

Cite this: *Chem. Sci.*, 2022, **13**, 236

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

Received 1st November 2021

Accepted 5th December 2021

DOI: 10.1039/d1sc06035j

rsc.li/chemical-science

Introduction

Substituted cyclobutanes can be found in many natural products,¹ and are useful building blocks in synthetic chemistry but their asymmetric synthesis is often challenging.² The cyclobutane motif has also received increased attention as a rigid scaffold and as an isostere in medicinal chemistry.³ So far 8 compounds that bear a cyclobutane ring have been approved by the FDA but their cyclobutyl moieties are generally simply substituted like in Boceprevir or Apalutamide (Fig. 1a) and none of them bear any stereogenic centres – which may be due to a scarcity of generally useful methods for the synthesis of complex, chiral cyclobutanes.^{4,5}

Most existing catalytic asymmetric approaches for cyclobutane synthesis rely either on ring-closure,^{6–13} or the functionalization of pre-formed four-membered rings using activating or directing groups.^{14–16} Direct addition reactions to unactivated cyclobutenes are rare,^{17–19} but attractive as they offer a modular entry to functionalized cyclobutanes and are generally not limited to specific substitution patterns.

We have reported Rh-catalysed asymmetric addition reactions of arylboronic acids to various cyclobutenes (Fig. 1b).²⁰ These reactions proceed *via* an asymmetric carbometallation step, followed by remote protonation or elimination to give a diverse range of arylated cyclobutanes. For cyclobutenes, the carbometallation step is associated with a very small release of olefinic

strain (1.9 kcal mol^{−1}) compared to the olefinic strain of other small, cyclic molecules like cyclopropene (27.7 kcal mol^{−1}).²¹ We became interested in the question if related but mechanistically distinct cyclobutene functionalization reactions with carbon-nucleophiles would be possible and identified an asymmetric hydrometallation-reductive elimination sequence as a viable strategy (Fig. 1c). A key advantage of this strategy is its high-atom economy and the avoidance of sensitive organometallic coupling partners.

Metal-catalysed hydroacylation,²² and especially Rh-catalysed hydroacylation reactions between alkenes and aldehydes are powerful tools for the synthesis of ketones and operate *via* a hydrometallation mechanism.²³ While intramolecular hydroacylation reactions are well established, the intermolecular Rh-catalysed hydroacylation is often associated with an undesired reductive decarbonylation, and many specific solutions for this problem involving chelating groups have been developed.²³ The use of *ortho*-hydroxybenzaldehydes (salicylaldehydes) represents one of the strategies and several useful asymmetric hydroacylations with terminal alkenes have been reported.^{24–26}

Internal alkenes represent significantly more challenging substrates in Rh-catalysed intermolecular hydroacylations, but a few reactions between norbornadienes or cyclopropenes and salicylaldehydes have been reported by the groups of Bolm and Dong, which are likely driven by the release of olefinic strain.^{27,28} Catalytic asymmetric carbofunctionalization reactions of strained alkenes that proceed *via* hydrometallation have also been reported with Nickel.²⁹ We wondered if a related process would be possible with cyclobutenes – despite the very small release of ring strain in the hydrometallation step.

^aDepartment of Chemistry, University of Oxford, 12 Mansfield Road, Oxford, OX1 3TA, UK. E-mail: stephen.fletcher@chem.ox.ac.uk

^bVertex Pharmaceuticals (Europe) Ltd, 86–88 Jubilee Avenue, Milton Park, Abingdon, OX14 4RW, UK

† Electronic supplementary information (ESI) available. CCDC 2116804. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/d1sc06035j



Results and discussion

We chose salicylaldehyde **1a** and cyclobutene **2** as our model substrates as they provide an entry to the bicyclic core of Belaperidone (see Fig. 1a). Our optimisation studies revealed that a catalytic system generated from $[\text{Rh}(\text{cod})\text{OH}]_2$ and MeDuphos (**L1**) gives **3a** in excellent yield, enantio- and diastereoselectivity (Table 1, entry 1). Prolonged reaction times led to a slight decrease in diastereomeric ratio. Under these conditions, salicylaldehyde **1a** was fully consumed, and decarbonylation of the aldehydes served as the major side-reaction (indicated by the disappearance of CHO signals in the ^1H NMR spectra).³⁰ The reaction does not proceed in absence of either Rh or phosphine ligand (Table 1, entries 2 and 3), while other ligand scaffolds provided only poor levels of enantioinduction in this reaction despite inducing high diastereomeric ratios (Table 1, entries 4–6). Slightly lower diastereoselectivity and yield was obtained with THF instead of toluene (Table 1, entry 7). Using benzaldehyde instead of salicylaldehyde did not provide the desired hydroacylation product (Table 1, entry 8) – highlighting the importance of a chelating group.

Having optimized conditions for **1a** and **2** in hand, we subsequently explored the scope of the transformation on both the salicylaldehyde and the cyclobutene component. Several substitution patterns, electron-withdrawing and electron-

donating functional groups, and halides are well tolerated with consistently excellent levels of enantioinduction (Scheme 1, **3a**–**3i**). In all cases, we isolated the pure *cis*–*trans* isomer.[‡] Remarkably, our catalytic system shows high chemoselectivity for the hydroacylation of the cyclobutene over a terminal alkene (**3b**).²⁴ For more electron-deficient salicyldehydes **1c**, **1d**, **1g** and **1h**, we observed unreacted aldehyde accompanied with decarbonylation under our standard reaction conditions. In these cases, better results and full conversion of the aldehyde was achieved with an increased catalyst loading of 5% of dimeric $[\text{Rh}(\text{cod})\text{OH}]_2$.

A range of different mono- and bicyclic *meso*-cyclobutenes are suitable substrates and give acylated cyclobutanes in good yields and in most cases with high enantiomeric excesses (Scheme 1, **4a**–**4f**). For all compounds, the major *trans*–*cis* diastereomer was isolated in pure form. The absolute configuration of **4b** was determined *via* X-ray crystallographic analysis. In our previous carbometallation study, (*cis*-cyclobut-3-ene-1,2-diyli)bis (methylene) diacetate (**2e**) underwent homo-allylic substitution reactions instead of hydroarylations with arylboronic acids.²⁰ Using the same substrate under our hydroacylation conditions we obtain the hydroacylation product **4e** – highlighting the difference between the carbometallation and hydrometallation pathways (*cf.* Fig. 1b and c).

Under related conditions using achiral ligand 1,1'-bis(diphenylphosphino)ferrocene (dpff), the achiral, spirocyclic

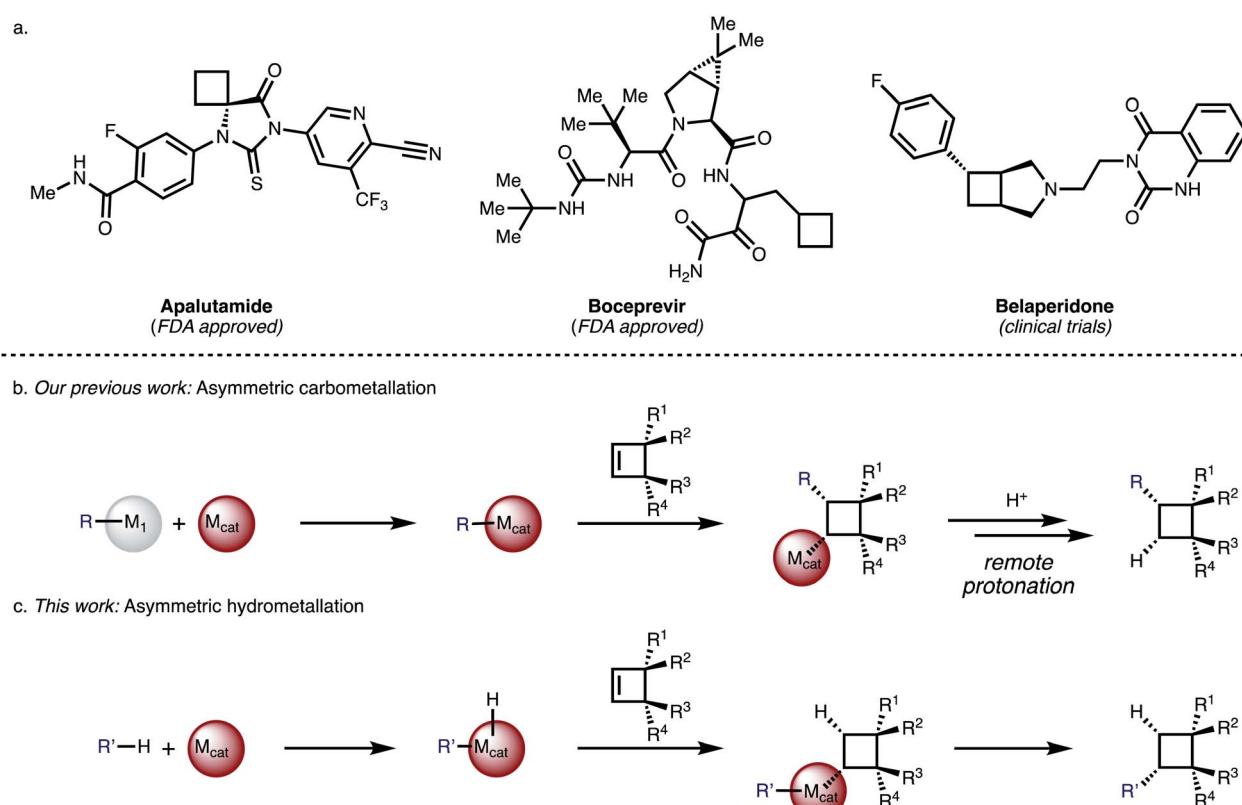


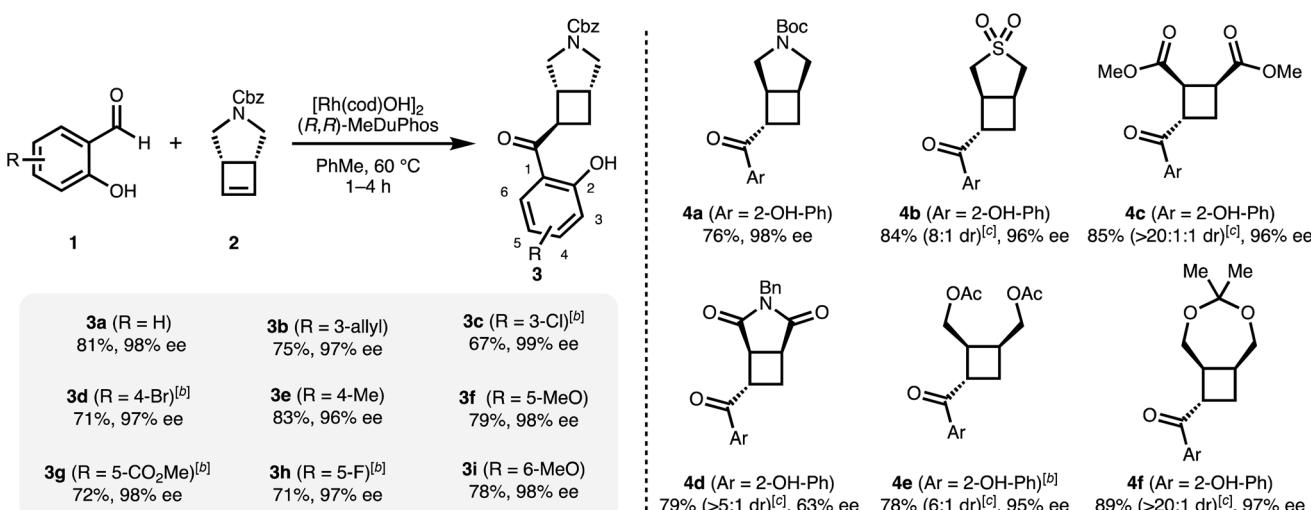
Fig. 1 (a) Examples of bioactive cyclobutanes. (b) Asymmetric carbometallation of cyclobutenes. (c) Asymmetric hydrometallation of cyclobutenes.

Table 1 Deviation from standard conditions^a

Entry	Variation from standard conditions	Time (h)	Yield ^b (%)	ee ^c (%)	dr ^d
1	None ^e	1	81	98	9 : 1
2	No Rh	20	0	—	—
3	No ligand	20	≤1	—	—
4	L2 instead of L1	20	86	32	>20 : 1
5	L3 instead of L1	2	86	−74	>20 : 1
6	L4 instead of L1	20	31	−12	>20 : 1
7	THF instead of PhMe	1	72	98	7 : 1
8	PhCHO instead of 1a	20	0%	—	—

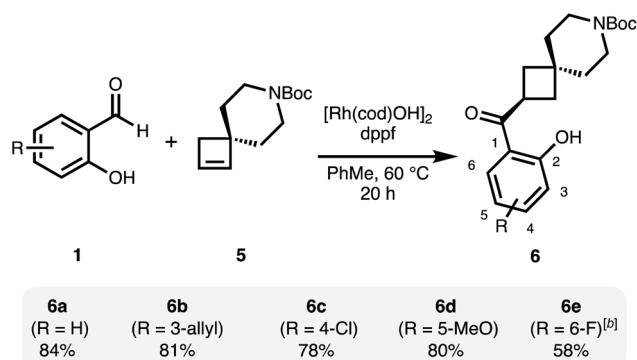
L1 L2 L3 (R = *c*-hex)
L4 (R = *t*-Bu)

^a [Rh(cod)OH]₂ (2.5 mol%), ligand (6 mol%), cyclobutene 2 (0.3 mmol), salicylaldehyde 1a (0.2 mmol), PhMe (0.2 M), 1–20 h. ^b Isolated yield of the major diastereoisomer. ^c The ee values were determined by SFC analysis on a chiral non-racemic stationary phase. ^d The dr values were estimated by non-calibrated SFC analysis of the unpurified reaction mixture. ^e Performed on 0.4 mmol scale.



Scheme 1 Asymmetric hydroacylation of cyclobutenes with different salicylaldehydes.^a ^a[Rh(cod)OH]₂ (2.5 mol%), MeDuphos (6 mol%), cyclobutene 2 (0.6 mmol), salicylaldehyde 1 (0.4 mmol), PhMe (0.2 M), 1–4 h. ^bIncreased catalyst loading of [Rh(cod)OH]₂ (5 mol%) and MeDuphos (12 mol%). ^cDiastereomeric ratios of the unpurified reaction mixtures determined by ¹H NMR spectroscopy. All yields refer to isolated yields of the major *trans*–*cis* diastereomer. Enantiomeric excesses determined by SFC analysis on a chiral non-racemic stationary phase.





Scheme 2 Regioselective hydroacylation of a spirocyclic, prochiral cyclobutene.^a ^a[Rh(cod)OH]₂ (2.5 mol%), dppf (6 mol%), cyclobutene 5 (0.6 mmol), salicylaldehyde 1 (0.4 mmol), PhMe (0.2 M), 20 h. ^bIncreased catalyst loading of [Rh(cod)OH]₂ (5 mol%) and dppf (12 mol%).

cyclobutane **6** is obtained from **5** as a single regioisomer (Scheme 2).³¹ Good yields were obtained with a small set of functionalized salicyldehydes.

Also here, more electron-deficient salicyldehydes were prone to an undesired decarbonylation pathway and therefore gave diminished yields (**6e**). The regioselectivity in this reaction is likely under steric control and is set in the initial hydro-metallation step.

The reaction of **1** with **2a** proceeds nicely at a 4 mmol scale gram-scale providing 1.2 g (84%, 98% ee) of **3a** (Scheme 3a) while lowering the excess of cyclobutene from 1.5 to 1.2 equivalents. The 2-hydroxybenzoyl moiety could serve as a handle for subsequent functionalization reactions (**7a**, **7b**) and the

phenolic OH group can be removed in a two-step protocol (**7c**) (Scheme 3b). Furthermore, reduction of the benzoyl group provides an entry to benzylated cyclobutanes (**7d**) (Scheme 3b).

Conclusions

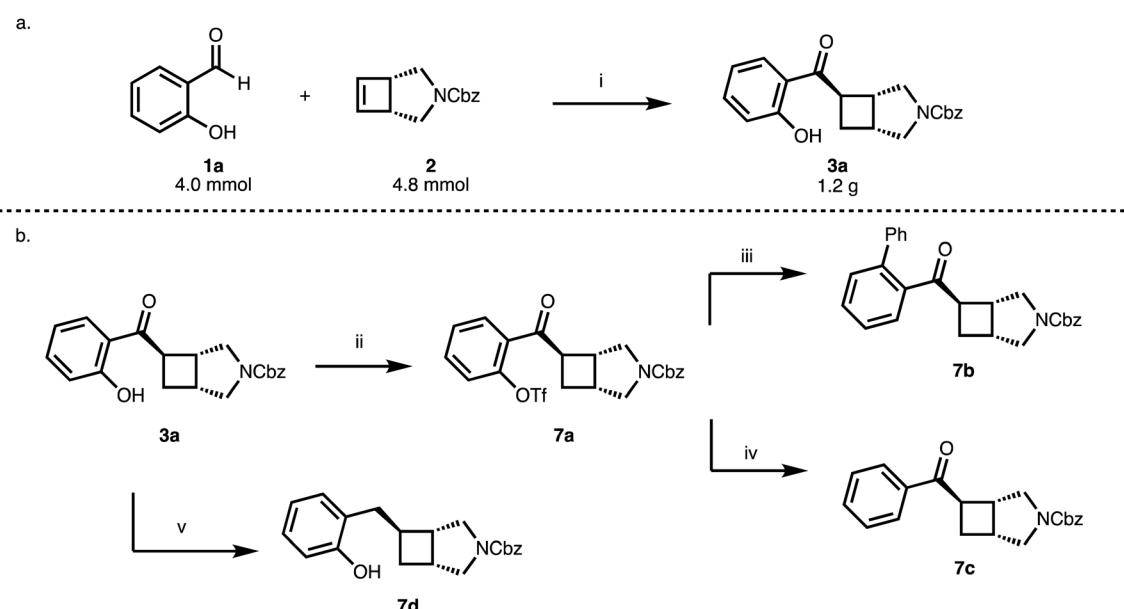
In summary, we have shown that the addition of Rh-H to weakly activated cyclobutenes is possible – exemplified with an asymmetric hydroacylation reaction of *meso*-cyclobutenes with salicylaldehydes. Furthermore, the hydroacylation of a spirocyclic cyclobutene proceeds with excellent regioselectivity. These reactions provide a modular entry to stereochemically complex, acylated cyclobutanes. Likely, other asymmetric Rh-catalysed addition reactions, that proceed *via* hydrometallation pathways, are feasible with cyclobutenes and those will be investigated in the future.

Data availability

Crystallographic data for **4b** has been deposited at the CCDC under 2116804 and can be obtained from <http://www.ccdc.cam.ac.uk>. All other data supporting this article have been uploaded as part of the supplementary material.

Author contributions

F. W. G. performed all experiments and conceived the study. S. P. F. and M. S. guided the research. F. W. G. and S. P. F. wrote the manuscript with contributions from M. S.



Scheme 3 (a) Up-scale to gram-scale. (b) Functionalization of the phenol and benzoyl moiety.^a ^a(i) [Rh(cod)OH]₂ (2.5 mol%), MeDuphos (6 mol%), 2 (4.8 mmol), **1a** (4.0 mmol), PhMe, 1 h, 60 °C, 84%, 98% ee; (ii) 2-PyrNTf₂, DMAP (10 mol%), NEt₃, CH₂Cl₂, 23 °C, 92%; (iii) PhB(OH)₂, K₂CO₃, [Pd(PPh₃)₄] (5 mol%), PhMe, 16 h, 110 °C, 67%; (iv) (CH₃)₂NH·BH₃, K₂CO₃, [Pd(PPh₃)₄] (5 mol%), CH₃CN, 6 h, 40 °C, 67%; (v) Et₃SiH, TFA, 5 h, 0–23 °C, 65%.



Conflicts of interest

There are no conflicts to declare.

Acknowledgements

The authors thank Dr Curtis Moore (Ohio State University) for X-ray crystallographic analysis of compound **4b**. Financial support from the UK Engineering and Physical Sciences Research Council (EP/N022246/1) is gratefully acknowledged. F. W. G. is grateful to the National Research Fund, Luxembourg, for an AFR PhD Grant (11588566); the EPSRC Doctoral Training Partnership (DTP) for a studentship (EP/N509711/1); and Vertex Pharmaceuticals for financial support.

Notes and references

‡ A precise determination of the diastereomeric ratios of the unpurified reaction mixture by ^1H NMR was not possible due to the broad (rotameric) peak shapes. However, these crude NMR spectra suggest similar diastereomeric ratios for compounds **3a–3i** and **4a** (approximately 7 : 1 to 10 : 1).

- 1 V. M. Dembitsky, *J. Nat. Med.*, 2008, **62**, 1–33.
- 2 E. Lee-Ruff and G. Mladenova, *Chem. Rev.*, 2003, **103**, 1449–1483.
- 3 M. R. Bauer, P. di Fruscia, S. C. C. Lucas, I. N. Michaelides, J. E. Nelson, R. I. Storer and B. C. Whitehurst, *RSC Med. Chem.*, 2021, **12**, 448–471.
- 4 <https://go.drugbank.com/>, accessed Aug 23, 2021.
- 5 S. O. Scholz, J. B. Kidd, L. Capaldo, N. E. Flikweert, R. M. Littlefield and T. P. Yoon, *Org. Lett.*, 2021, **23**, 3496–3501.
- 6 Y. Xu, M. L. Conner and M. K. Brown, *Angew. Chem., Int. Ed.*, 2015, **54**, 11918–11928.
- 7 R. Brimioule and T. Bach, *Science*, 2013, **342**, 840–843.
- 8 J. Du, K. L. Skubi, D. M. Schultz and T. P. Yoon, *Science*, 2014, **344**, 392–396.
- 9 Y. M. Wang, N. C. Bruno, Á. L. Placeres, S. Zhu and S. L. Buchwald, *J. Am. Chem. Soc.*, 2015, **137**, 10524–10527.
- 10 D. K. Kim, J. Riedel, R. S. Kim and V. M. Dong, *J. Am. Chem. Soc.*, 2017, **139**, 10208–10211.
- 11 V. V. Pagar and T. v. RajanBabu, *Science*, 2018, **361**, 68–72.
- 12 S. C. Patel, M. W. Smith, J. A. M. Mercer, K. Suzuki and N. Z. Burns, *Org. Lett.*, 2021, **23**, 6530–6535.
- 13 M. M. Parsutkar, V. V. Pagar and T. V. RajanBabu, *J. Am. Chem. Soc.*, 2019, **141**, 15367–15377.
- 14 M. Luparia, M. T. Oliveira, D. Audisio, F. Frebault, R. Goddard and N. Maulide, *Angew. Chem., Int. Ed.*, 2011, **50**, 12631–12635.
- 15 K. J. Xiao, D. W. Lin, M. Miura, R. Y. Zhu, W. Gong, M. Wasa and J. Q. Yu, *J. Am. Chem. Soc.*, 2014, **136**, 8138–8142.
- 16 C. Zhong, Y. Huang, H. Zhang, Q. Zhou, Y. Liu and P. Lu, *Angew. Chem., Int. Ed.*, 2020, **59**, 2750–2754.
- 17 M. Guisán-Ceinos, A. Parra, V. Martín-Heras and M. Tortosa, *Angew. Chem., Int. Ed.*, 2016, **55**, 6969–6972.
- 18 L. Nóvoa, L. Trulli, A. Parra and M. Tortosa, *Angew. Chem., Int. Ed.*, 2021, **60**, 11763–11768.
- 19 S. Feng, H. Hao, P. Liu and S. L. Buchwald, *ACS Catal.*, 2020, **10**, 282–291.
- 20 F. W. Goetzke, A. M. L. Hell, L. van Dijk and S. P. Fletcher, *Nat. Chem.*, 2021, **13**, 880–886.
- 21 K. B. Wiberg, *Angew. Chem., Int. Ed.*, 1986, **25**, 312–322.
- 22 M. C. Willis, *Chem. Rev.*, 2010, **110**, 725–748.
- 23 R. T. Davison, E. L. Kuker and V. M. Dong, *Acc. Chem. Res.*, 2021, **54**, 1236–1250.
- 24 M. von Delius, C. M. Le and V. M. Dong, *J. Am. Chem. Soc.*, 2012, **134**, 15022–15032.
- 25 M. M. Coulter, K. G. M. Kou, B. Galligan and V. M. Dong, *J. Am. Chem. Soc.*, 2010, **132**, 16330–16333.
- 26 Y. Inui, M. Tanaka, M. Imai, K. Tanaka and H. Suemune, *Chem. Pharm. Bull.*, 2009, **57**, 1158–1160.
- 27 R. T. Stemmler and C. Bolm, *Adv. Synth. Catal.*, 2007, **349**, 1185–1198.
- 28 D. H. T. Phan, K. G. M. Kou and V. M. Dong, *J. Am. Chem. Soc.*, 2010, **132**, 16354–16355.
- 29 R. Kumareswaran, M. Nandi and T. V. RajanBabu, *Org. Lett.*, 2003, **23**, 4345–4348.
- 30 C. M. Beck, S. E. Rathmill, Y. L. Park, J. Chen, R. H. Crabtree, L. M. Liable-Sands and A. L. Rheingold, *Organometallics*, 1999, **18**, 5311–5317.
- 31 L. Nóvoa, L. Trulli, I. Fernández, A. Parra and M. Tortosa, *Org. Lett.*, 2021, **23**, 7434–7438.

