

Cite this: *Chem. Sci.*, 2022, 13, 2418

All publication charges for this article have been paid for by the Royal Society of Chemistry

Received 9th November 2021

Accepted 29th January 2022

DOI: 10.1039/d1sc06234d

rsc.li/chemical-science

Polycyclic heteroaromatics via hydrazine-catalyzed ring-closing carbonyl–olefin metathesis†

Eun Kee Cho, Phong K. Quach, Yunfei Zhang, Jae Hun Sim and Tristan H. Lambert *

The use of hydrazine-catalyzed ring-closing carbonyl–olefin metathesis (RCCOM) to synthesize polycyclic heteroaromatic (PHA) compounds is described. In particular, substrates bearing Lewis basic functionalities such as pyridine rings and amines, which strongly inhibit acid catalyzed RCCOM reactions, are shown to be compatible with this reaction. Using 5 mol% catalyst loadings, a variety of PHA structures can be synthesized from biaryl alkenyl aldehydes, which themselves are readily prepared by cross-coupling.

Polycyclic heteroaromatic (PHA) structures comprise the core framework of many valuable compounds with a diverse range of applications (Fig. 1A).¹ For example, polycyclic azines (*e.g.* quinolines) are embedded in many alkaloid natural products, including diplamine² and eupolauramine³ to name just a few. These types of structures are also of interest for their biological activity, such as with the inhibitor of the Src-SH3 protein–protein interaction shown in Fig. 1A.⁴ Many nitrogenous PHAs are also useful as ligands for transition metal catalysis, as exemplified by the widely used ligand 1,10-phenanthroline.⁵ Meanwhile, chalcogenoarenes⁶ such as dinaphthofuran⁷ and benzodithiophene⁸ have attracted high interest for both their medicinal properties⁹ and especially for their potential use as organic light-emitting diodes (OLEDs), organic photovoltaics (OPVs), and organic field-effect transistors (OFETs).¹⁰ These and numerous other examples have inspired the development of a wide variety of strategies to construct PHAs.^{1,11–14} Although these approaches are as varied as the structures they target, the wide range of molecular configurations within PHA chemical space and the challenges inherent in exerting control over heteroatom position and global structure make novel syntheses of these structures a topic of continuing interest.

One potentially advantageous strategy for PHA synthesis is the use of ring-closing carbonyl–olefin metathesis¹⁵ (RCCOM) to forge one of the PHA rings, starting from a suitably disposed alkenyl aldehyde precursor **2** that can be easily assembled by cross-coupling (Fig. 1B). In related work, the application of RCCOM to form polycyclic aromatic hydrocarbons (PAHs) was reported by Schindler in 2017.¹⁶ In this case, 5 mol% FeCl₃ catalyzed the metathesis of substrates to form phenanthrenes and related compounds in high yields at room temperature. This method was highly attractive for its efficiency, its use of an

earth-abundant metal catalyst, and the production of benign acetone as the only by-product. Nevertheless, one obvious drawback to the use of Lewis acid activation is that the presence of any functionality that is significantly more Lewis basic than the carbonyl group can be expected to strongly inhibit these reactions (Fig. 1C). Such a limitation thus renders this method incompatible with a wide swath of complex molecules, especially PHAs comprised of azine rings. This logic argues for a mechanistically orthogonal RCCOM approach that allows for the synthesis of PHA products with a broader range of ring systems and functional groups.

We have developed an alternative approach to catalytic carbonyl–olefin metathesis that makes use of the condensation of 1,2-dialkylhydrazines **5** with aldehydes to form hydrazone ions **6** as the key catalyst–substrate association step.^{17–19} This interaction has a much broader chemoorthogonality profile than Lewis acid–base interactions and should thus be much less prone to substrate inhibition than acid-catalyzed approaches. In this Communication, we demonstrate that hydrazine-catalyzed RCCOM enables the rapid assembly of PHAs bearing basic functionality (Fig. 1D).

For our optimization studies, we chose biaryl pyridine aldehyde **7** as the substrate (Table 1). Using 5 mol% of the hydrazine salt **10** furnished the RCCOM product **8** in 67% yield after 15 h at 80 °C in a sealed vial with THF as a solvent (entry 1). The [2.2.2]-bicyclic hydrazine²⁰ salt **11** was also productive (entry 2), albeit somewhat less so. Notably, iron(III) chloride generated no conversion at either ambient or elevated temperatures (entries 3 and 4). Trifluoroacetic acid (TFA) was similarly ineffective (entry 5). Meanwhile, a screen of various solvents revealed that, while the transformation could occur in a range of media (entries 6–9), THF was optimal. Finally, by raising the temperature to 90 °C (entry 10) or 100 °C (entry 11), up to 96% NMR yield (85% isolated yield) of adduct **8** could be obtained in the same time period.

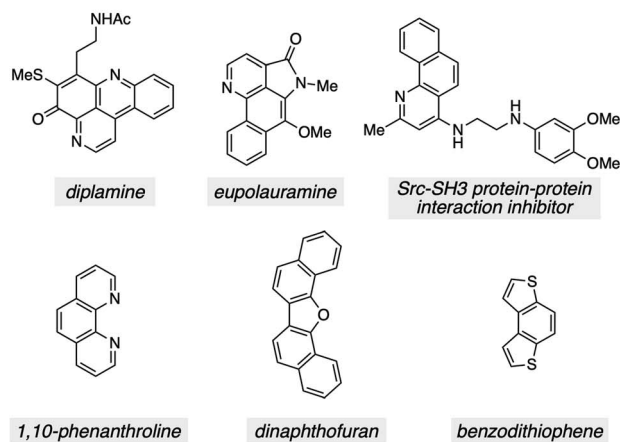
Using the optimized conditions, we explored the synthesis of various PHAs (Fig. 2). In addition to benzo[*h*]isoquinoline (**8**),

Department of Chemistry and Chemical Biology, Cornell University, Ithaca, New York 14853, USA. E-mail: tristan.lambert@cornell.edu

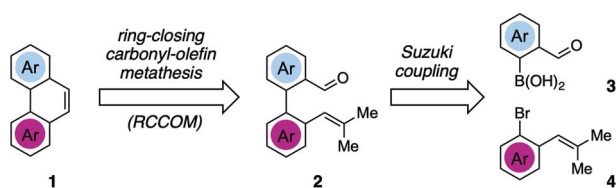
† Electronic supplementary information (ESI) available. See DOI: 10.1039/d1sc06234d



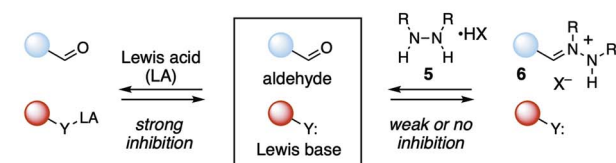
A. Examples of polycyclic heteroaromatics (PHAs)



B. Rapid assembly of PHAs via RCCOM



C. Lewis acid vs. hydrazine catalysis in the presence of Lewis bases



D. Hydrazine-catalyzed RCCOM (this work)

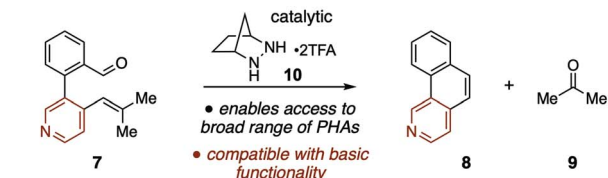


Fig. 1 (A) Examples of PHAs. (B) RCCOM strategy for PHA synthesis. (C) Lewis base inhibition for Lewis acid vs. hydrazine catalyzed RCCOM. (D) Hydrazine-catalyzed RCCOM for PHA synthesis.

products **12** and **13** with fluorine substitution at various positions could be generated in good yields. Similarly, benzoisoquinolines **14** and **15** bearing electron-donating methoxy groups and the dioxole-fused product **16** were also accessed efficiently. Furthermore, a phenolic ether product **17** with a potentially acid-labile *N*-Boc group was generated in modest yield. We found that an even more electron-donating dimethylamino group was also compatible with this chemistry, allowing for the production of **18** in 68% yield. On the other hand, adduct **19** bearing a strongly electron-withdrawing trifluoromethyl group was isolated in only modest yield. The naphtho-fused isoquinoline **20** could be generated as well; however, 20 mol% catalyst was required to realize a 35% yield. The thiophene-fused product **21** was furnished in much better yield, also with the higher catalyst loading. Although not a heterocyclic

Table 1 Optimization studies^a

Entry	Catalyst	Solvent	Temp. (°C)	8 yield (%)
1	10	THF	80	67
2	11	THF	80	53
3	FeCl ₃	DCE	rt	0
4	FeCl ₃	DCE	80	0
5	TFA	THF	80	0 ^b
6	10	<i>i</i> -PrOH	80	31
7	10	CH ₃ CN	80	28
8	10	EtOAc	80	26
9	10	Toluene	80	24
10	10	THF	90	87
11	10	THF	100	96 ^c

10 **11**

^a Conditions: substrate **8** (0.2 mmol) and 5 mol% catalyst in 0.4 mL of solvent (0.5 M) in a 5 mL sealed tube were heated to the temperature indicated for 15 h. Yields were determined by ¹H NMR using CH₂Br₂ as an internal standard. ^b 2 equiv. of TFA was used. ^c 85% isolated yield.

system, we found that the reaction to form phenanthrene (**22**) was well-behaved, providing that compound in 83% yield. In addition, an amino-substituted phenanthrene **23** was also formed in good yield. Other thiophene-containing PAHs such as **24–26** were produced efficiently. On the other hand, adduct **27** was generated only in low yield. Naphthofuran (**28**), which is known to have antitumor and oestrogenic properties,²¹ was synthesized in good yield. Finally, pharmaceutically important structures such as benzocarbazole²² **29** and naphthoimidazole²³ **30** could be accessed in moderate yields with increased catalyst loading.

We also examined the scope of the olefin substitution pattern (Table 2). For this screen, we reacted biaryl substrates with 5 mol% hydrazinium salt **10** in THF at 100 °C in a sealed vial. The trisubstituted 2-methyl-1-propenyl substrate **7** was by far superior to the others in terms of reactivity and yield (entry 1), reaching full conversion in 15 h as already discussed.

The vinyl substrate **31** led to very little desired product (entry 2), while the propenyl substrate **32** (2 : 1 mixture of *E* and *Z* isomers) was somewhat improved but still low-yielding (entry 3). Finally, styrenyl substrates **33** and **34** (entries 4 and 5) led to improved yields relative to **31** and **32**, with the *cis* isomer **34** being slightly more efficient (entry 5).

In order to better understand the facile nature of this RCCOM reaction, we conducted DFT calculations for each step of the proposed reaction pathway (Fig. 3A). Condensation of the substrate **7** with [2.2.1]-hydrazinium **10** to afford the hydrazonium *Z*-**35** was found to be exergonic by $-13 \text{ kcal mol}^{-1}$. Isomerization of *Z*-**35** to *E*-**35** comes at a cost of $\sim 3 \text{ kcal mol}^{-1}$, but the



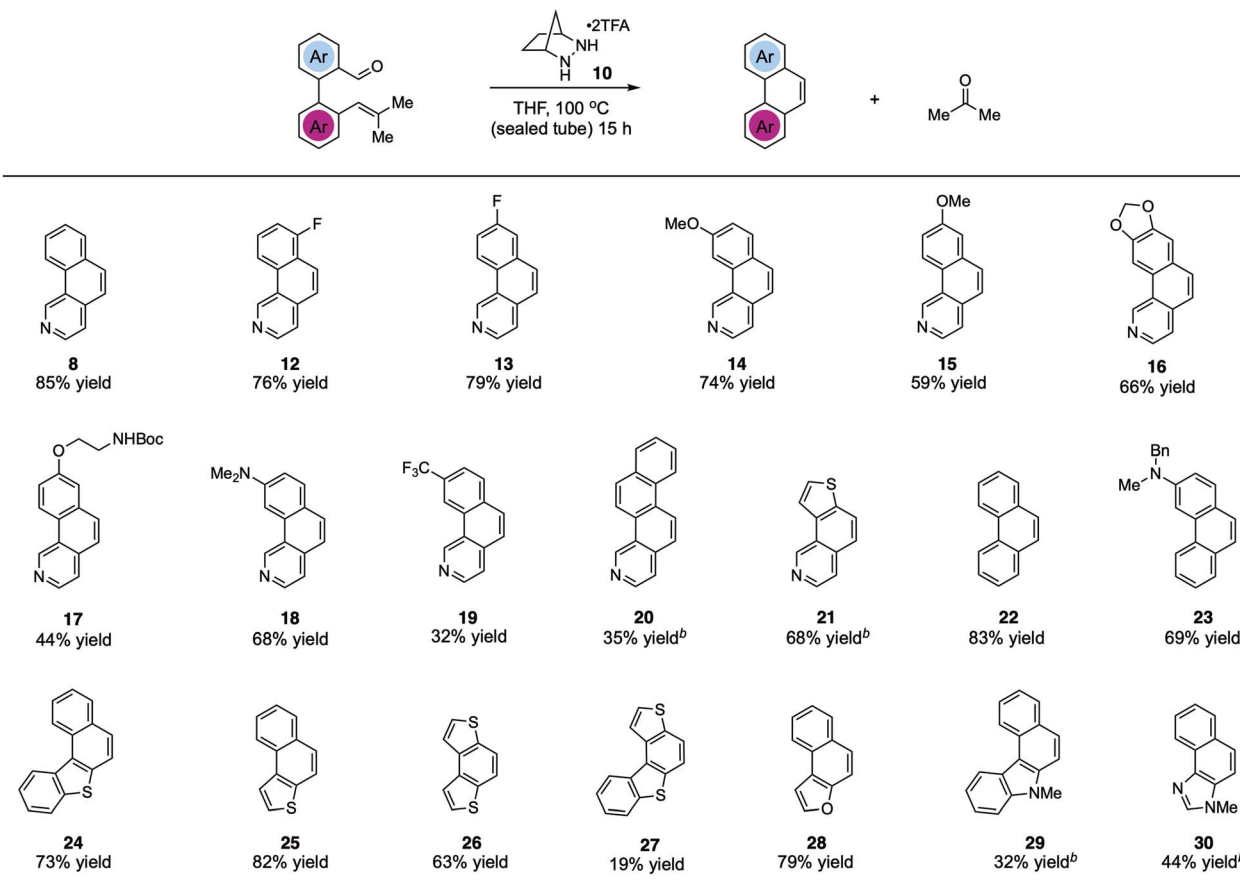


Fig. 2 Substrate scope studies for hydrazine **1**-catalyzed RCCOM synthesis of polycyclic heteroaromatics. ^a Conditions: substrate and catalyst **1**·(TFA)₂ (5 mol%) in THF (0.5 M) were heated to 100 °C in a 5 mL sealed tube for 15 h. Yields were determined on purified products. ^b 20 mol% catalyst.

Table 2 Screen of the olefin substituent^a

Entry	Substrate	Time (h)	Yield (%)
1		15	96
2		48	5
3 ^b		48	27
4		48	54
5		48	64

^a Conditions: 5 mol% **10** in THF (0.5 M) in a 5 mL sealed tube were heated to the temperature indicated for 15–48 h. Conversions and yields were determined by ¹H NMR using CH₂Br₂ as an internal standard. ^b Mixture of *E/Z* (2 : 1) isomers.

total activation energy for cycloaddition (*cf.* **36**), taking into account this isomerization, was still relatively modest at only +21.0 kcal mol⁻¹ with an overall exergonicity of -11.1 kcal mol⁻¹. The energetic change for proton transfer in the conversion of cycloadduct **37a** to the cycloreversion precursor **37b** was negligible (+1.2 kcal mol⁻¹). Interestingly, including the proton migration step, the cumulative energy barrier for cycloreversion **38** was found to be only +21.7 kcal mol⁻¹, nearly the same as for the cycloaddition. Undoubtedly, the formation of an aromatic ring greatly facilitates this step relative to other types of substrates. Unsurprisingly, the cycloreversion to produce benzoisoquinoline **8** along with hydrazonium **39** was calculated to be strongly exergonic. Finally, the hydrolysis of **39** to regenerate hydrazinium catalyst **10** (and acetone) required an energy input approximately equal to that gained from the condensation with the substrate to form **35**.

Given the low activation energy barriers of both the cycloaddition and cycloreversion steps, we reasoned it should be possible for the reaction to proceed at a relatively low temperature. In fact, we observed 82% conversion of biaryl aldehyde **7** to cycloadduct **37** (72%) and benzoisoquinoline **8** (10%) at 40 °C over 6 hours. Attempts to isolate the cycloadduct **37** resulted in complete conversion to **8** during column chromatography. Meanwhile, at 60 °C over approximately 4 hours, 95% of the starting material **7**,



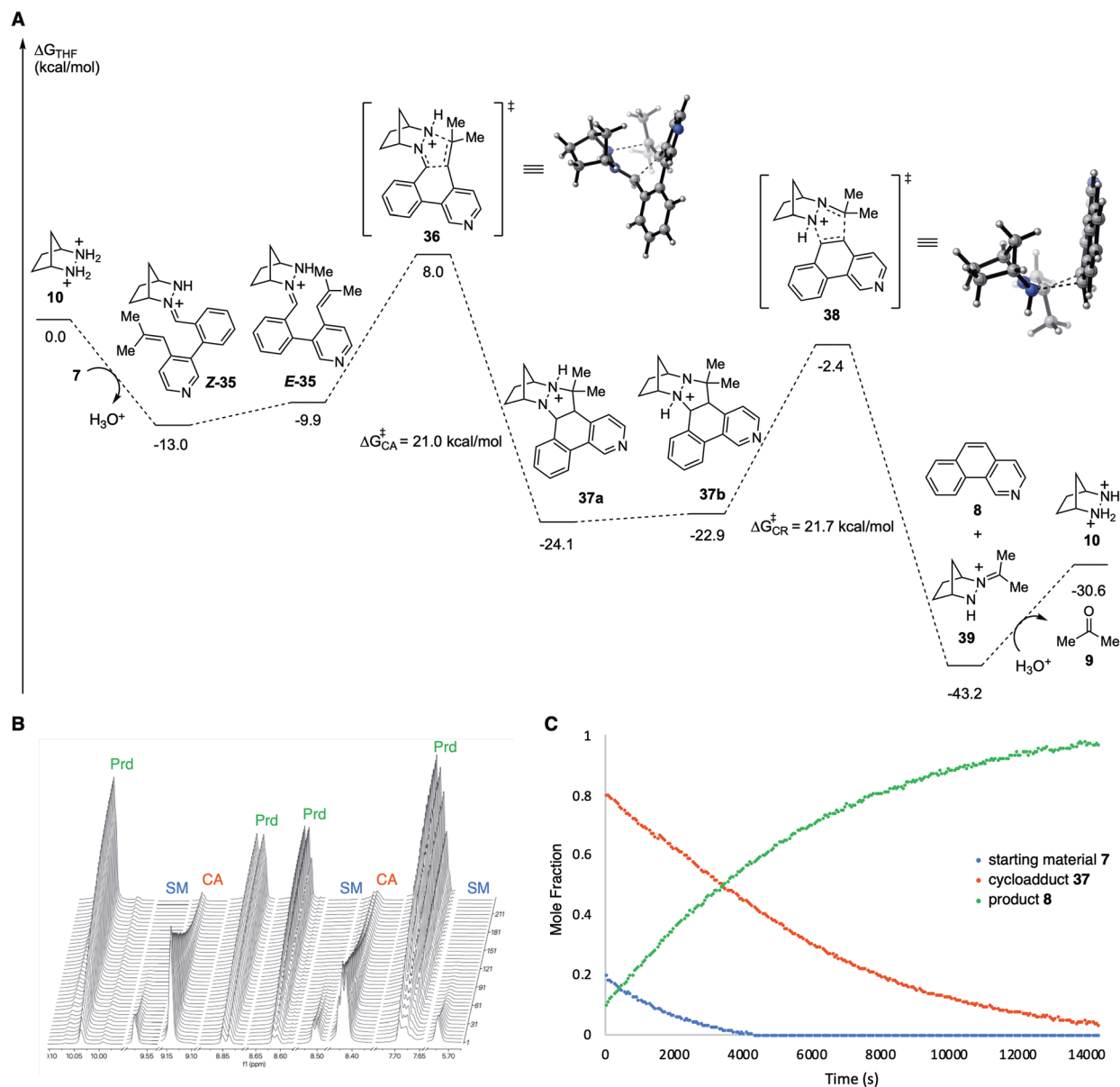


Fig. 3 (A) Computational study of hydrazine **10**-catalyzed RCCOM of biaryl aldehyde **7**. Calculations were performed at the PCM(THF)-M06-2X/6-311+G(d,p)//6-31G(d) level of theory.^{24,25} All energies are given in units of kcal mol⁻¹. (B) ¹H NMR spectroscopy of the RCCOM reaction of **7** catalyzed by **10** at 60 °C in THF-*d*8 with mesitylene as internal standard for 5 hours. (C) Plot of the data showing conversion vs. time. SM = starting material **7**; CA = cycloadduct **37**; Prd = product **8**.

via the intermediate cycloadduct **37**, was converted to benzoisquinoline product **8** (Fig. 3B and C). The rate of consumption of the cycloadduct was consistent with first-order behavior, and upon fitting, revealed the rate constant for cycloreversion as $k_{\text{CR}} = 2.14 \times 10^{-4} \text{ s}^{-1}$, with a half-life of 54 minutes. These observations corroborate the computational results, in particular showing that the cycloreversion step is quite facile with these types of substrates compared to other hydrazine-catalyzed COM reactions we have investigated¹⁷ and that cycloaddition and cycloreversion have energetically similar activation energies.

In conclusion, the development of catalytic carbonyl-olefin metathesis reactions has opened new possibilities for the rapid construction of complex molecules. The current work

demonstrates this strategy as a means to rapidly access polycyclic heteroaromatics, which often require lengthy sequences that can be complicated by the presence of basic functionality. The ability of the hydrazine catalysis platform to accommodate such functional groups provides a novel approach to polycyclic heteroaromatic synthesis and greatly expands the landscape of structures accessible by RCCOM.

Data availability

Data for this work, including experimental procedures, characterization data for all new compounds, and DFT computational details are provided in the ESI.†



Author contributions

T. H. L. conceived of and directed the project. E. K. C., P. K. Q., Y. Z., and J. H. S. conducted the experiments and collected and analyzed the data. P. K. Q. performed all DFT calculations. T. H. L., E. K. C., and P. K. Q. wrote the manuscript.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

Financial support for this work was provided by NIH R35 GM127135. This work made use of the Cornell University NMR Facility, which is supported in part^{1–25} by the NSF through MRI award CHE-1531632.

References

- 1 M. Stępień, E. Gońka, M. Żyła and N. Sprutta, *Chem. Rev.*, 2017, **117**, 3479–3716.
- 2 D. R. Appleton, A. N. Pearce and B. R. Copp, *Tetrahedron*, 2010, **66**, 4977–4986.
- 3 C. Hoarau, A. Couture, H. Cornet, E. Deniau and P. Grandclaoudon, *J. Org. Chem.*, 2001, **66**, 8064–8069.
- 4 N. Atatreh, C. Stojkoski, P. Smith, G. W. Booker, C. Dive, A. D. Frenkel, S. Freeman and R. A. Bryce, *Bioorg. Med. Chem. Lett.*, 2008, **18**, 1217–1222.
- 5 P. G. Sammes and G. Yahioğlu, *Chem. Soc. Rev.*, 1994, **23**, 327–334.
- 6 L. Zhang, S. M. Fakhouri, F. Liu, J. C. Timmons, N. A. Ran and A. L. Briseno, *J. Mater. Chem.*, 2011, **21**, 1329–1337.
- 7 C. Mitsui, T. Okamoto, H. Matsui, M. Yamagishi, T. Matsushita, J. Soeda, K. Miwa, H. Sato, A. Yamano, T. Uemura and J. Takeya, *Chem. Mater.*, 2013, **25**, 3952–3956.
- 8 G. R. Stephenson, S. Cauteruccio and J. Doucet, *Synlett*, 2014, **25**, 701–707.
- 9 R. S. Keri, K. Chand, S. Budagumpi, S. Balappa Somappa, S. A. Patil and B. M. Nagaraja, *Eur. J. Med. Chem.*, 2017, **138**, 1002–1033.
- 10 P. Kumaresan, S. Vegiraju, Y. Ezhumalai, S. L. Yau, C. Kim, W.-H. Lee and M.-C. Chen, *Polymers*, 2014, **6**, 2645–2669.
- 11 Y. Xia, Z. Liu, Q. Xiao, P. Qu, R. Ge, Y. Zhang and J. Wang, *Angew. Chem., Int. Ed.*, 2012, **51**, 5714–5717.
- 12 W. A. L. van Otterlo and C. B. de Koning, *Chem. Rev.*, 2009, **109**, 3743–3782.
- 13 A. Iuliano, P. Piccioli and D. Fabbri, *Org. Lett.*, 2004, **6**, 3711–3714.
- 14 A.-E. Gies and M. Pfeffer, *J. Org. Chem.*, 1999, **64**, 3650–3654.
- 15 H. Albright, A. J. Davis, J. L. Gomez-Lopez, H. L. Vonesh, P. K. Quach, T. H. Lambert and C. S. Schindler, *Chem. Rev.*, 2021, **121**, 9359–9406.
- 16 C. C. McAtee, P. S. Riehl and C. S. Schindler, *J. Am. Chem. Soc.*, 2017, **139**, 2960–2963.
- 17 T. H. Lambert, *Synlett*, 2019, **30**, 1954–1965.
- 18 Y. Zhang, J. Jermaks, S. N. MacMillan and T. H. Lambert, *ACS Catal.*, 2019, **9**, 9259–9264.
- 19 Y. Zhang, J. H. Sim, S. N. MacMillan and T. H. Lambert, *Org. Lett.*, 2020, **22**, 6026–6030.
- 20 J. Jermaks, P. K. Quach, Z. M. Seibel, J. Pomarole and T. H. Lambert, *Chem. Sci.*, 2020, **11**, 7884–7895.
- 21 D. S. Uppalapati, R. S. R. Dachuru and S. V. Sunkara, *J. Heterocycl. Chem.*, 2021, **58**, 1695–1699.
- 22 S. Chen, L. Wang, J. Zhang, Z. Hao, H. Huang and G.-J. Deng, *J. Org. Chem.*, 2017, **82**, 11182–11191.
- 23 R. F. S. Menna-Barreto, A. Henriques-Pons, A. V. Pinto, J. A. Morgado-Diaz, M. J. Soares and S. L. De Castro, *J. Antimicrob. Chemother.*, 2005, **56**, 1034–1041.
- 24 Y. Zhao and D. G. Truhlar, *Theor. Chem. Acc.*, 2008, **120**, 215–241.
- 25 W. J. Hehre, L. Radom, P. v. R. Schleyer and J. Pople, *Ab Initio Molecular Orbital Theory*, Wiley, New York, 1986.

