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Asymmetric transfer hydrogenation of boronic acid pinacol ester (Bpin)-containing acetophenones†

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A series of Bpin-containing acetophenone derivatives were reduced by asymmetric transfer hydrogenation (ATH), using Noyori–Ikariya catalysts, with formic acid/triethylamine, to alcohols in high ee when the Bpin is in the *para*- or *meta*-position. Substrates containing *ortho*-Bpin groups were reduced in lower ee, with formation of a cyclic boron-containing group. The products were converted to substituted derivatives using Pd-catalysed coupling reactions. The results represent the first examples of ATH of Bpin-containing ketones.

Introduction

The asymmetric transfer hydrogenation (ATH) of ketones, to give enantiomerically-enriched alcohols, using Noyori–Ikariya catalysts [(arene)Ru(TsDPEN)Cl] such as **1** and derivatives such as **2–5** (Fig. 1),[1] has been successfully applied extensively to a wide range of ketone substrates. Excellent results have been obtained for the ATH of acetophenone derivatives,[2] acetylenic ketones,[3] fluorinated derivatives,[4] as well as dynamic kinetic resolutions of a number of substrate classes.[5] Functional groups which are known to be compatible with Noyori–Ikariya catalysts include oxygenated, nitrogen-containing, carboxy groups, and halides.[1–5]

The ATH of acetophenone derivatives containing halides, particularly bromide and iodide, offers the possibility to functionalise the alcohol product through a number of processes, for example Pd-catalysed coupling reactions (Fig. 2a).[6] In these cases, the coupling partners typically contain a boronic acid, or Bpin group.[7] However, the requisite boron-containing aryl or vinyl reagent might not be readily available for the couplings and in these cases it would be advantageous for the ATH product to contain a boronic acid or Bpin since this would allow couplings to be carried out using the corresponding aryl or vinylic halides (Fig. 2b). To our surprise, a search of the literature indicated that the Ru-catalysed ATH of Bpin ketones has not previously been reported. The enzyme-catalysed resolution of Bpin-containing 1-arylethanols,[8a] and their kinetic resolution through oxidation,[8b] have been reported, as has their synthesis through the use of alcohol dehydrogenases (ADHs) for the asymmetric reduction of Bpin-containing ketones.[8c,d] Given the lack of data on ATH of boron-containing substrates, we investigated the ATH of a range of Bpin-containing acetophenone derivatives.

Results and discussion

In our initial tests, we investigated the ATH of the known 4-Bpin substituted acetophenone **6**, which was prepared *via* palladium-catalysed coupling reaction of 4-bromophenone with B_2pin_2.[9] Despite the lack of literature precedents, the reduction proceeded cleanly, using formic acid/triethylamine 5 : 2 azeotrope (FA/TEA) as the reductant, 1 mol% of catalyst and DCM as a co-solvent, to give the corresponding alcohol **7** in full conversion and in 98% ee, using a range of ATH cata-

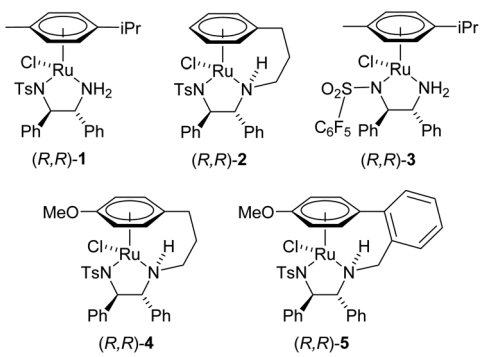

Fig. 1 Catalysts commonly used in asymmetric transfer hydrogenation (ATH) of ketones, and in this study.

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†Electronic supplementary information (ESI) available: General experimental details, experimental data for the preparation and ATH of all substrates, NMR and chiral HPLC spectra. See DOI: https://doi.org/10.1039/d2ob00569g

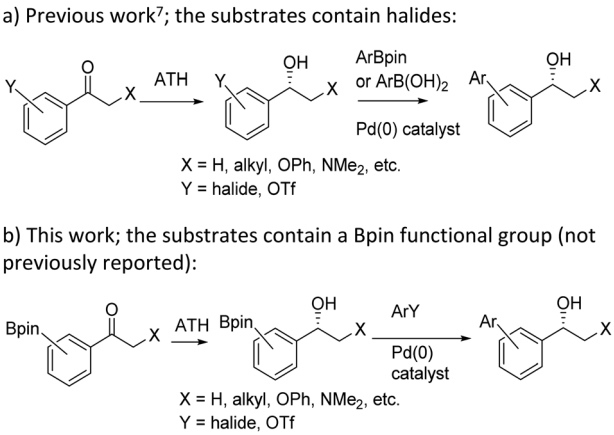
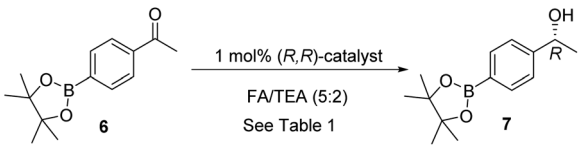


Fig. 2 (a) Asymmetric transfer hydrogenation (ATH) of substituted acetophenone substrates and subsequent coupling reactions. (b) ATH of Bpin-containing substrates followed by Pd-catalysed couplings.

Table 1 ATH of *p*-Bpin-acetophenone[a]



Entry	Catalyst	Co-solvent	Time/h	Yield/%	ee/%
1	(*R*,*R*)-**1**	DCM	72	56	98
2	(*R*,*R*)-**2**	DCM	24	90	98
3	(*R*,*R*)-**3**	DCM	72	52	98
4	(*R*,*R*)-**4**	DCM	24	53	98
5	(*R*,*R*)-**5**	DCM	24	53	97
6	(*R*,*R*)-**2**	None	24	72	98
7	(*R*,*R*)-**2**	MeOH	24	50	98
8	(*R*,*R*)-**2**	MeCN	24	58	98

[a] Full conversion was observed in each case.

lysts (Table 1). The 3C-tethered catalyst **2** gave the product in full conversion in 24 h, therefore this was selected for solvent screening. Alternative solvents, however, and a reaction without solvent, gave no improvement (Table 1).

Alcohol product **7** has been reported in asymmetric form,[8] and the *R*-configuration was confirmed by comparison of the optical rotation and the HPLC retention time data to the published values. Product **7** was converted to the known 4-Ph derivative **8** using a palladium-catalysed coupling with bromobenzene (Fig. 3), underlining the utility of the Bpin-containing products.[8a]

This was extended to a range of further Bpin-containing substrates, (Fig. 4). *para*- and *meta*-Bpin substituted acetophenones were reduced in full conversion and high ee to products **9–15** (Fig. 4a). The *meta*-substituted Bpin product **9** has been reported in asymmetric form, and a comparison of optical rotation and HPLC data served to confirm its *R*-configuration.[8a] Substituents at the α-position of the ketone, including Me, Ph, phenoxy and morpholine, were all tolerated.

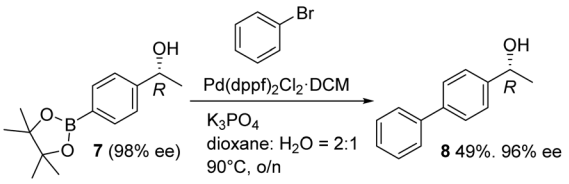


Fig. 3 Conversion of Bpin-containing ATH product to the 4-phenyl derivative.

In contrast, an *ortho*-Bpin-substituted substrate **16** gave a cyclic benzoboroxole **17**, which has previously been reported in racemic form,[10] in much lower ee (Fig. 4b). The ee and configuration of the *ortho* Bpin product was established as *S* by comparison with the known product **18** of its Pd-catalysed coupling with 2-bromopyridine (Fig. 4b).[11] It is not clear why the configuration of **17** is reversed relative to the *para*- and *meta*-substituted derivatives. The low ee reflects a marginal energy difference between reduction modes in this case.

In the case of **12** (97% ee), a palladium-catalysed reaction was used to substitute Bpin with Me, giving the previously-reported alcohol (*S*)-**19** in 96% ee. The direct reduction of 20 with the same ATH catalyst enantiomer also resulted in the formation of (*S*)-**19**, in 96% ee (Fig. 4c).[12] In this case, the configuration of the product generated through either pathway, with catalyst (*R*,*R*)-**2**, was identical, indicating that similar directing effects were operating in both cases. In addition, the *R*-configuration and ee of the propiophenone reduction product **14** (which could not be directly established by chiral HPLC) was confirmed by conversion to the known derivative 1-([1,1′-biphenyl]-4-yl)propan-1-ol **21** (Fig. 4d) through the [Pd(dppf)$_2$Cl$_2$·DCM]-catalysed reaction with PhBr (63% yield, 94% ee).[13]

A further series of substrates, containing aromatic rings opposing a *para*-Bpin-containing aryl group, were reduced, to products **22–24** (Fig. 5). Although ATH was successful, the product ee's were much lower than the earlier series. An almost racemic product **22** was formed from the ketone containing an unsubstituted phenyl ring,[14] although this could be improved to 55% (product **23**) through the introduction of an *ortho*-methoxy group, possibly the result of increase steric hindrance forcing the OMe ring into a less hindered position, as has been reported for similar catalysts.[15] A *para*-methoxy substituted ring gave a product **24** of intermediate ee (20%).

A series of *ortho*-Bpin-containing substrates were also tested, again containing a range of aromatic groups. The ee's of the products **25–28** were again low in all cases, indicating that the catalyst cannot readily distinguish between the aromatic rings flanking the ketone in each case.[10] Due to the low ee values of the products, the absolute configurations of the products in Fig. 5 could not be confirmed.

To underline the value of the products, further transformations using Pd-catalysed couplings were investigated. Products **29–32**, of couplings of Bpin derivatives with 2-Br styrene and 2-bromofuran were prepared (Fig. 6) without sig-

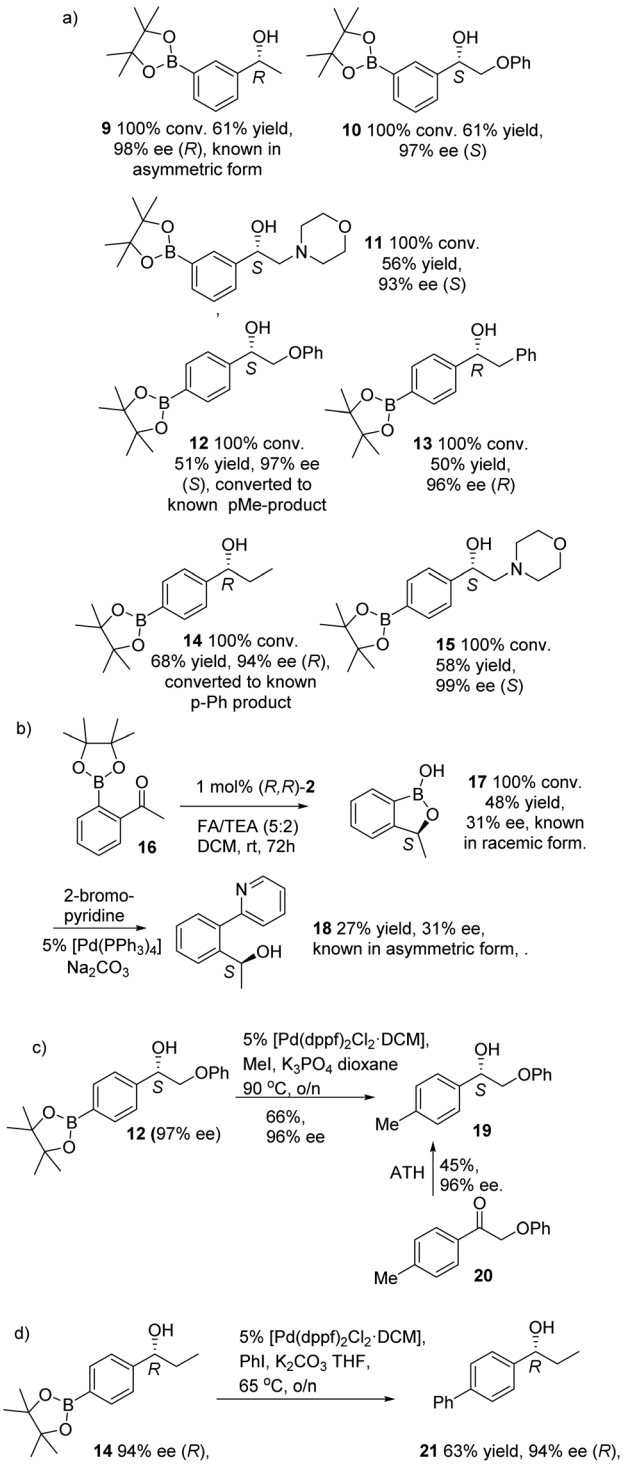


Fig. 4 ATH products of Bpin-containing acetophenones; (a) *para*- and *meta*-substituted products. Conditions; 1 mol% catalyst (*R*,*R*)-**2**, FA/TEA, DCM, rt, 72 h (except for **9** and **14** which require 24 h). (b) ATH of *ortho*-Bpin acetophenone. (c) Introduction of a *para*-Me group to **12** gives the same product enantiomer as formed by direct ATH of **20** under identical conditions. (d) Pd-Catalysed conversion of (*R*)-**14** to known (*R*)-**21** to establish its configuration and ee. Products are novel unless otherwise indicated.

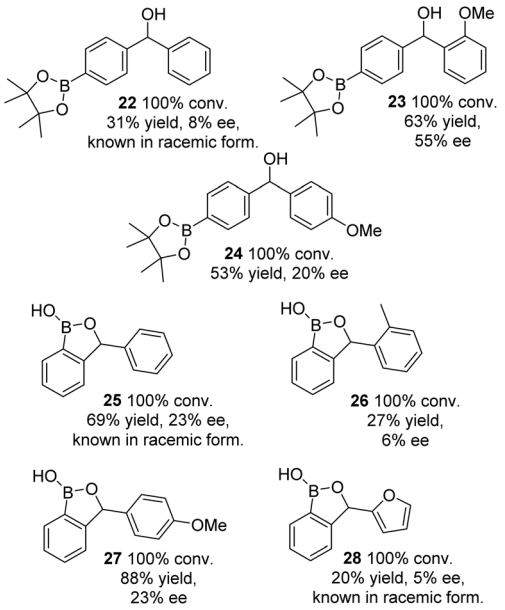


Fig. 5 ATH products of Bpin-containing ketones containing aromatic rings. Conditions; 1 mol% catalyst (*R*,*R*)-**2**, FA/TEA, DCM, 72 h, rt. The product configurations were not confirmed. Products are novel unless otherwise indicated.

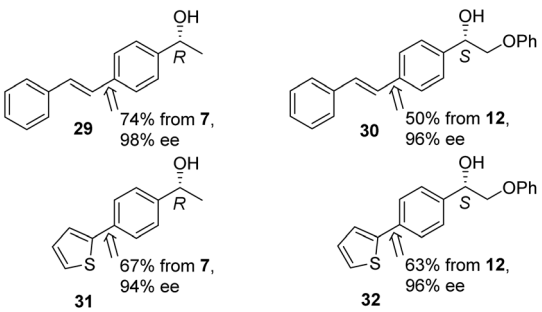


Fig. 6 Coupling products of 4-Bpin reduction products; arrow indicates position of new bond. Conditions: ArBr or ArCH = CHBr, [Pd(dppf)$_2$Cl$_2$·DCM], dioxane, water, K_3PO_4, 90 °C, o/n. Starting material **7** was of 98% ee and **12** was of 97% ee.

nificant loss of ee in the products. Compound **29** has been prepared through the ATH of a halogenated ketone linked to a Pd-catalysed coupling with styryl boronic acid, *i.e.* complementary to our strategy.[6b]

Conclusion

In conclusion, we report the first application of asymmetric transfer hydrogenation, using highly practical Noyori–Ikariya catalysts, to the enantioselective reduction of ketones containing Bpin functional groups. *para*- and *meta*-Bpin-substituted acetophenones give products of very high ee whilst *ortho*-Bpin-containing substrates are reduced in low ee, with the formation of a cyclic product. The products can be converted to a

number of products using Pd-catalysed cross coupling reactions with aryl and vinyl halides, providing a valuable complementary strategy to the use of Pd-catalysed couplings of halide-containing ATH products.

Data sharing statement

The research data (and/or materials) supporting this publication can be accessed at **https://wrap.warwick.ac.uk/**.

Author contributions

YZ planned the investigations, completed the synthetic chemistry, analysed the data and contributed to writing the paper. MW provided supervision, planned the investigations, analysed the data and contributed to writing the paper.

Conflicts of interest

There are no conflicts to declare.

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Notes and references

1 (*a*) D. Wang and D. Astruc, *Chem. Rev.*, 2015, **115**, 6621–6686; (*b*) A. E. Cotman, *Chem. – Eur. J.*, 2021, **27**, 39–53; (*c*) A. A. Mishra and B. M. Bhanage, *Chirality*, 2021, **33**, 337–378; (*d*) R. Noyori and S. Hashiguchi, *Acc. Chem. Res.*, 1997, **30**, 97–102; (*e*) H. G. Nedden, A. Zanotti-Gerosa and M. Wills, *Chem. Rec.*, 2016, **16**, 2623–2643.

2 (*a*) A. Fujii, S. Hashiguchi, N. Uematsu, T. Ikariya and R. Noyori, *J. Am. Chem. Soc.*, 1996, **118**, 2521–2522; (*b*) S. Hashiguchi, A. Fujii, J. Takehara, T. Ikariya and R. Noyori, *J. Am. Chem. Soc.*, 1995, **117**, 7562–7563; (*c*) A. Kišić, M. Stephan and B. Mohar, *Org. Lett.*, 2013, **15**, 1614–1617; (*d*) A. A. Mishra and B. M. Bhanage, *ChemistrySelect*, 2019, **4**, 14032–14035; (*e*) J. Li, Z. Lin, Q. Huang, Q. Wang, L. Tang, J. Zhu and J. Deng, *Green Chem.*, 2017, **19**, 5367–5370; (*f*) A. M. R. Hall, D. B. G. Berry, J. N. Crossley, A. Codina, I. Clegg, J. P. Lowe, A. Buchard and U. Hintermair, *ACS Catal.*, 2021, **11**, 13649–13659; (*g*) D. Zhang, T. Cheng, Q. Zhao, J. Xu and G. Liu, *Org. Lett.*, 2014, **16**, 5764–5767; (*h*) A. Kišić, M. Stephan and B. Mohar, *Adv. Synth. Catal.*, 2015, **357**, 2540–2546; (*i*) S. Lan, H. Zhang, Z. Chen, S. Yang and X. Fang, *Adv. Synth. Catal.*, 2021, **363**, 2071–2077.

3 (*a*) K. Matsumura, S. Hashiguchi, T. Ikariya and R. Noyori, *J. Am. Chem. Soc.*, 1997, **119**, 8738–8739; (*b*) V. K. Vyas, R. C. Knighton, B. M. Bhanage and M. Wills, *Org. Lett.*, 2018, **20**, 975–978; (*c*) D. Brandt, A. Dittoo, V. Bellosta and J. Cossy, *Org. Lett.*, 2015, **17**, 816–819; (*d*) Z. Fang and M. Wills, *Org. Lett.*, 2014, **16**, 374–377; (*e*) K. Siva Nagi Reddy and G. Sabitha, *Tetrahedron Lett.*, 2017, **58**, 1198–1201; (*f*) K. Takahashi, Y. Arai and T. Honda, *Tetrahedron Lett.*, 2017, **58**, 4048–4050; (*g*) N. Arai, H. Satoh, N. Utsumi, K. Murata, K. Tsutsumi and T. Ohkuma, *Org. Lett.*, 2013, **15**, 3030–3033; (*h*) G. Kumaraswamy, V. Narayanarao, P. Shanigaram and G. Balakishan, *Tetrahedron*, 2015, **71**, 8960–8964.

4 (*a*) D. Šterk, M. Stephan and B. Mohar, *Org. Lett.*, 2006, **8**, 5935–5938; (*b*) B. Mohar, M. Stephan and U. Urleb, *Tetrahedron*, 2010, **66**, 4144–4149; (*c*) A. E. Cotman, D. Cahard and B. Mohar, *Angew. Chem., Int. Ed.*, 2016, **55**, 5294–5298; (*d*) L.-S. Zheng, P. Phansavath and V. Ratovelomanana-Vidal, *Org. Lett.*, 2018, **20**, 5107–5111; (*e*) M. Wu, T. Cheng, M. Ji and G. Liu, *J. Org. Chem.*, 2015, **80**, 3708–3713; (*f*) T. Wang, E. M. Phillips, S. M. Dalby, E. Sirota, S. Axnanda, C. S. Shultz, P. Patel, J. H. Waldman, E. Alwedi, X. Wang, K. Zawatzky, M. Chow, N. Padivitage, M. Weisel, M. Whittington, J. Duan and T. Lu, *Org. Process Res. Dev.*, 2022, **26**, 543–550; (*g*) R. M. Betancourt, P. Phansavath and V. Ratovelomanana-Vidal, *J. Org. Chem.*, 2021, **86**, 12054–12063; (*h*) T. Touge, H. Nara, M. Kida, K. Matsumura and Y. Kayaki, *Org. Lett.*, 2021, **23**, 3070–3075.

5 (*a*) P.-G. Echeverria, T. Ayad, P. Phansavath and V. Ratovelomanana-Vidal, *Synthesis*, 2016, 2523–2539; (*b*) C. G. Goodman, D. T. Do and J. S. Johnson, *Org. Lett.*, 2013, **15**, 2446–2449; (*c*) B. Mohar, A. Valleix, J.-R. Desmurs, M. Felemez, A. Wagner and C. Mioskowski, *Chem. Commun.*, 2001, 2572–2573; (*d*) V. K. Vyas and B. M. Bhanage, *Org. Lett.*, 2016, **18**, 6436–6439; (*e*) Z.-Q. Hu, X. Li, L.-X. Liu, C.-B. Yu and Y.-G. Zhou, *J. Org. Chem.*, 2021, **86**, 17453–17461; (*f*) G. S. Caleffi, J. d. O. C. Brum, A. T. Costa, J. L. O. Domingos and P. R. R. Costa, *J. Org. Chem.*, 2021, **86**, 4849–4858; (*g*) G. V. More, P. V. Malekar, R. G. Kalshetti, M. H. Shinde and C. V. Ramana, *Tetrahedron Lett.*, 2021, **66**, 152831; (*h*) P. Ciesielski and P. Metz, *Nat. Commun.*, 2020, **11**, 3091; (*i*) Y.-M. Zhang, Q.-Y. Zhang, D.-C. Wang, M.-S. Xie, G.-R. Qu and H.-M. Guo, *Org. Lett.*, 2019, **21**, 2998–3002.

6 (*a*) L. C. Rocha, I. G. Rosset, R. F. Luiz, C. Raminelli and A. L. M. Porto, *Tetrahedron: Asymmetry*, 2010, **21**, 926–929; (*b*) X. Shu, R. Jin, Z. Zhao, T. Cheng and G. Liu, *Chem. Commun.*, 2018, **54**, 13244–13247; (*c*) M. Planellas, R. Pleixats and A. Shafir, *Adv. Synth. Catal.*, 2012, **354**, 651–662; (*d*) S. Ganesamoorthy, K. Shanmugasundaram and R. Karvembu, *J. Mol. Catal. A: Chem.*, 2013, **371**, 118–124; (*e*) M. Cubinak, V. Eigner and T. Tobrman, *Adv. Synth. Catal.*, 2018, **360**, 4604–4614; (*f*) S.-C. A. Lin, Y.-H. Liu, S.-M. Peng and S.-T. Liu, *Organometallics*, 2020, **39**, 123–131.

7 G. Dilauro, F. Messa, F. Bona, S. Perrone and A. Salomone, *Chem. Commun.*, 2021, **57**, 10564–10567.
8 (*a*) L. H. Andrade and T. Barcellos, *Org. Lett.*, 2009, **11**(14), 3052–3055; (*b*) D. J. Palmeira, L. S. Araujo, J. C. Abreu and L. H. Andrade, *J. Mol. Catal. B: Enzym.*, 2014, **110**, 117–125; (*c*) T. Barcellos, K. Tauber, W. Kroutil and L. H. Andrade, *Tetrahedron: Asymmetry*, 2011, **22**, 1772–1777; (*d*) K. S. Madden, P. M. T. Todd, K. Urata, A. J. Russell, K. A. Vincent and H. A. Reeve, *ChemRxiv*, 2020, 1–64, DOI: **10.26434/chemrxiv.12532301.v1**.
9 J. Ratniyom, N. Dechnarong, S. Yotphan and S. Kiatisevi, *Eur. J. Org. Chem.*, 2014, 1381–1385.
10 (*a*) D. S. Gunasekera, D. J. Gerold, N. S. Aalderks, J. S. Chandra, C. A. Maanu, P. Kiprof, V. V. Zhdankin and M. V. Ram Reddy, *Tetrahedron*, 2007, **63**, 9401–9405; (*b*) J. Zhu, Y. Wei, D. Lin, C. Ou, L. Xie, Yu Zhao and W. Huang, *Org. Biomol. Chem.*, 2015, **13**, 11362–11368; (*c*) Y.-H. Yan, Z.-F. Li, X.-L. Ning, J. Deng, J.-L. Yu, Y. Luo, Z. Wang, G. Li, G.-B. Li and Y.-C. Xiao, *Bioorg. Med. Chem. Lett.*, 2021, **41**, 127956.
11 E. Liardo, N. Rios-Lombardia, F. Moris, J. Gonzalez-Sabin and F. Rebolledo, *Eur. J. Org. Chem.*, 2018, 3031–3035.
12 K. Huang, M. Ortiz-Marciales, W. Correa, E. Pomales and X. Y. López, *J. Org. Chem.*, 2009, **74**, 4195–4202.
13 Q. Wang, S. Li, C.-J. Hou, T.-T. Chu and X.-P. Hu, *Appl. Organomet. Chem.*, 2019, **33**, e5108.
14 Y. Ashikari, T. Kawaguchi, K. Mandai, Y. Aizawa and A. Nagaki, *J. Am. Chem. Soc.*, 2020, **142**, 17039–17047.
15 (*a*) Y. Zheng, J. Martinez-Acosta, M. Khimji, L. C. Barbosa, G. J. Clarkson and M. Wills, *ChemCatChem*, 2021, **13**, 4384–4391; (*b*) T. Touge, H. Nara, M. Fujiwhara, Y. Kayaki and T. Ikariya, *J. Am. Chem. Soc.*, 2016, **138**, 10084–10087; (*c*) B. Wang, H. Zhou, G. Lu, Q. Liu and X. Jiang, *Org. Lett.*, 2017, **19**, 2094–2097; (*d*) Q. Liu, C. Wang, H. Zhou, B. Wang, J. Lv, L. Cao and Y. Fu, *Org. Lett.*, 2018, **20**, 971–974; (*e*) Y. Zheng, G. J. Clarkson and M. Wills, *Org. Lett.*, 2020, **22**, 3717–3721.