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## Borane promoted aryl transfer reaction for the synthesis of $\alpha$ -aryl functionalised $\beta$ -hydroxy and $\beta$ -keto esters†

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The synthesis of a series of  $\alpha$ -aryl or  $\alpha$ -alkyl functionalised  $\beta$ -hydroxy and  $\beta$ -keto esters has been achieved by reacting  $\alpha$ -diazooesters with boranes, and aldehydes, ketones, anhydrides, nitriles, esters or isocyanates. In a mild reaction protocol, 26 examples are presented in yields up to 73%.

Diazo compounds are useful building blocks in organic synthesis.<sup>1</sup> They are typically activated by transition metals,<sup>2</sup> however, in recent times, the use of catalytic amounts of a borane as an alternative to transition metal mediated carbene generation has become more popular.<sup>3</sup> The reaction of diazo compounds with equimolar amounts of trialkyl or triaryl boranes has been shown to lead to the insertion of the carbene into the C–B bond and is generally well explored.<sup>4</sup> For example, Stephan *et al.*<sup>5</sup> reported in 2013 the generation of boron enolates by reacting ethyl  $\alpha$ -diazomethylacetate and B(C<sub>6</sub>F<sub>5</sub>)<sub>3</sub> in CH<sub>2</sub>Cl<sub>2</sub> at –78 °C (*cf.* Scheme 1A). The aryl group migration from boron to carbon was confirmed by NMR spectroscopy analysis, revealing the formation of the *E*- and *Z*-boron enolate products in a 4:1 ratio in 42% yield. This reactivity led to the synthesis of new bulky, secondary and tertiary substituted Lewis acidic boranes.<sup>5</sup> Already, as early as in the 1970s, Hooz *et al.* conducted the first studies by trapping boron enolates generated from diazo precursors with aldehydes,<sup>6</sup> ketones,<sup>9</sup> dimethylethylenammonium iodide,<sup>7</sup> *N*-bromo- or *N*-chlorosuccinimide<sup>8</sup> and nitriles (Scheme 1B–E).<sup>9</sup> Later, Miranda *et al.*<sup>10</sup> prepared 1,3-diketones and  $\beta$ -keto

esters from reacting  $\alpha$ -diazocarbonyl compounds with BR<sub>3</sub> (R = ethyl, *n*-propyl, phenyl) and aldehydes followed by oxidation (Scheme 1E).<sup>13</sup> To explore further the utility of this approach, we developed the scope for the use of electrophilic aryl boranes as arylation reagents with diazo compounds.<sup>11</sup> Initially, the treatment of various  $\alpha$ -diazooesters with different triaryl boranes gave similar boron enolates as mentioned above. Basic aqueous work-up of these enolates gave  $\alpha$ -aryl functionalised esters in up to 99% yield (Scheme 1F) which we also demonstrated could be applied towards an intermediate in the synthesis of antidepressant diclofensine which had previously been reported using rhodium-based catalysts.<sup>6,12</sup> It was also found that the more Lewis acidic boranes are able to transfer more than one aryl group.<sup>5,6,13</sup> However, using 2-benzyloxy-substituted diazo compounds as starting materials, biologically important 3,3-disubstituted benzofuranone deriva-

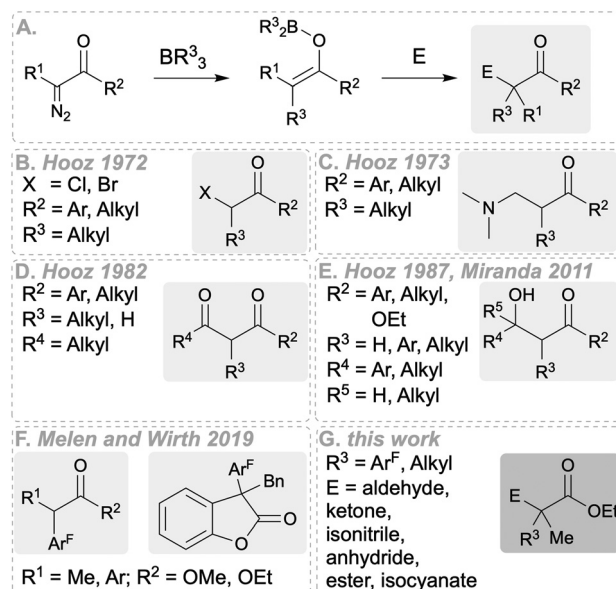
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Scheme 1 Previous and current work.



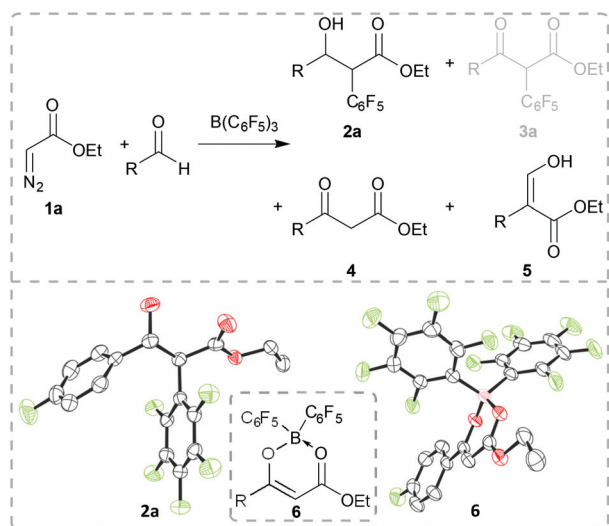
tives could be synthesised (Scheme 1F). Here, the boron enolate formed after the aryl transfer from  $B(Ar^F)_3$  ( $Ar^F$  = fluorinated aryl) intramolecularly attacks the benzyl group generating a quaternary carbon centre. Subsequent cyclisation leads to the benzofuranone heterocycle.<sup>6</sup> In this study we investigate alternative synthetic applications of the boron enolate formed after aryl transfer from  $B(Ar^F)_3$  to the diazo precursor, since the previous studies concentrated mostly on diazo carbonyl compounds and alkylboranes, and a wider scope was not investigated (see Scheme 1 for comparison). Therefore, we decided to explore other electrophiles such as aldehydes, ketones, imines, alkylhalides, nitriles, isocyanates, esters and acid chlorides in a three-component reaction with  $\alpha$ -diazoesters and fluorinated triaryl boranes, as the incorporation of fluorinated aromatic rings is important for drug synthesis or for medicinal applications.<sup>14</sup> For a complete picture, we also included  $BEt_3$  in our studies.

Our initial studies investigated the reaction of commercially available ethyl diazoacetate **1a** with  $B(C_6F_5)_3$  in the presence of aldehydes. Reaction of **1a** with 4-fluorobenzaldehyde and 1 equiv.  $B(C_6F_5)_3$  for 20 h at 45 °C gave a mixture of products including  $\alpha$ -aryl substituted  $\beta$ -hydroxy ester **2a**,  $\beta$ -keto ester **4** and an unidentified compound (Scheme 2). A small crop of crystals of this latter compound was isolated from the solution which was identified as compound **6** by single crystal X-ray diffraction (Scheme 2, bottom right). We propose that **6** is formed *en route* to product **4**. When using catalytic amounts of  $B(C_6F_5)_3$  (0.1 equiv.) under the same reaction conditions **4**, **5** and **6** could be identified in the  $^1H$  NMR spectrum of the crude reaction mixture (see the ESI for details†). The formation of compound **3a** was not observed. The unselective reaction of diazo compound **1a** with other Lewis acids has already been described in the literature.<sup>15</sup> However, with 1 equiv. of  $B(C_6F_5)_3$

in  $CH_2Cl_2$  for 20 h at room temperature, **2a** could be isolated in 74% yield as a diastereomeric mixture (dr: 1 : 0.07). The solid-state structure of *2S,3R*-**2a** could be verified *via* X-ray diffraction analysis (Scheme 2, bottom left).

Considering the difficulties in the selective synthesis of  $\alpha$ -aryl substituted  $\beta$ -hydroxy esters **2** with **1a** as a starting material, we investigated ethyl  $\alpha$ -diazomethylacetate **1b** as an alternative. Indeed, a more selective reaction is observed with 4-fluorobenzaldehyde,  $B(C_6F_5)_3$ , and diazo ester **1b** as model substrates (Table 1). Under the same reaction conditions as above, the 1 : 1 : 1 reaction of **1b** with 4-fluorobenzaldehyde and  $B(C_6F_5)_3$  gave the product **2b** in 62% yield and a 1 : 0.10 diastereomeric ratio (Table 1, entry 1). Screening of the solvents showed that  $CH_2Cl_2$  gave the best isolated yields and diastereomeric ratio, with less polar toluene and hexane giving 41% and 40% yields respectively (Table 1, entries 2–3). Variation of the temperature to room temperature (20 °C) in  $CH_2Cl_2$  and 60 °C in 1,2-dichloroethane ( $C_2H_4Cl_2$ ) (Table 1, entries 4 and 5) both showed significantly lower yields of 43% and 31% yield, respectively. When the reaction time was extended from 20 h to 24 h and 30 h (Table 1, entries 6 and 7), a better conversion of the aldehyde starting material was detected in the  $^1H$  NMR spectrum of the crude reaction mixture (see ESI for details†). However, the isolated yields from the product mixture were similar. Consequently, a reaction time of 24 h was chosen. Lastly, the amount of  $B(C_6F_5)_3$  was changed since we have previously shown that  $B(C_6F_5)_3$  can transfer more than one of its aryl rings.<sup>6</sup> Substoichiometric amounts of borane (0.8 and 0.6 equiv.) however lead to poorer diastereomeric ratios and lower yields (Table 1, entries 8 and 9). Using more than 1 equiv. of  $B(C_6F_5)_3$  showed no advantage (Table 1, entry 10).

With the optimised reaction conditions in hand, we explored the substrate scope for the synthesis of  $\alpha$ -substituted



**Scheme 2** Reaction of ethyl diazoacetate **1a**, with 4-fluorobenzaldehyde and  $B(C_6F_5)_3$  ( $R$  = 4-fluorophenyl; top). Solid-state structure of compound **2a** (bottom left) and **6** (bottom right). Thermal ellipsoids drawn at 50% probability. Carbon: black; oxygen: red; boron: pink; fluorine: green. H atoms omitted for clarity.

**Table 1** Optimisation of the reaction conditions

Entry	$B(C_6F_5)_3$ (equiv.)	Solvent	Temp. (°C)	Time (h)	dr <sup>a</sup>	Yield <b>2b</b> <sup>b</sup> (%)
1	1.0	$CH_2Cl_2$	45	20	1 : 0.10	62
2	1.0	Toluene	45	20	1 : 0.14	41
3	1.0	Hexane	45	20	1 : 0.12	40
4	1.0	$CH_2Cl_2$	20	20	1 : 0.10	43
5	1.0	$C_2H_4Cl_2$	60	20	1 : 0.26	31
6	1.0	$CH_2Cl_2$	45	24	1 : 0.10	72
7	1.0	$CH_2Cl_2$	45	30	1 : 0.10	70
8	0.8	$CH_2Cl_2$	45	24	1 : 1.15	56
9	0.6	$CH_2Cl_2$	45	24	1 : 1.15	45
10	1.2	$CH_2Cl_2$	45	24	1 : 1.15	52

<sup>a</sup> dr determined by  $^{19}F$  NMR analysis of the crude reaction mixture.

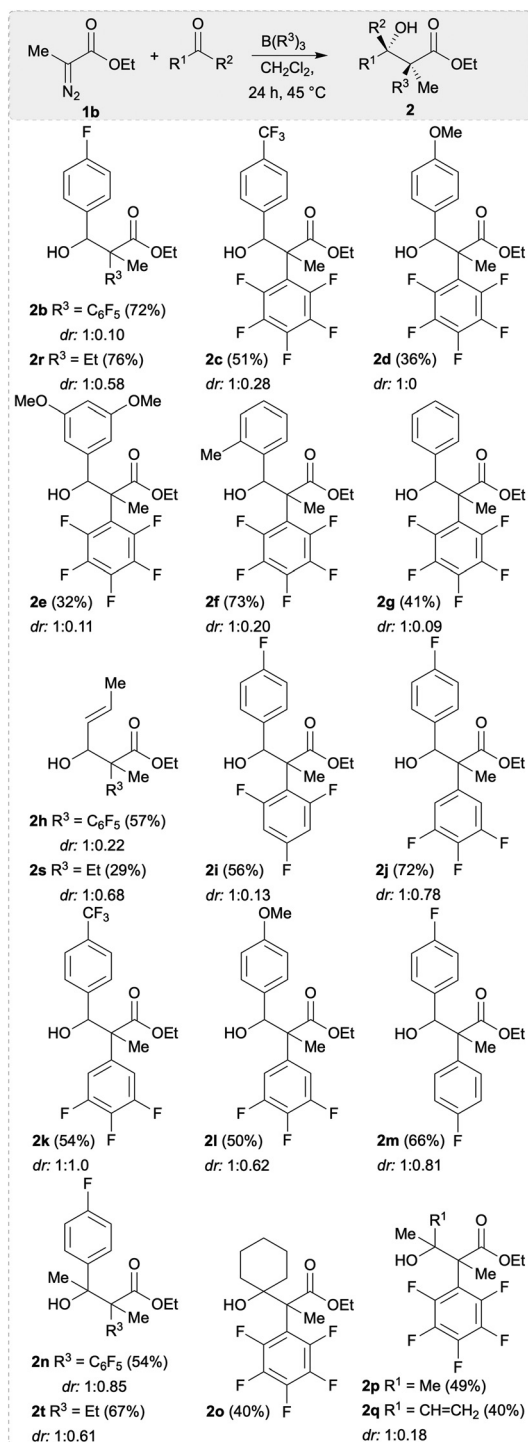
<sup>b</sup> Reported yields are isolated yields of both diastereoisomers. All the reactions were carried out on a 0.16 mmol scale. **1b** (1 equiv.), 4-fluorobenzaldehyde (1 equiv.), and  $B(C_6F_5)_3$ , and 2.0 mL of solvent were used.



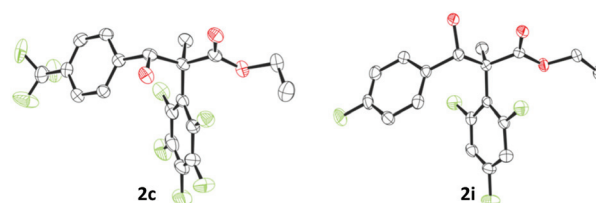
$\beta$ -hydroxy esters **2**. Firstly, **1b**,  $B(R^3)_3$  ( $R^3 = C_6F_5$ , Et) and aldehydes were used bearing electron-withdrawing, neutral, and electron-releasing groups giving  $\beta$ -hydroxy esters **2b–2h**, **2r,s** in yields up to 73% (Scheme 3). The conversion of aldehydes with

electron withdrawing substituents was found to be better than electron-releasing groups (*cf.* **2b** in 72% *vs.* **2e** in 32% yield). The highest yield could be achieved for **2f** (73%) using the *ortho*-methyl substituted benzaldehyde as a substrate. The diastereomeric selectivity for the arylated compounds **2b–2h** was quite good (*e.g.* 1 : 0.09 for **2g**) and the diastereoisomers could be separated *via* preparative thin layer chromatography (TLC) giving a major and a minor product. Crystals of the minor compound of **2c** and the major compound of **2i** could be formed by slow evaporation of a saturated  $CHCl_3$  solution (Fig. 1). Based on this we find that the minor compound of **2c** is racemic  $2S^*,3R^*$ -alcohol and the major compound of **2i** is racemic  $2S^*,3S^*$ -alcohol. From this we propose that the major isomer formed are the racemic  $2S^*,3S^*$ -alcohols through a 6-membered Zimmerman-Traxler transition state. We then investigated other boranes ( $B(Ar^F)_3$ ;  $Ar^F = 3,4,5-F_3C_6H_2$ ; 2,4,6- $F_3C_6H_2$ ; 4- $FC_6H_4$ ) in the reaction giving  $\beta$ -hydroxy esters **2i–2m** in yields up to 72%. However, we observed lower diastereoselectivities when using boranes which are devoid of *ortho*-fluorine atoms or bearing an ethyl group (compounds **2r**, **2s**, and **2j–2m**, Scheme 3). Interestingly, the less Lewis acidic  $BPh_3$  did not work for these reactions.<sup>6</sup> To further expand the scope of  $\beta$ -hydroxy esters, we investigated other electrophiles such as imines, alkyl halides, and ketones. While reactions with imines and alkyl halides were unsuccessful, treatment of **1b** and  $B(C_6F_5)_3$  or  $BEt_3$  with various ketones yielded compounds **2n–2q**, and **2t** (Scheme 3).

This concept was then applied to the synthesis of  $\beta$ -keto esters **3b–3h** (Scheme 4). Compound **3b** could be synthesised using benzoic anhydride, benzonitrile or benzoyl chloride as substrates, however when using benzoic anhydride the best yields were obtained (60%). In case of benzonitrile, an additional acidic work up was performed to hydrolyse the initially formed  $\beta$ -imine into **3b**. With benzoyl chloride, **3b** only formed as a minor product with **7d** isolated as the main product from an otherwise complex crude reaction mixture (see below, Schemes 4 and 5). When using an ester such as methyl propiolate as electrophile, **3c** was isolated in 36% as the main product. No reaction at the unsaturated carbon-carbon bond occurred as was already observed in the synthesis of compounds **2h** and **2q**. The amino functionalised  $\alpha$ -aryl substituted  $\beta$ -keto esters **3d–3f** and **3h** were synthesised using isocyanates in the three-component reaction (Scheme 4). In case of the  $C_6F_5$  transfer, electron rich aryl isocyanates bearing



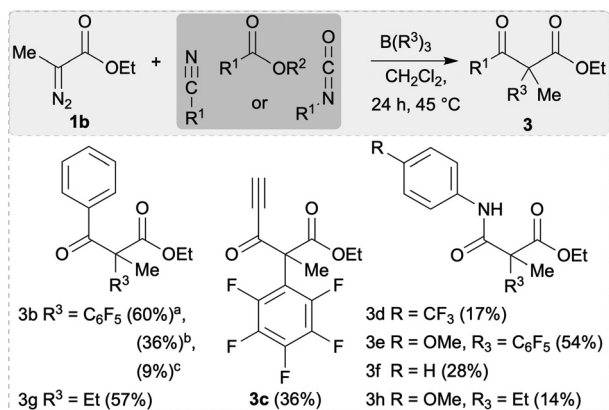
**Scheme 3** Substrate scope of the synthesised  $\beta$ -hydroxy esters. Yields reported are isolated. Reactions were carried out on a 0.16 mmol scale. **1b** (1 equiv.), aldehyde/ketone (1 equiv.),  $B(R^3)_3$  (1 equiv.;  $R^3 = C_6F_5$ , Et), and 2.0 mL of  $CH_2Cl_2$  were used.



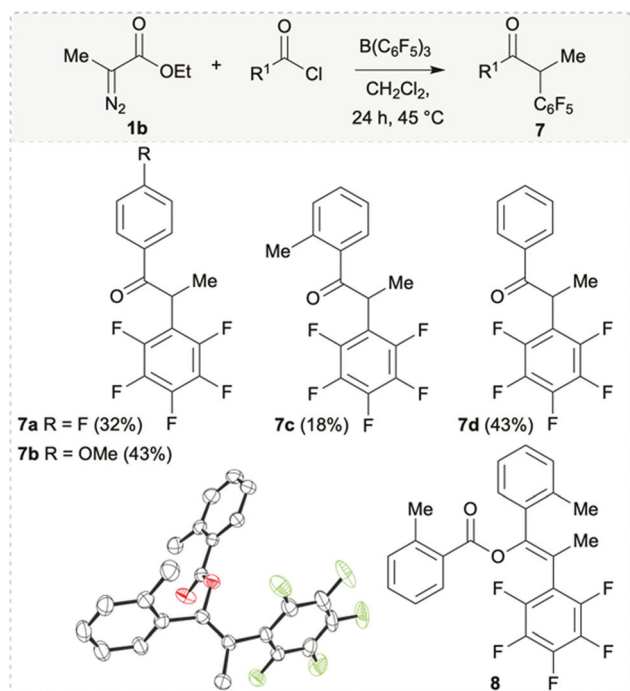
**Fig. 1** Solid-state structure of compound **2c** (left) and **2i** (right). Thermal ellipsoids drawn at 50% probability. Carbon: black; oxygen: red; fluorine: green. H atoms omitted for clarity.







**Scheme 4** Substrate scope of the synthesised  $\beta$ -keto esters. Yields reported are isolated. All the reactions were carried out on a 0.16 mmol scale. **1b** (1 equiv.), electrophile (1 equiv.),  $B(R^3)_3$  (1 equiv.;  $R^3 = C_6F_5$ , Et), and 2.0 mL of  $CH_2Cl_2$  were used. <sup>a</sup>Yield using benzoic anhydride. <sup>b</sup>Yield using benzonitrile. <sup>c</sup>Yield using benzoyl chloride.



**Scheme 5** Substrate scope of the synthesised ketones. Yields reported are isolated. All the reactions were carried out on a 0.16 mmol scale. **1b** (1 equiv.), acid chloride (1 equiv.),  $B(C_6F_5)_3$  (1 equiv.), and 2.0 mL of  $CH_2Cl_2$  were used. Solid-state structure of compound **8** (bottom). Thermal ellipsoids drawn at 50% probability. Carbon: black; oxygen: red; fluorine: green. H atoms omitted for clarity.

a *p*-OMe gave the highest yield (**3e**, 54%) whereas *p*- $CF_3$  isocyanate gave **3d** in just 13% yield. Using  $BEt_3$  in this reaction, compound **3h** could only be isolated in 14% yield which is a significantly lower product formation compared to **3e**.

As alluded earlier, treatment of **1b** and  $B(C_6F_5)_3$  with acid chlorides does not give the desired  $\beta$ -keto esters. Instead, we

observe the formation of compounds **7a–d** isolated in 18–43% yield (Scheme 5). In these reactions, the nucleophilic attack of the boron enolate to the acid chloride took place with a formal decarboxylation step. Conditions for the release of  $CO_2$  from  $\beta$ -keto esters usually involves strong acidic/basic conditions,<sup>16</sup> metal salts,<sup>17</sup> or elevated temperatures.<sup>18</sup> A few examples where boric acid promotes decarboxylation of  $\beta$ -keto esters have also been reported.<sup>19</sup> From the reaction that yielded compound **7c**, a small crop of crystals of another compound was isolated from the solution which was identified as compound **8** by single crystal X-ray diffraction (Scheme 5, bottom). Here, reaction with two equivalents of the acid chloride had taken place indicating that acid chlorides are too reactive for these reactions under the applied conditions.

In conclusion, we synthesised 21 examples of  $\alpha$ -aryl and 5 examples of  $\alpha$ -alkyl functionalised  $\beta$ -hydroxy and  $\beta$ -keto esters. This is a three-component reaction with ethyl  $\alpha$ -diazomethylacetate **1b**, boranes  $B(R^3)_3$  ( $R^3 = C_6F_5$ , Et), and electrophiles such as aldehydes, ketones, anhydrides, nitriles, esters and isocyanates. On the other hand, the reaction of ethyl  $\alpha$ -diazomethylacetate **1b**,  $B(C_6F_5)_3$  and acid chlorides resulted in the elimination of the ester functionality and yielded ketones **7a–d**.

## Conflicts of interest

There are no conflicts to declare.

## Acknowledgements

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## Notes and references

- (a) K. A. Mix, M. R. Aronoff and R. T. Raines, *ACS Chem. Biol.*, 2016, **11**, 3233; (b) A. Ford, H. Miel, A. Ring, C. N. Slattery, A. R. Maguire and M. A. McKerver, *Chem. Rev.*, 2015, **115**, 9981.
- B. D. Bergstrom, L. A. Nickerson, J. T. Shaw and L. W. Souza, *Angew. Chem., Int. Ed.*, 2021, **60**, 6864.
- (a) A. Dasgupta, E. Richards and R. L. Melen, *ACS Catal.*, 2022, **12**, 442; (b) X.-Y. Wu, W.-X. Gao, Y.-B. Zhou, M.-C. Liu and H.-Y. Wu, *Adv. Synth. Catal.*, 2022, **364**, 750.
- H. Li, Y. Zhang and J. Wang, *Synthesis*, 2013, 3090.
- R. C. Neu, C. Jiang and D. W. Stephan, *Dalton Trans.*, 2013, 42, 726.
- J. Hooz, J. Oudenes, J. L. Roberts and A. Benderly, *J. Org. Chem.*, 1987, **52**, 1347.
- J. N. Bridson and J. Hooz, *J. Am. Chem. Soc.*, 1973, **95**, 602.
- J. N. Bridson and J. Hooz, *Can. J. Chem.*, 1972, **50**, 2387.
- J. Oudenes and J. Hooz, *Synth. Commun.*, 1982, **12**, 189.



- 10 M. A. Sanchez-Carmona, D. A. Contreras-Cruz and L. D. Miranda, *Org. Biomol. Chem.*, 2011, **9**, 6506.
- 11 M. Santi, D. M. C. Ould, J. Wenz, Y. Soltani, R. L. Melen and T. Wirth, *Angew. Chem., Int. Ed.*, 2019, **58**, 7861.
- 12 J. Ghorai and P. Anbarasan, *J. Org. Chem.*, 2015, **80**, 3455.
- 13 R. C. Neu and D. W. Stephan, *Organometallics*, 2012, **31**, 46.
- 14 D. Barnes-Seeman, J. Beck and C. Springer, *Curr. Top. Med. Chem.*, 2014, **14**, 855.
- 15 (a) A. K. Gupta, M. Mukherjee, G. Hu and W. D. Wulff, *J. Org. Chem.*, 2012, **77**, 7932; (b) M. R. Frutos, M. M. Díaz-Requejo and P. J. Pérez, *Chem. Commun.*, 2009, 5153; (c) D. Benito-Garagorri, J. Wiedermann, M. Pollak, K. Mereiter and K. Kirchner, *Organometallics*, 2007, **26**, 217.
- 16 (a) K. Kundu and S. K. Nayak, *J. Nat. Prod.*, 2017, **80**, 1176; (b) D. Landini and F. Rolla, *J. Org. Chem.*, 1982, **47**, 154; (c) C. R. Schmid, *Tetrahedron Lett.*, 1992, **33**, 757; (d) K. L. Kaestle, M. K. Anwer, T. K. Audhya and G. Goldstein, *Tetrahedron Lett.*, 1991, **32**, 327; (e) Y. Yamamoto, T. Furuta, J. Matsuo and T. Kurata, *J. Org. Chem.*, 1991, **56**, 5737.
- 17 Z.-W. Chen, D.-N. Ye, Y.-P. Qian, M. Ye and L.-X. Liu, *Tetrahedron*, 2013, **69**, 6116.
- 18 Q. Zhang and D. P. Curran, *Adv. Synth. Catal.*, 2003, **345**, 329.
- 19 (a) P. Delbecq, J.-P. Celerier and G. Lhommet, *Tetrahedron Lett.*, 1990, **31**, 4873; (b) J. M. Lalancette and A. Lachance, *Tetrahedron Lett.*, 1970, **45**, 3903.

