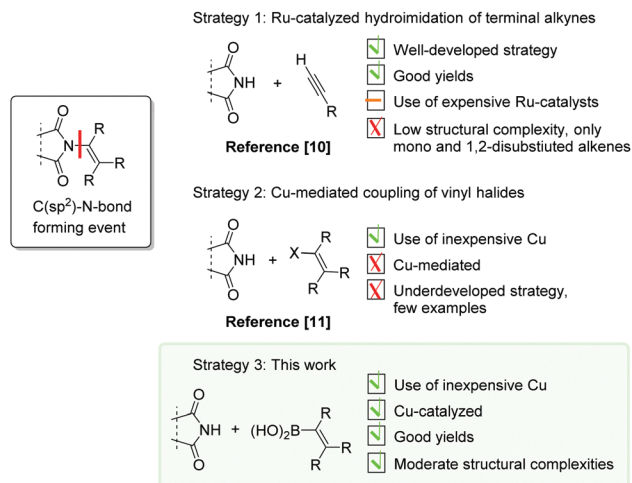
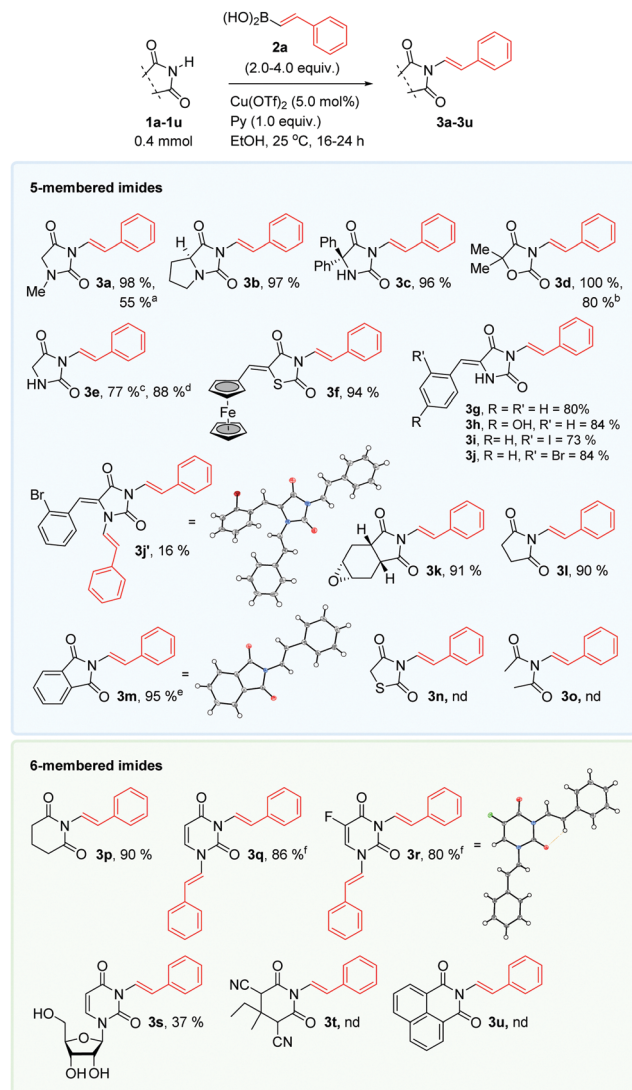
Fig. 2 Prior developments in the area of C(sp²)-N-bond formation.

Table 1 Reaction optimization

| # | Catalyst | 2a (equiv.) | Additive/base (equiv.) | Solvent | Time (h) | Yield ^a (%) |
|----------------|--|-------------|-------------------------|---------|----------|------------------------|
| 1 | Cu(OTf) ₂ | 3.0 | Py (1.0) | EtOH | 9/15 | 98/97 ^b |
| 2 | Cu(NO ₃) ₂ ^c | 3.0 | Py (1.0) | EtOH | 24 | 96 |
| 3 | CuCl | 3.0 | Py (1.0) | EtOH | 24 | 95 |
| 4 | Cu(OTf) ₂ | 2.0 | Py (1.0) | EtOH | 24 | 94 |
| 5 ^d | Cu(OTf) ₂ | 1.0 | Py (1.0) | EtOH | 24 | 71 |
| 6 | Cu(OTf) ₂ | 3.0 | Py (1.0) | DMF | 24 | 26 |
| 7 | Cu(OTf) ₂ | 3.0 | Py (1.0) | PhMe | 24 | 0 |
| 8 | Cu(OTf) ₂ | 3.0 | Et ₃ N (1.0) | EtOH | 24 | 8 |
| 9 | Cu(OTf) ₂ | 3.0 | <i>t</i> -BuOK (1.0) | EtOH | 18 | 22 |
| 10 | — | 3.0 | <i>t</i> -BuOK (2.0) | EtOH | 24 | 0 |
| 11 | Cu(OTf) ₂ | 3.0 | LiHMDS (1.0) | EtOH | 18 | 3 |

Conditions: *N*-Methylhydantoin **1a** (0.20 mmol, 1.0 equiv.), boronic acid **2a** (as specified), catalyst (0.010 mmol, 0.050 equiv.), additive/base (as specified) in solvent (as specified, 1 mL). ^a ¹H NMR yield using mesitylene as internal standard. ^b Isolated yield. ^c The (hemi)pentahydrate salt was used. ^d Reaction performed at 40 °C.

of the alkene double bond was observed in all cases. The anti-epileptic drug phenytoin **1c** was conveniently derivatized in excellent yield. Hydantoin **1e** was also smoothly alkenylated. The aldol adduct **1h** was smoothly *N*-3-alkenylated and not *O*-alkenylated, in excellent yield. We typically observed *N*-1, *N*-3-bisalkenylated hydantoins as byproducts in these reactions, such as the disubstituted hydantoin **3j'**. Phthalimide **3m** and glutarimide **3p** were obtained in excellent yields. Uracils are privileged structures in drug discovery.¹⁹ Uracil **1q**, the chemotherapy medication 5-fluorouracil **1r** and the nucleoside uridine **1s** were bis-alkenylated to **3q**, **3r** and **3s**, respectively. These results show that the method can conjugate drugs and nucleosides and provide uracils cumbersome to access.²⁰ Lastly, 2,4-thiazolidinedione **1n** was unreactive, but the ferrocenyl derivative **3f** was obtained in excellent yield.

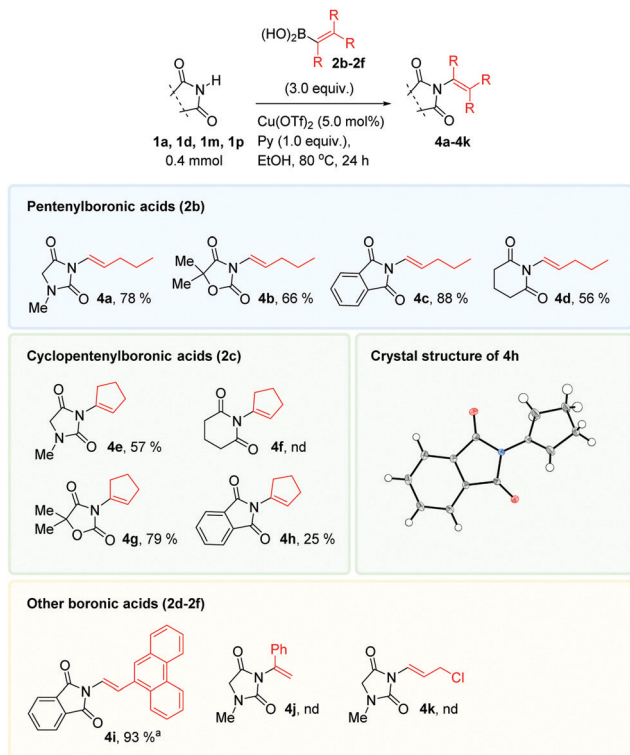


Scheme 1 Imide scope of the reaction. Conditions: imide **1a-1u** (0.40 mmol, 1.0 equiv.), boronic acid **2a** (1.2 mmol, 3.0 equiv.), Cu(OTf)₂ (0.020 mmol, 0.050 equiv.), pyridine (0.40 mmol, 1.0 equiv.) and EtOH (2 mL). ^a (*E*)-Styryl-9-BBN was used as coupling partner. ^b CuCl (5.0 mol%) was used as catalyst. ^c 2.0 equiv. boronic acid **2a** was used. ^d Reaction performed at 1.5 mmol scale. ^e Reaction performed at 0.40 and 1.0 mmol scale. ^f 4.0 equiv. boronic acid **2a** was used.

The method is applicable to cyclic imides, and not linear imides, as imide **1o** failed to react under our conditions. As suggested by Wasielewski *et al.*²¹ the carbonyl groups can adopt a parallel, coplanar conformation²² and may chelate to Cu(II)-ions. The chelation is likely detrimental for the coupling reaction.

A selection of alkenylboronic acids **2b-2f** were next investigated with some imides, Scheme 2. The performance of the coupling reaction varied. The 1-pentenyl reagent **2b** transferred in good to moderate yields, depending on the imide substrate. The cyclopentenyl coupling partner **2c** was challenging, likely imposing a high steric demand in relevant Cu-species in the catalytic cycle. The coupled product **4g** was obtained in good yield, but the six membered product **4f** was not detected.





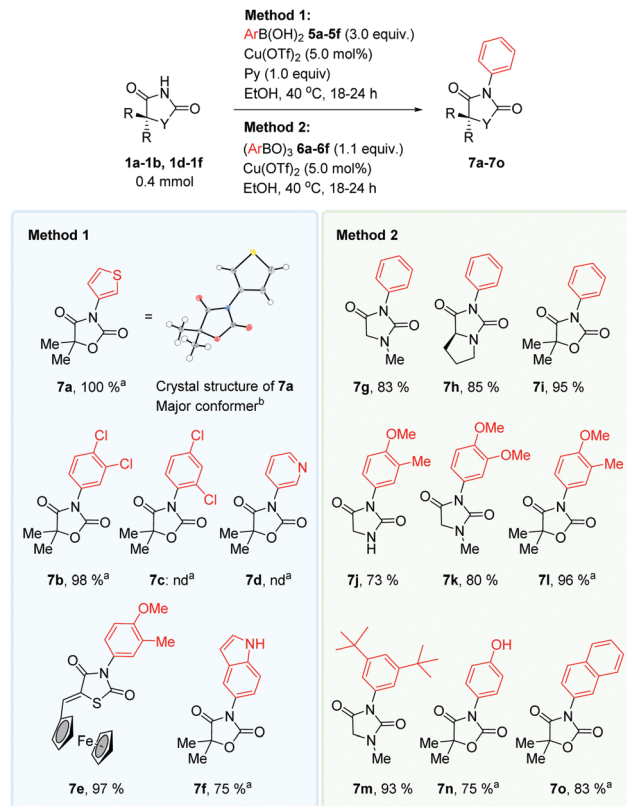
Scheme 2 Alkenylboronic acid scope. Conditions: imide **1a**, **1d**, **1m** or **1p** (0.40 mmol, 1.0 equiv.), boronic acid **2b–2f** (1.2 mmol, 3.0 equiv.), Cu(OTf)₂ (0.020 mmol, 0.050 equiv.), pyridine (0.40 mmol, 1.0 equiv.) and EtOH (2 mL). ^a Reaction performed at 0.18 mmol scale at 25 °C.

The 1,1,2-trisubstituted alkenes obtained, are not currently accessible employing the Ru-catalyzed methods mentioned in the introduction.

Our earlier work¹⁷ spurred an interest in employing arylboronic acids for *N*-arylation. Although the Cu-catalyzed or -mediated arylation of imides has been documented earlier,²³ the use of such conditions is sparingly described²⁴ using the pharmaceutically relevant hydantoin, 2,4-oxazolidinedione and related frameworks as substrates.

The method was high yielding and tolerable to diverse aryl groups, Scheme 3. The reaction performance varied if the arylboronic acid (method 1), or the corresponding anhydride (triarylboroxine, method 2) was employed. It is not possible to draw a conclusion as to which method operates best with which substrate. The pyridine likely has several key functions, such as being a Cu-ligand, acting as a base, and stabilizing boroxines *in situ*.²⁵

The method smoothly transferred electron-rich aryl groups to form products such as **7j**, **7k**, **7l**, **7m** and **7n** in mostly excellent yields. Electron-rich heterocyclic fragments were also efficiently coupled. The thiophenyl product **7a** was obtained in excellent yield, and the indolyl product **7f** was obtained in good yield. The pyridinyl product **7d** was not obtained. The electron-poor 3,4-dichlorophenyl group coupled to afford product **7b** in excellent yield, whereas the 2,4-dichlorophenyl group did not couple. We attribute this to the steric hinderance of the



Scheme 3 Scope of *N*-arylation. Method 1: hydantoin **1a**, **b** or **1d–1f** (0.40 mmol, 1.0 equiv.), boronic acid **5a–5f** (1.2 mmol, 3.0 equiv.), Cu(OTf)₂ (0.020 mmol, 0.050 equiv.), pyridine (0.020 mmol, 1.0 equiv.) in EtOH (2 mL). Method 2: hydantoin **1a**, **b** or **1d–1f** (0.40 mmol, 1.0 equiv.), boroxine **6a–6f** (0.44 mmol, 1.1 equiv.), Cu(OTf)₂ (0.020 mmol, 0.050 equiv.). ^a Reaction performed on 0.14 mmol scale. ^b Only the major conformer of the thiophene-ring is shown.

chlorine atom in the 2-position of the aryl group. Electronically neutral phenyl and naphthyl groups coupled in good yields.

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Conflicts of interest

There are no conflicts to declare.

Notes and references

- B. Metayer, A. Angeli, A. Mingot, K. Jouvin, G. Evano, C. T. Supuran and S. Thibaudau, *J. Enzyme Inhib. Med. Chem.*, 2018, **33**, 804–808.
- H. Uhr, C. Boie, H. Rieck, B.-W. Krueger, U. Heinemann, R. Market, M. Vaupel, M. Kugler, K. Stenzel, U. Wachendorff-Neumann, A. Mauler-Machnik, K.-H. Kuck, P. Loesel and S.-I. Narabu,



- Preparation of aryloxydithiazole and aryloxydithiazine dioxides as pesticides and fungicides, Patent DE 19918294, 2000.
- 3 (a) A. D. Brown, M. E. Bunnage, C. A. L. Lane, R. A. Lewthwaite, P. A. Glossop, K. James and D. A. Price, Preparation of formylamino hydroxyphenyl phenylacetamide derivatives as β 2 adrenoceptor agonists, Patent US 20050215590 A1, 2005; (b) D. L. Kirkpatrick and M. Indarte, Preparation of N-substituted thiazolecarboxamides for inhibiting CNKSR1, Patent US 20160304533 A1, 2016; (c) S. Louzoun Zada, K. D. Green, S. K. Shrestha, I. M. Herzog, S. Garneau-Tsodikova and M. Fridman, *ACS Infect. Dis.*, 2018, **4**, 1121–1129.
 - 4 (a) T. Ogawa and H. Yamada, Preparation of N-styrylphthalimide derivatives as nonlinear organic optical materials, Patent JP 08176107, 1996; (b) S. Otsu, K. Ofuku and N. Kagawa, Semiconductor for photoelectric conversion material, photoelectric converter, and photoelectrochemical cell, Patent, JP 2005019124, 2003.
 - 5 N. Cachet, G. Genta-Jouve, E. L. Regalado, R. Mokrini, P. Amade, G. Culioli and O. P. J. Thomas, *J. Nat. Prod.*, 2009, **72**(9), 1612–1615.
 - 6 (a) E. Alacid and C. Najera, *Adv. Synth. Catal.*, 2008, **350**, 1316–1322; (b) W. Susanto, C.-Y. Chu, W. J. Ang, T.-C. Chou, L.-C. Lo and Y. Lam, *J. Org. Chem.*, 2012, **77**, 2729–2742; (c) F. de Nanteuil and J. Waser, *Angew. Chem., Int. Ed.*, 2013, **52**, 9009–9013; (d) J. Szudkowska-Frątczak, G. Hreczycho and P. Pawluć, *Org. Chem. Front.*, 2015, **2**, 730–738; (e) E. Landagaray, M. Ettaoussi, M. Rami, J. A. Boutin, D.-H. Caignard, P. Delagrangre, P. Melynyk, P. Berthelot and S. Yous, *Eur. J. Med. Chem.*, 2017, **127**, 621–631.
 - 7 (a) S. K. Murphy, M. Zeng and S. B. Herzon, *Science*, 2017, **356**, 956–959; (b) P. Kramer, J. Schonfeld, M. Bolte and G. Manolikakes, *Org. Lett.*, 2018, **20**, 178–181.
 - 8 J. Dai, W. Ren, W. Chang, P. Zhang and Y. Shi, *Org. Chem. Front.*, 2017, **4**, 297–302.
 - 9 (a) Z. J. Song, M. D. Tellers, P. G. Dormer, D. Zewge, J. M. Janey, A. Nolting, D. Steinhuebel, S. Oliver, P. N. Devine and D. M. Tschäen, *Org. Process Res. Dev.*, 2014, **18**, 423–430; (b) H. Lingua, F. Vibert, D. Mouysset, D. Siri, M. P. Bertrand and L. Feray, *Tetrahedron*, 2017, **73**, 3415–3422; (c) W.-M. Cheng, R. Shang and Y. Fu, *Nat. Commun.*, 2018, **9**, 5215–5223; (d) W. Lin, W. Li, D. Lu, F. Su, T.-B. Wen and H.-J. Zhang, *ACS Catal.*, 2018, **8**, 8070–8076.
 - 10 (a) L. J. Goossen, M. Blanchot, C. Brinkmann, K. Goossen, R. Karch and A. J. Rivas-Nass, *Org. Chem.*, 2006, **71**, 9506–9509; (b) M. Arndt, K. S. M. Salih, A. Fromm, L. J. Goossen, F. Menges and G. Niedner-Schatteburg, *J. Am. Chem. Soc.*, 2011, **133**, 7428–7449; (c) A. E. Buba, M. Arndt and L. J. Goossen, *J. Organomet. Chem.*, 2011, **696**, 170–178; (d) E. Semina, P. Tuzina, F. Bienewald, A. S. K. Hashmi and T. Schaub, *Chem. Commun.*, 2020, **56**, 5977–5980.
 - 11 (a) R. G. R. Bacon and A. Karim, *J. Chem. Soc., Perkin Trans. 1*, 1973, 278–280; (b) T. Ogawa, T. Kiji, K. Hayami and H. Suzuki, *Chem. Lett.*, 1991, 1443–1446.
 - 12 D. G. Kohler, S. N. Gockel, J. L. Kennemur, P. J. Waller and K. L. Hull, *Nat. Chem.*, 2018, **10**, 333–340.
 - 13 (a) L. V. Desai and M. S. Sanford, *Angew. Chem., Int. Ed.*, 2007, **46**, 5737–5740; (b) Z. Song and W. Yi, *Adv. Synth. Catal.*, 2016, **358**, 2727–2732.
 - 14 J.-Q. Chen, J.-H. Li and Z.-B. Dong, *Adv. Synth. Catal.*, 2020, **362**, 3311–3331.
 - 15 (a) R. J. Perner, C.-H. Lee, M. Jiang, Y.-G. Gu, S. DiDomenico, E. K. Bayburt, K. M. Alexander, K. L. Kohlhaas, M. F. Jarvis, E. L. Kowaluk and S. S. Bhagwat, *Bioorg. Med. Chem. Lett.*, 2005, **14**, 2803–2807; (b) G. A. Molander, L. N. Cavalcanti, B. Canturk, P.-S. Pan and L. E. Kennedy, *J. Org. Chem.*, 2009, **74**, 7364–7369; (c) J. Hu, B. Cheng, X. Yang and T.-P. Loh, *Adv. Synth. Catal.*, 2019, **361**, 4902–4908.
 - 16 (a) Y. Bolshan and R. A. Batey, *Angew. Chem., Int. Ed.*, 2008, **47**, 2109–2112; (b) J.-W. Jiao, H.-Y. Bi, P.-S. Zou, Z.-X. Wang, C. Liang and D.-L. Mo, *Adv. Synth. Catal.*, 2018, **360**, 3254–3259; (c) L. Steemers, L. Wijsman and J. H. van Maarseveen, *Adv. Synth. Catal.*, 2018, **360**, 4241–4245; (d) J. Li, Z. Zhang, L. Wu, W. Zhang, P. Chen, Z. Lin and G. Liu, *Nature*, 2019, **574**, 516–521.
 - 17 L. Neerbye Berntsen, A. Nova, D. S. Wragg and A. H. Sandtorv, *Org. Lett.*, 2020, **22**, 2687–2691.
 - 18 (a) L. Konnert, F. Lamaty, J. Martinez and E. Colacino, *Chem. Rev.*, 2017, **117**, 13757–13809; (b) P. Thilmany, P. Gerard, A. Vanoost, C. Deldaele, L. Petit and G. Evano, *J. Org. Chem.*, 2019, **84**, 394–400.
 - 19 A. Palasz and D. Ciez, *Eur. J. Med. Chem.*, 2015, **97**, 582–611.
 - 20 R. Dalpozzo, A. De Nino, L. Maiuolo, A. Procopio, R. Romeo and G. Sindona, *Synthesis*, 2002, 172–174.
 - 21 E. T. Chernick, M. J. Ahrens, K. A. Scheidt and M. R. Wasielewski, *J. Org. Chem.*, 2005, **70**, 1486–1489.
 - 22 C. S. Kraihanzel and S. C. Grenda, *Inorg. Chem.*, 1965, **4**, 1037–1042.
 - 23 Z.-G. Zheng, J. Wen, N. Wang, B. Wu and X. Q. Yu, *Beilstein J. Org. Chem.*, 2008, **4**, 40.
 - 24 H. M. Hügel, C. J. Rix and K. Fleck, *Synlett*, 2006, 2290–2292.
 - 25 A. L. Korich and P. M. Iovine, *Dalton Trans.*, 2010, **39**, 1423–1431.

