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Copper catalyzed tandem conjugated borylation–aldol reaction

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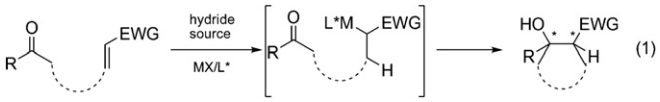
ABSTRACT

We investigated the tandem conjugated borylation–aldol reaction catalyzed by copper complexes. After identification and optimisation of the catalytic system, the scope of the reaction was evaluated and the diastereoselectivity was studied on both linear and cyclic activated alkenes. Finally, the use of some selected borylated aldol adducts in two classical transformations was investigated.

1. Introduction

Domino reactions are processes in which several bonds are formed in one step without isolating intermediates, change the conditions of reaction or add reagents.[1] These reactions are ecologically and economically favourable because work, time and materials are spared. Amongst domino reaction, reductive aldol has been developed as an efficient alternative one pot procedure for the production of aldol derivatives without the need to generate a metal enolate prior to the condensation with an aldehyde or a ketone. Versions based on various transition metals catalysts[2] were reported, in particular with copper.[3] Since the pioneering work of Maruoka[4] and Chiu,[5] intramolecular racemic[5,6] and enantioselective[7] as well as intermolecular racemic[8] and enantioselective[9] methods were developed based on this metal. These reactions are proposed to proceed by the in situ formation of a metal enolate through the conjugated reduction of a metal hydride species onto the Michael acceptor (Scheme 1). Then, the generated nucleophile is trapped by the electrophile to form the aldol-type adduct after final reaction with the hydride source.

We recently reported a modified version of this reaction using silylboranes as pronucleophiles and (meth)acryloyloxazolidinones as Michael acceptors leading to stereocontrolled aldol adducts.[10] Since the first reports of copper catalyzed conjugated addition of boronic esters on activated olefins by Hosomi and Miyaura, numerous improvements were achieved by addition of alcohol additives.[11] Additions to alkynes and recently to 1,3-enynes were then developed.[12] Enantioselective versions followed with applications to α,β-unsaturated esters, nitriles, amides and ketones based on various ligands.[13] However, only few examples, always based on cyclic substrates, involve the use of such catalytic systems in tandem reactions. Therefore, we were attracted by using this methodology in tandem borylation–aldol reaction.



Scheme 1. General reductive aldol.

2. Results and discussion

We started our investigations by the identification of the most effective catalytic system (Table 1) on a model reaction between methyl acrylate **1**, benzaldehyde **2** and bis-(pinacolato)-diboron **3**. We first envisioned the use of the previously described catalyst based on *N*-heterocyclic carbenes[8] **6** (entry 1) but no activity was observed in toluene for this complex. As polar solvents can have a strong influence on reaction outcomes by activation/stabilisation of key catalytic intermediates in copper (I) chemistry, we were inspired by the work of Sawamura et al.[14] Therefore, we tried DMF as a co-solvent (entry 2) and obtained a complete conversion of the starting acrylate, but the desired product **4** was only observed as the minor product in the crude ^{1}H NMR spectra along with the major product **5**, which arises from a formal hydroboration of the Michael

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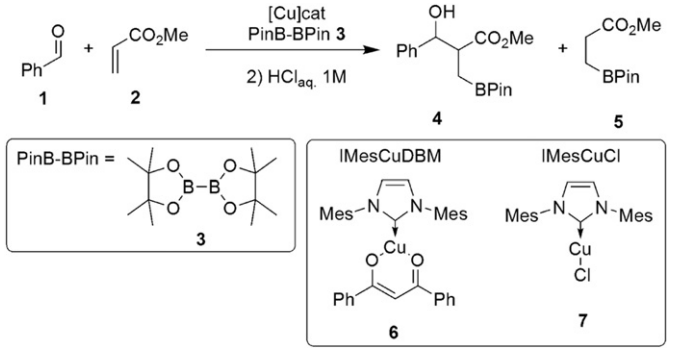
Table 1
First optimisation of the catalytic system[a]



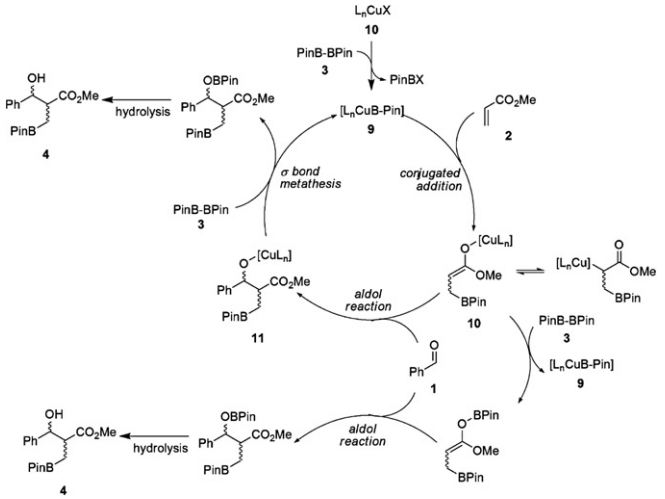
Entry	Catalytic system	Solvent	**4**/**5**[b]
1	IMESCuDBM (1 mol %)	Toluene	No reaction
2		DMF	1/1.6
3	IMesCuCl, *t*-BuOK (1 mol %)	THF	1/2.3
4	CuCl, *t*-BuOK, (*rac*)-BINAP (5 mol %)	THF	1/1.5
5	[$(Ph_3P)_3CuF{\cdot}2MeOH$] **8** (1 mol %), (*rac*)-BINAP (2 mol %)	Toluene	20/1

[a] All reactions were carried out at 21 °C under an oxygen-free argon atmosphere containing **1** (1 equiv), **2** (1 equiv) and **3** (1.2 equiv) at 0.2 M and concentrated under reduced pressure after 16 h before NMR analysis.
[b] Determined by NMR analysis.

acceptor. As our NHC based precatalyst does not seem to be activated by the diboron derivative in non polar solvents, we turned to a well described catalytic system developed by Nolan for the hydrosilylation of hindered ketones.[15] Using IMesCuCl **7** activated by potassium *tert*-butoxide in THF (entry 3) however gave a decreased selectivity for the formation of the domino adduct **4**. We then focused on the use of diphosphine ligands and first tried the in situ catalytic system formed with copper(I) chloride, potassium *tert*-butoxide and (*rac*)-BINAP[16] as ligand (entry 4). Using those reaction conditions, we still observed the simple addition adduct **5** as the major product. Fortunately, when using [$(Ph_3P)_3CuF{\cdot}2MeOH$][17] **8** as the copper source in combination with (*rac*)-BINAP in toluene (entry 5), we obtained an excellent 20 to 1 ratio in favour of the desired product. From the observations summarized in Table 1, it appears that the presence of salts, i.e., KCl, is detrimental to the formation of the domino adduct **4** and favours the simple addition adduct **5**. It might be postulated that the presence of such salts lead to a non-negligible amount of retro-aldol reaction, leading to boronic ester **5** and benzaldehyde **1**.

The suggested catalytic cycle (Scheme 2) starts with the generation of the active copper–boron **9** species from precatalyst **10** and bis(pinacolato)diboron **3**. After conjugated addition of the boronate moiety on the electrophilic double bond of methyl acrylate **2**, the resulting copper enolate **10** reacts then with benzaldehyde **1** to give the copper alkoxide **11**. This last intermediate undergoes σ-bond metathesis with the diboron **3** to regenerate the active catalyst **9** and a boronate ester, which yields, after hydrolysis, the expected aldol adduct **4**. We also noticed that no competitive addition of the boronate nucleophile occurs directly on the aldehyde, contrasting with this common side reaction encountered when using hydrosilanes.[8,9e]

However, care should be taken when drawing such a catalytic cycle, while there is an ever increasing number of studies that involve copper enolate intermediates, the true nature of such intermediates still remain elusive and thus care should be taken when trying to extrapolate classical hard metal(oid) enolate chemistry (such as Li, Ti and boron) to very soft transition metal enolates such as Cu(I). Indeed, there are still few examples of well

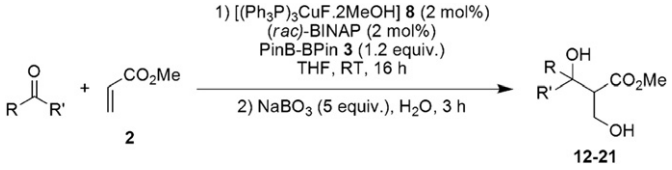


Scheme 2. Postulated catalytic cycle.

identified soft transition metal in the literature (such as Rh(I), Pd(II) and Ni(II)),[18] and it has been shown in most cases that such species are actually C-bonded metal enolates. The nucleophilic intermediate species involved in our mechanism can then be either an O- or a C-bonded enolate (both species can also be considered as formed and in equilibrium of the two tautomers). This information is of course of high importance as the control of the geometry of an O-enolate is known to have a profound influence on the stereochemical outcome of the aldol process. However, the possible formation of a C-bonded enolate would involve the formation of a chiral metal bonded carbon centre and the stereochemical outcome of the aldol process with such species is still far from obvious with the lack of information on such intermediates in the literature. Furthermore, the reaction of the copper enolate with the electrophile could occur through an open or a closed TS and there are still no proof in the literature that copper bonded enolates favour one pathway over the other.[19] Finally, a fast transmetallation of the copper enolate with the diboron **3** can also be postulated to give rise to the formation of a boron enolate. In that case, the stereochemical outcome of the aldol condensation will be mainly driven by control of the *Z*/*E* geometry of the boron enolate.[20] We have not been so far able to isolate or identify such an intermediate in our experiments but this hypothesis cannot still be ruled out in our postulated mechanistic cycle.

We then evaluated the scope of the reaction, by varying the aldol electrophilic carbonyl partners. As we found that primary boronate derivatives, such as **4** are rather unstable on silica gel, reaction products were isolated after oxidation of the boronic moiety under mild conditions.[11c] THF was also used as solvent because of the poor miscibility, required for the oxidation step, of toluene with water. This reaction proved quite versatile regarding the electrophilic counterpart and the results are summarized in Table 2. We observed a better reproducibility for our reaction when the catalyst loading was raised to 2 mol %. The reaction between methyl acrylate and benzaldehyde (entry 1) led to the formation of corresponding diol with an excellent isolated yield. The diastereomeric ratio measured by NMR was 1 to 1 and this lack of diastereoselectivity was observed with every other electrophiles. When using electron poor aromatic aldehydes (entries 2 and 3), yields were slightly lower. Using *para*-anisaldehyde as an electron rich aromatic aldehyde (entry 4) led to a similar yield. The reaction with a heteroaromatic aldehyde, 2-furyl carboxaldehyde (entry 5), gave also a good isolated yield. With a primary aliphatic aldehyde (entry 6), the yield was slightly decreased but with cyclohexanecarboxaldehyde (entry 7), an excellent result was obtained.

Table 2
Scope of the reaction with electrophiles[a]



Entry	R	R′	Yield[b,c] (%)	Product
1	Ph	H	91	**12**
2	*p*-Cl–Ph	H	68	**13**
3	*p*-CF_3–Ph	H	73	**14**
4	*p*-OMe–Ph	H	74	**15**
5	2-Furyl	H	77	**16**
6	Ph–CH_2–CH_2–	H	67	**17**
7	Cy	H	92	**18**
8	*t*-Bu	H	70	**19**
9	Ph	Me	76	**20**
10	–$(CH_2)_5$–		89	**21**

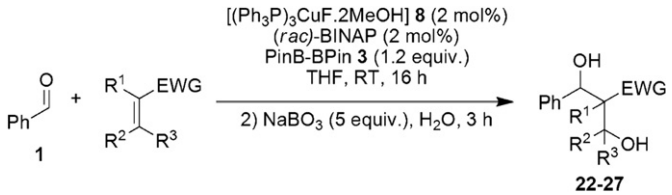
[a] All reactions were carried out at 21 °C under an oxygen-free argon atmosphere containing the electrophile (1 equiv), **2** (1 equiv) and **3** (1.2 equiv) at 0.2 M.
[b] Isolated yield.
[c] Products were isolated as 1 to 1 diastereoisomeric ratio.

Even the reaction with pivaldehyde (entry 8) gave an interesting yield. Moderate to very good yields were obtained with ketones (entries 9 and 10), showing the high reactivity of the copper enolate intermediate.

We then evaluated the scope with different electron-deficient olefins using benzaldehyde as a model electrophile (Table 3).

We first examined the effect of the substituents around the double bond. When methyl methacrylate (entry 1) was used, the desired product was isolated with a good yield, showing of the possibility of building chiral quaternary carbon centre through an α substitution on the Michael acceptor. On the other hands, the introduction of substituent at the β-position (entry 2) led to a diminished catalytic activity as monitored by TLC. The diastereoselectivity was very low as the four possible diastereoisomers were detected by NMR impeding us to isolate and characterize the product. When a β disubstituted ester was used (entry 3), no reaction occurred, showing the major importance of β- compared to α substitution. Replacing an α,β-unsaturated ester by an enone (entry 4), afforded the desired aldol adduct with a good yield. Using

Table 3
Scope of the reaction with electrodeficient olefins[a]

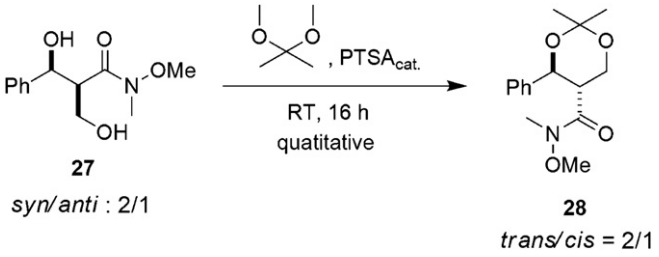


Entry	EWG	R^1	R^2	R^3	Yield[b] (%)	Product
1	CO_2Me	Me	H	H	79	**22**
2	CO_2Me	H	Me	H	—[c]	**23**
3	CO_2Me	H	Me	Me	—[d]	**24**
4	C(O)Me	H	H	H	69	**25**
5	CN	H	H	H	76	**26**
6	C(O)N(Me)OMe	H	H	H	72 (2/1)[e]	**27**

[a] All reactions were carried out at 21 °C under an oxygen-free argon atmosphere containing benzaldehyde (1 equiv), Michael acceptor (1 equiv) and **3** (1.2 equiv) at 0.2 M unless otherwise stated.
[b] Isolated yield.
[c] ^{1}H NMR analysis showed a 1/1/0.8/0.5 diastereoisomeric ratio.
[d] No reaction after 36 h.
[e] Diastereoisomeric ratio determined by NMR.

acrylonitrile as Michael acceptor (entry 5) conducted to the corresponding product with a slightly improved yield. With Weinreb acrylamide, the expected adduct was isolated with a good yield and with a diastereomeric ratio of 2 to 1 in favour of *syn* isomer.

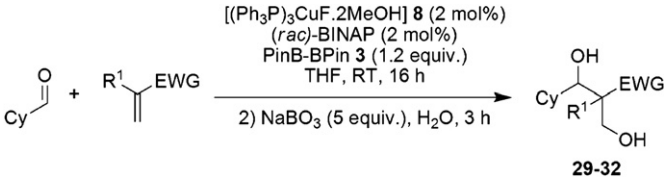
For this adduct the relative configuration of the major diastereoisomer was determined after treatment of diol **27** with 2,2-dimethoxypropane in the presence of a catalytic amount of PTSA (Scheme 3). Dioxolane **28** was obtained in quantitative yield and NMR analysis showed unambiguously a trans relationship between the amide and the phenyl for the major adduct.



Scheme 3. Determination of the relative configuration of **27**.

As a low diastereoselectivity was achieved with benzaldehyde, we ran out a new set of experiments with a more reactive and sterically demanding aldehyde (Table 4). When using cyclohexanecarboxaldehyde with a representative set of Michael acceptors, we were pleased to observe that a good reactivity was retained as the corresponding adducts were isolated with good overall yields and that modest, albeit significant diastereoselectivities were obtained with this aldehyde.

Table 4
Scope of the reaction with cyclohexanecarboxaldehyde[a]



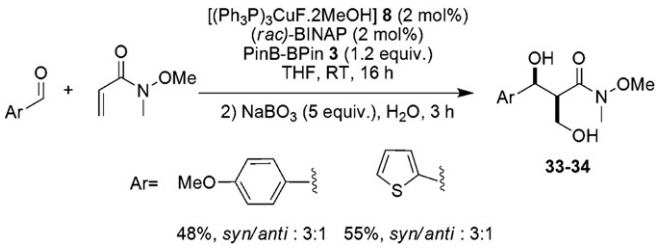
Entry	EWG	R^1	Yield[b] (%)	*syn*/*anti*[c,d]	Product
1	CO_2Et	Me	87	2/1	**29**
2	C(O)Me	H	77	60/40	**30**
3	CN	H	87	3/1	**31**
4	C(O)N(Me)OMe	H	73	3/1	**32**

[a] All reactions were carried out at 21 °C under an oxygen-free argon atmosphere containing cyclohexanecarboxaldehyde (1 equiv), Michael acceptor (1 equiv) and **3** (1.2 equiv) at 0.2 molarity unless otherwise stated.
[b] Isolated yield.
[c] Diastereoisomeric ratio determined by ^{1}H NMR.
[d] Relative configuration determined by ^{1}H NMR after cyclisation as the corresponding dioxolane.

Indeed, ethyl methacrylate (entry 1) led to an excellent yield and a 2 to 1 *syn*/*anti* ratio, while methyl vinylketone (entry 2) gave a lowered selectivity as well as a slightly lower yield. Using acrylonitrile (entry 3), a very good yield was achieved and an interesting 3 to 1 ratio in favour of *anti* isomer was obtained. Weinreb acrylamide (entry 4) gave a comparable yield and an improved diastereoselectivity. Relative configurations were determined using the same methodology as for compound **27**.

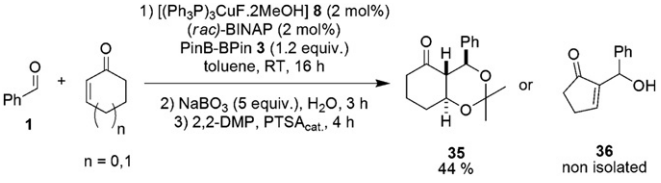
As we observed modest, albeit significant diastereoselectivities with the Weinreb acrylamide, we first retained this Michael acceptor and carried out a preliminary substrate scope with two aromatic aldehydes. The domino reaction was then carried out using the standard catalytic system with *p*-anisaldehyde and 2-furyl

carboxaldehyde. While the isolated yields for adducts **33**–**34** after oxidation remained quite modest, we were able to confirm a 3/1 *syn*/*anti* ratio for both electrophiles (Scheme 4). Those observations are quite promising as they might be a good starting point for further optimisations and development of an enantioselective reaction based on the use of a proper chiral ligand. Such adducts are particularly promising as transformations can be carried out on both the amide group and on the boronate using well known methodologies (vide supra).



Scheme 4. Tandem reaction using Weinreb acrylamide.

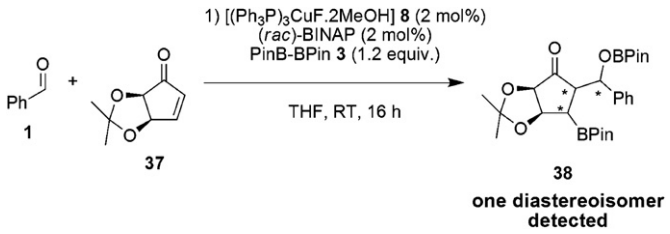
While modest diastereoselectivities were observed with acyclic Michael acceptors, we also decided to check the reactivity of simple cyclic enones as models. As the true nature of the enolate intermediate that will react with the aldehyde has still not been established (Scheme 2) as well as the transition state involved in the aldol process between the metal enolate and the aldehyde, previsions on the stereochemical outcome of cyclic substrates are not straightforward, although a recent study by the group of Hoveyda gave one example of a highly diastereoselective tandem conjugated addition–aldol reaction on cyclohexenone using a chiral NHC–copper(I) complex.[21] Furthermore, an early study of tandem conjugated addition–aldol reaction with hydroboranes and Stryker's reagents as the catalyst was reported to yield high diastereoslectivities in favour of the anti-aldol adduct on cycloalkenones with the intervention of an intermediate *E*-boron enolate. We then tested cyclohexenone and cyclopentenone as model substrates and found different behaviour depending on the ring size of the Michael acceptor. In all cases, the boron ester arising from the tandem process was identified in the crude reaction mixture by ^{1}H NMR but was not isolated and was directly oxidised to the corresponding diol, which was then protected as a dioxolane (Scheme 5) in a one pot sequence for relative configuration determination.



Scheme 5. Tandem reaction using cyclic enones.

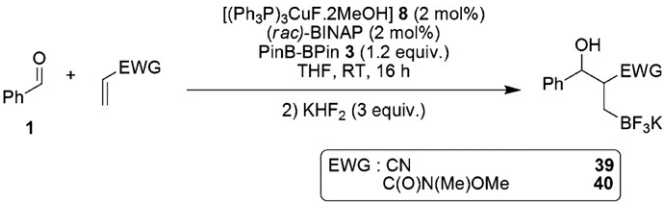
Although the unoptimised yield with cyclohexenone is modest, only one diastereoisomer was detected in the crude reaction mixture prior to oxidation. In contrast, we were disappointed by the spontaneous dehydration after boronic ester oxidation when using cyclopentenone, although diastereocontrol was very good. In this case, every attempt to prevent water elimination failed.

We also investigated the use of a functionalised chiral Michael acceptor and focussed on the enantiopure enone **37**, which was easily prepared from D-ribose using a protocol from the literature.[22] After reaction in the standard catalytic conditions, the desired adduct **38** was obtained as the major product and only one diastereoisomer was detected in the crude reaction mixture, meaning that the absolute configuration of three new centres is controlled (Scheme 6). As the oxidation of the boronate ester was not possible for cyclopentenone, we have not yet been able to isolate the pure adduct and confirm the stereochemistry of the newly formed chiral carbon centres.



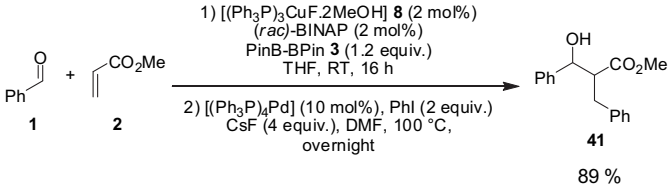
Scheme 6. Tandem reaction using enantiopure cyclic enone.

As stated earlier, all the optimisations and isolated yields of the domino adducts were carried out on the diols resulting from the perborate oxidation of the crude boronate ester. As we observed that the crude ^{1}H NMR spectrum of the boronate esters taken after simple evaporation of the reaction mixture were usually very clean, we decided to carry out some attempts to isolate those functionalised boron derivatives and our choice focussed naturally on the preparation of stable and versatile trifluoroborate salts,[23] which can be easily obtained by reaction of alkylboronate esters with potassium bifluoride. Our choice was strongly motivated by two reports from the groups of Molander[23c] and Yun[13e] who reported the preparation of potassium β-trifluoroborato amides and esters via the copper catalyzed addition of diboron **3** on Michael acceptors followed by treatment with KHF_2. However, the reported procedure proved troublesome in our hand (Scheme 7) and a full characterisation of salts **39** and **40** was impossible due to the low solubility of those salts in various solvents.



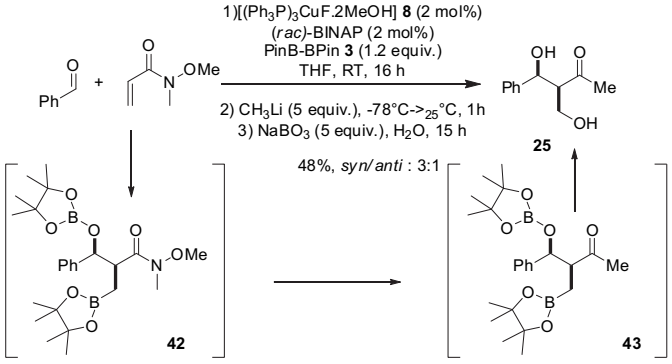
Scheme 7. Attempts at isolation of aldol adducts as trifluoroborate salts.

Organoboronate derivatives are versatile intermediates in organic synthesis and their main application is found in the Suzuki cross-coupling reaction. We carried out a one pot experiment to avoid the isolation of the boronate ester and to keep the hydroxyl group of the crude adduct protected as a borate ester to avoid potential retro-aldol reaction with the base required for the cross-coupling reaction. Thus, after condensation of benzaldehyde **1**, methyl acrylate **2** and diboron **3** using the standard catalytic conditions, the solvent was evaporated from the crude reaction mixture without any work-up and replaced by DMF. The Suzuki reaction was then directly carried out with iodobenzene using $Pd(PPh_3)_4$ as a catalyst and caesium carbonate as a base using an optimised protocol from the literature.[24] We were pleased to observe that the corresponding adduct **41** could be isolated as a separable mixture of *syn*/*anti* diastereoisomers in an excellent 89% yield for the two steps (Scheme 8). This preliminary experiment shows that it is potentially possible to have access to structural diversity on this family of adducts by simple variation of the aldehyde electrophile and Suzuki coupling electrophilic partner.



Scheme 8. Domino borylation–aldol–Suzuki coupling.

In order to go further in the synthetic versatility of three component adducts, we finally checked the transformation of a model adduct bearing a Weinreb amide group. The condensation of benzaldehyde, Weinreb acrylamide and diboron **3** was carried out with a 2 mol % of the copper(I) catalytic system to deliver the intermediate borate ester **42**. The intermediate bearing a temporary protection on the hydroxyl group was not isolated and directly reacted with a large excess of methyl lithium to carry out the transformation of the amide group into the corresponding methyl ketone **43** (Scheme 9). Final oxidation of the boronate ester by sodium perborate delivered the desired keto-diol 24 in a 48% overall yield for the three steps and a 3/1 *syn*/*anti* ratio.



Scheme 9. One-pot post transformation of a Weinreb amide.

3. Conclusions

We developed an efficient procedure for the tandem borylation–aldol reaction based on copper catalysis. The best conditions are the use of the air-stable copper fluoride complex **8** in combination with a commercially available diphosphine and the reaction is very fast at room temperature. A wide variety of aldehydes as well as ketones may be used and leads to good to excellent yields. Regarding the Michael acceptor, the catalytic system tolerates α substitution but is sensitive to β-substitution. Different types of electronwithdrawing groups on the Michael acceptor may be employed and low level diastereoselection are observed with linear substrates. The use of cyclic substrates increases dramatically the diastereoselectivity and enantiopure substrates lead to the control the absolute configuration of three new contiguous centres. Although the isolation of products as trifluoroborate salts is troublesome, it is possible to combine our protocol with Suzuki coupling.

We are currently working on the development of a chiral ligand based enantioselective version of this reaction studying the scope of the transformation of the boronic esters with a focus on the Weinreb amides.

4. Experimental section

4.1. General experimental methods

Nuclear magnetic resonance spectra (NMR) of proton (^{1}H) and carbon (^{13}C) were recorded on Bruker-250, Bruker-300 and Bruker-500 spectrometer. Tetramethylsilane was used as internal standard for ^{1}H and ^{13}C. Chemical shift are given in part per million (ppm), and multiplicity given as follows: singlet (s), doublet (d), triplet (t), quadruplet (q), multiplet (m) and broad (br). Coupling constant *J* are given in Hertz (Hz). Mass spectra were obtained using a ThermoFinnigan LCQ Quantum spectrometer for electrospray ionization (ESI) and atmospheric pressure chemical ionization (APCI) or using a FinniganMat TSQ7000 for chemical ionization (CI). High resolution mass spectrometry (HMRS) was performed by Dr. Lisa D. Harris at the Mass Spectrometry Facility of the University College of London. Infrared spectra (IR) were recorded on a Shimadzu FTIR-8400S spectrometer. Wave numbers a given in cm^{-1}. Solvents are of analytical grade or distilled before use: toluene was distilled on sodium under an argon atmosphere. THF was distilled on sodium/benzophenone under an argon atmosphere. Commercial reagents were purchased by Acros, Sigma–Adrich, ABCR, TCI or Apolo scientific and used as received unless stated otherwise. Aldehydes were distilled before used. Flash column chromatography was performed on ROCC 60 (40–63 μm) silica gel. Thin layer chromatography (TLC) was carried out on commercially available MERCK 5179, 250 mesh with fluorescent indicator 60 PF254, and revealed under UV at 254 nm and with a solution of *para*-anisaldehyde in ethanol (10% w/v) or a basic solution of $KMnO_4$. IMesCuDBM,[8] IMesCuCl,[15] [$(Ph_3P)_3CuF\cdot 2MeOH$],[17] Weinreb acrylamide[25] and cyclopentenone **38**[18] were prepared according to protocols from the literature.

4.2. General procedure for tandem reaction borylation–aldolisation

A dried flask was loaded with [$(Ph_3P)_3CuF\cdot 2MeOH$] (9.3 mg, 0.01 mmol, 0.02 equiv) and (*rac*)-BINAP (6.2 mg, 0.01 mmol, 0.02 equiv). The system was closed with a septum and after 3 vacuum/argon cycles, the solvent (2.5 mL) was added by syringe. After dissolution of the solids, the Michael acceptor (0.5 mmol, 1 equiv) and the electrophile (0.5 mmol, 1 equiv) were added. Bis(pinacolato)diboron (152 mg, 0.6 mmol, 1.2 equiv) was added, and the mixture was stirred overnight. Water (2.5 mL) and $NaBO_3\cdot H_2O$ (249 mg, 2.5 mmol, 5 equiv) were added and the biphasic mixture was stirred for a further 3 h. EtOAc (5 mL) was added, the aqueous phase was saturated with NaCl and the phases were separated. The aqueous phase was extracted with EtOAc (3×5 mL) and the combined organic phases were dried over Na_2SO_4 and concentrated under reduced pressure. The product was finally purified by flash chromatography on silica gel. As pinacol is a common byproduct found in some analytical samples, a distillation under vacuum lead to the pure aldol adducts. Unless otherwise stated, the products were isolated as mixture of unseparable *syn*/*anti* isomers. N.B. When toluene was used as solvent, MeOH (2 mL) was added to the mixture for the oxidation step.

4.2.1. Methyl 3-hydroxy-2-(hydroxymethyl)-3-phenylpropanoate ***12****.* The product was isolated using the general procedure as a colourless oil (91%) after flash chromatography on silica gel using P.E./EtOAc as eluent (65/35). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.48 (br s, 0.5H, O*H*), 2.80–2.91 (dd, *J*=5.7 and 4.5 Hz, 0.5H, *H*CO$_2$Me), 2.91–2.97 (dt, *J*=7.2 and 2.1 Hz, 0.5H, *H*CO$_2$Me), 3.01 (br s, 0.5H, O*H*), 3.34 (d, *J*=4.5 Hz, 0.5H, C*H*$_2$OH), 3.63 (d, *J*=5.7 Hz, 1H, C*H*$_2$OH), 3.66 and 3.71 (s, 3H, C*H*$_3$O), 3.75 (br s, 0.5H, O*H*), 3.95 (d, *J*=2.1 Hz, 1H, C*H*$_2$OH), 5.04 (dd, *J*=7.2 and 4.5 Hz, 0.5H, C*H*OH), 5.27 (t, *J*=4.5 Hz, 0.5H, C*H*OH), 7.27–7.35 (m, 5H, C*H*ar.). ^{13}C NMR (75 MHz, $CDCl_3$): δ 52.2 (*C*HCO$_2$Me), 53.4 (O*C*H$_3$), 54.6 (O*C*H$_3$), 60.9 (O*C*H$_2$), 61.6 (O*C*H$_2$), 73.1 (*C*HOH), 74.1 (*C*HOH), 125.9 (*C*Har.), 126.3 (*C*Har.), 127.9 (*C*Har.), 128.2 (*C*Har.), 128.6 (*C*Har.), 128.7 (*C*Har.), 141.4 (*C*ar.), 141.4 (*C*ar.), 173.6 (*C*O$_2$Me), 174.3 (*C*O$_2$Me). LRMS (APCI) *m*/*z*: 103.1 (35%), 131.1 (100%), 163.1 (45%). IR (film, cm^{-1}): 3419, 2952, 1720,

1436, 1197, 1026, 702. HRMS (ESI) calculated for $C_{11}H_{14}O_4Na$ ($[M+Na]^+$) 233.0790, found 233.0800 (4.3 ppm).

4.2.2. Methyl 3-(4-chlorophenyl)-3-hydroxy-2-(hydroxymethyl) propanoate ***13***. The product was isolated using the general procedure as a colourless oil (68%) after flash chromatography on silica gel using P.E./*i*-PrOH as eluent (90/10). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.79–2.94 (m, 1H, *H*CO_2Me), 3.64 and 3.67 (s, 3H, C*H*$_3$O), 3.80–3.90 (m, 2H, C*H*$_2$OH), 5.13 (d, *J*=6.5 Hz, 0.5H, C*H*OH), 5.30 (d, *J*=5.6 Hz, 0.5H, C*H*OH), 7.45 (d, *J*=7.5 Hz, 2H, C*H*ar.), 7.57 (d, *J*=7.5 Hz, 2H, C*H*ar.) ^{13}C NMR (75 MHz, $CDCl_3$): δ 51.0 (*C*HCO_2Me), 51.9 (*C*HCO_2Me), 52.3 (O*C*H$_3$), 61.1 (O*C*H$_2$), 61.6 (O*C*H$_2$), 67.0 (*C*HOH), 68.3 (*C*HOH), 107.1 (*C*Har.), 107.5 (*C*Har.), 110.4 (*C*Har.), 142.3 (*C*ar.), 142.5 (*C*ar.), 153.8 (Cl*C*ar.), 154.2 (Cl*C*ar.), 173.1 (*C*O_2Me), 173.7 (*C*O_2Me). LRMS (CI) *m*/*z*: 244.9 (35%), 226.8 (20%), 212.8 (15%), 196.8 (100%). HRMS (CI) calculated for $C_{11}H_{14}O_4^{35}Cl$ $[M+H]^+$: 245.05806, found: 245.05882 (3.1 ppm). IR (film, cm^{-1}): 3369, 2952, 1728, 1436, 1325, 1261, 1195, 1164, 1120, 1066, 1014, 835, 723.

4.2.3. Methyl 3-hydroxy-2-(hydroxymethyl)-3-(4-(trifluoromethyl) phenyl)propanoate ***14***. The product was isolated using the general procedure as a colourless oil (73%) after flash chromatography on silica gel using P.E./*i*-PrOH as eluent (90/10). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.82 (q, *J*=4.5 Hz, 0.5H, *H*CO_2Me), 2.93 (q, *J*=5.4 Hz, 0.5H, *H*CO_2Me), 3.66 (s, 1.5H, C*H*$_3$O), 3.68 (s, 1.5H, C*H*$_3$O), 3.80–3.98 (m, 2H, C*H*$_2$OH), 5.15 (d, *J*=6.6 Hz, 0.5H, C*H*OH), 5.30 (d, *J*=5.7 Hz, 0.5H, C*H*OH), 7.47 (d, *J*=6.9 Hz, 2H, C*H*ar.), 7.60 (d, *J*=8.1 Hz, 2H, C*H*ar.). ^{13}C NMR (75 MHz, $CDCl_3$): δ 52.2 (*C*HCO_2Me), 53.6 (*C*HCO_2Me), 54.2 (O*C*H$_3$), 60.9 (O*C*H$_2$), 61.3 (O*C*H$_2$), 72.2 (*C*HOH), 73.3 (*C*HOH), 118.7, 122.3, 125.9, 129.5 (q, J_{C-F}=270.6 Hz, *C*F$_3$), 125.4 (*C*Har.), 125.8 (*C*Har.), 126.4 (*C*Har.), 126.6 (*C*Har.), 128.6 (*C*Har.), 128.8 (*C*Har.), 129.9 (q, J_{C-F}=32 Hz, *C*CF$_3$), 130.0 (q, J_{C-F}=32 Hz, *C*CF$_3$), 131.9 (*C*Har.), 132.1 (*C*Har.), 132.2 (*C*Har.), 132.3 (*C*Har.), 145.6 (*C*ar.), 145.7 (*C*ar.), 173.0 (*C*O_2Me), 173.6 (*C*O_2Me). LRMS (CI) *m*/*z*: 278.9 (100%), 230.8 (10%). HRMS (CI) calculated for $C_{12}H_{14}O_4F_3$ $[M+H]^+$: 279.08440, found: 279.08445 (0.02 ppm). IR (film, cm^{-1}): 3369, 2952, 1730, 1325, 1249, 1166, 1120, 1016, 833.

4.2.4. Methy 3-hydroxy-2-(hydroxymethyl)-3-(4-methoxyphenyl)propanoate ***15***. The product was isolated using the general procedure as a colourless oil (74%) after flash chromatography on silica gel using P.E./*i*-PrOH as eluent (90/10). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.78–2.92 (m, 1H, *H*CO_2Me), 3.60 and 3.68 (s, 3H, C*H*$_3$OC(O)), 3.75 (s, 3H, C*H*$_3$OPh), 3.55–3.99 (m, 2H, C*H*$_2$OH), 4.95 (d, *J*=7.7 Hz, 0.5H, C*H*OH), 5.13 (d, *J*=7.3 Hz, 0.5H, C*H*OH), 6.84 (d, *J*=8.2 Hz, 2H, C*H*ar.), 7.23 (d, *J*=7.2 Hz, 2H, C*H*ar.) ^{13}C NMR (75 MHz, $CDCl_3$): δ 52.0 (*C*HCO_2Me), 52.1 (*C*HCO_2Me), 54.1 (O*C*H$_3$), 54.8 (*C*H$_3$OPh), 55.3 (*C*H$_3$OPh), 61.2 (O*C*H$_2$), 61.3 (O*C*H$_2$), 72.5 (*C*HOH), 73.6 (*C*HOH), 113.8 (*C*Har.), 113.9 (*C*Har.), 127.2 (*C*Har.), 127.5 (*C*Har.), 133.5 (*C*ar.), 133.7 (*C*ar.), 159.1 (MeO*C*ar.), 159.3 (MeO*C*ar.), 173.3 (*C*O_2Me), 174.4 (*C*O_2Me). LRMS (CI) *m*/*z*: 240.9 (55%), 192.8 (55%), 160.8 (100%), 128.2 (25%), 137.1 (60%). HRMS (CI) calculated for $C_{12}H_{17}O_5$ $[M+H]^+$: 241.10760, found: 241.10776 (0.66 ppm). IR (film, cm^{-1}): 3421, 2952, 1728, 1514, 1247, 1174, 1029, 833.

4.2.5. Methyl 3-(furan-2-yl)-3-hydroxy-2-(hydroxymethyl)propanoate ***16***. The product was isolated using the general procedure as a colourless oil (77%) after flash chromatography on silica gel using P.E./*i*-PrOH as eluent (90/10). ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.01–3.17 (m, 1H, *H*CO_2Me), 3.71 and 3.74 (s, 3H, C*H*$_3$O), 3.76–4.01 (m, 2H, C*H*$_2$OH), 5.07 (d, *J*=6.6 Hz, 0.5H, C*H*OH), 5.25 (d, *J*=5.6 Hz, 0.5H, C*H*OH), 6.30–6.32 (m, 2H, C*H*ar.), 7.36 (d, *J*=0.6 Hz, 1H, C*H*ar.). ^{13}C NMR (75 MHz, $CDCl_3$): δ 51.0 (*C*HCO_2Me), 51.9 (*C*HCO_2Me), 52.3 (O*C*H$_3$), 61.1 (O*C*H$_2$), 61.5 (O*C*H$_2$), 67.0 (*C*HOH), 68.3 (*C*HOH), 107.1 (*C*Har.), 107.5 (*C*Har.), 110.4 (*C*Har.), 142.3 (*C*Har.), 142.5 (*C*Har.), 153.8 (*C*ar.), 154.2 (*C*ar.), 173.1 (*C*O_2Me), 173.7 (*C*O_2Me). LRMS (CI) *m*/*z*: 200.8 (100%), 182.8 (45%), 154.9 (35%), 152.8 (65%), 138.8 (85%). HRMS (CI) calculated for $C_9H_{13}O_5$ $[M+H]^+$: 201.07630, found: 201.07644 (0.70 ppm). IR (film, cm^{-1}): 3419, 2952, 1728, 1436, 1325, 1261, 1168, 1010, 746.

4.2.6. Methyl 3-hydroxy-2-(hydroxymethyl)-5-phenylpentanoate ***17***. The product was isolated using the general procedure as a colourless oil (67%) after flash chromatography on silica gel using P.E./*i*-PrOH as eluent (90/10). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.80–2.00 (m, 2H, C*H*$_2$CHOH), 2.50–2.75 (m, 2H, C*H*$_2$Ph), 2.80–2.90 (m, 1H, *H*CO_2Me), 3.19 (br s, 2H, O*H*), 3.73 (s, 3H, C*H*$_3$O), 3.87–4.17 (m, 3H, C*H*$_2$OH and C*H*OH), 7.18–7.32 (m, 5H, C*H*ar.). ^{13}C NMR (75 MHz, $CDCl_3$): δ 32.1 (*C*H$_2$Ph), 32.2 (*C*H$_2$Ph), 36.9 (*C*H$_2$CHOH), 37.1 (*C*H$_2$CHOH), 51.9 (*C*HCO_2Me), 52.0 (*C*HCO_2Me), 52.1 (O*C*H$_3$), 52.2 (O*C*H$_3$), 61.0 (O*C*H$_2$), 62.2 (O*C*H$_2$), 70.7 (*C*HOH), 70.9 (*C*HOH), 125.9 (*C*Har.), 128.5 (*C*Har.), 132.0 (*C*Har.), 132.2 (*C*Har.), 141.7 (two peaks) (*C*ar.), 174.0 (*C*O_2Me), 174.1 (*C*O_2Me). LRMS (CI) *m*/*z*: 238.9 (20%), 188.8 (45%), 170.8 (25%), 142.8 (100%). HRMS (CI) calculated for $C_{13}H_{19}O_4$ $[M+H]^+$: 239.12833, found: 239.12782 (2.13 ppm). IR (film, cm^{-1}): 3417, 2950, 1731, 1436, 1336, 1263, 1193, 1068, 1029, 698.

4.2.7. Methyl 3-cyclohexyl-3-hydroxy-2-(hydroxymethyl)propanoate ***18***. The product was isolated using the general procedure as a colourless oil (92%) after flash chromatography on silica gel using P.E./EtOAc as eluent (65/35). ^{1}H NMR (300 MHz, $CDCl_3$): major isomer δ 0.8–2.1 (m, 11H, C*H*cy.), 2.73 (q, *J*=4.2 Hz, 1H, *H*CO_2Me), 3.77 (s, 3H, C*H*$_3$O), 3.84 (dd, *J*1=7.5 Hz, *J*2=4.2 Hz, 1H, C*H*$_2$OH), 4.03 (d, *J*=3.6 Hz, 2H, C*H*$_2$OH and C*H*OH). Minor isomer: δ 0.8–2.1 (m, 11H, C*H*cy.), 2.83 (q, *J*=5 Hz, 1H, *H*CO_2Me), 3.56 (dd, *J*1=7.7 Hz, *J*2=3.5 Hz, 1H, C*H*$_2$OH), 3.76 (s, 3H, C*H*$_3$O), 3.97 (t, *J*=5.5 Hz, 2H, C*H*$_2$OH and C*H*OH). ^{13}C NMR (75 MHz, $CDCl_3$): major isomer δ 25.9 (*C*H$_2$cy.), 26.4 (*C*H$_2$cy.), 29.4 (*C*H$_2$cy.), 41.2 (*C*Hcy.), 48.3 (*C*HCO_2Me), 52.2 (O*C*H$_3$), 61.0 (O*C*H$_2$), 76.7 (*C*HOH), 174.9 (*C*O_2Me). Minor isomer: δ 25.9 (*C*H$_2$cy.), 26.1 (*C*H$_2$cy.), 29.6 (*C*H$_2$cy.), 42.0 (*C*Hcy.), 48.7 (*C*HCO_2Me), 52.0 (O*C*H$_3$), 63.6 (O*C*H$_2$), 76.5 (*C*HOH), 174.5 (*C*O_2Me). LRMS (APCI) *m*/*z*: 216.8 (100%), 198.5 (75%), 100.8 (25%). HRMS (ESI) calculated for $C_{11}H_{20}O_4Na$ ($[M+Na]^+$) 239.1259, found 239.1256 (1.2 ppm). IR (film, cm^{-1}): 3419, 2925, 2852, 1731, 1436, 1259, 1172, 1118, 723, 696.

4.2.8. Methyl 3-hydroxy-2-(hydroxymethyl)-4,4-dimethylpentanoate ***19***. The product was isolated using the general procedure as a colourless oil (70%) after flash chromatography on silica gel using P.E./*i*-PrOH as eluent (90/10). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.90 and 0.91 (s, 9H, (C*H*$_3$)$_3$C), 2.70–2.90 (m, 1H, *H*CO_2Me), 3.05 (br s, 0.5H, O*H*), 3.20 (br s, 0.5H, O*H*), 3.70 and 3.71 (s, 3H, C*H*$_3$O), 3.85–4.10 (m, 3H, C*H*$_2$OH and C*H*OH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 25.9 (*C*H$_3$C), 26.2 (*C*H$_3$C), 29.4 (CH$_3$*C*), 29.8 (CH$_3$*C*), 46.9 (*C*HCO_2Me), 48.4 (*C*HCO_2Me), 52.2 (O*C*H$_3$), 62.6 (O*C*H$_2$), 64.6 (O*C*H$_2$), 78.7 (*C*HOH), 79.1 (*C*HOH), 174.9 (*C*O_2Me), 175.7 (*C*O_2Me). LRMS (CI) *m*/*z*: 191.1 (100%), 173.0 (95%), 155.1 (99%), 141.1 (48%). HRMS (CI) calculated for $C_9H_{19}O_4$ $[M+H]^+$: 191.12833, found: 191.12834 (0.05 ppm). IR (film, cm^{-1}): 3444, 2954, 1733, 1436, 1166, 723.

4.2.9. Methyl 3-hydroxy-2-(hydroxymethyl)-3-phenylbutanoate ***20***. The product was isolated using the general procedure as a colourless oil (76%) after flash chromatography on silica gel using P.E./EtOAc as eluent (65/35). ^{1}H NMR (300 MHz, $CDCl_3$): first isomer: δ 1.60 (s, 3H, C*H*$_3$C), 2.46 (br t, *J*=5.9 Hz, 1H, *H*CO_2Me), 2.95 (dd, *J*1=5.2 and 4.2 Hz, 1H, C*H*$_2$OH), 3.64–3.72 (m, 2H, C*H*$_2$OH and O*H*), 3.81 (s, 3H, C*H*$_3$O), 4.21 (s, 1H, O*H*), 7.26–7.42 (m, 5H, C*H*ar.). Second isomer: δ 1.57 (s, 3H, C*H*$_3$C), 2.62 (br t, *J*=5.3 Hz, 1H, *H*CO_2Me), 3.12 (dd, *J*1=6 Hz, *J*2=4 Hz, 1H, C*H*$_2$OH), 3.52 (s, 3H, C*H*$_3$O), 4.01–4.08 (m, 1H, C*H*$_2$OH), 4.21–4.25 (m, 2H, O*H*), 7.26–7.40 (m, 5H, C*H*ar.). ^{13}C NMR (75 MHz, $CDCl_3$): first isomer: δ 30.2 (*C*CH$_3$), 52.3 (O*C*H$_3$), 56.1 (*C*HCO_2Me), 62.2 (*C*H$_2$OH), 75.6 (*C*OH), 124.6 (*C*Har.), 127.2 (*C*Har.),

128.6 (CHar.), 145.0 (Car.), 175.1 (CO_2Me). Second isomer: δ 28.1 (CCH_3), 52.1 (OCH_3), 55.7 ($CHCO_2Me$), 61.7 (CH_2OH), 75.6 (COH), 124.4 (CHar.), 127.2 (CHar.), 128.4 (CHar.), 147.0 (Car.), 174.7 (CO_2Me). LRMS (CI) *m/z*: 117.2 (25%), 107.2 (50%), 105.7 (25%), 89 (30%), 70.9 (100%). HRMS (ESI) calculated for $C_{12}H_{16}O_4Na$ ($[M+Na]^+$): 247.0946, found 247.0943 (1.2 ppm). IR (film, cm^{-1}): 3419, 2952, 1720, 1436, 1197, 1026, 702.

4.2.10. Methyl 3-hydroxy-2-(1-hydroxycyclohexyl)propanoate ***21***. The product was isolated using the general procedure as a colourless oil (89%) after flash chromatography on silica gel using P.E./EtOAc as eluent (65/35). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.10–1.80 (m, 10H, CHcy.), 2.64 (dd, *J*=6.2 and 4.1 Hz, 1H, HCO_2Me), 3.40 (br s, 1H, OH), 3.76 (s, 3H, CH_3O), 3.96 (dd, *J*=11.3 and 4.1 Hz, 1H, CH_2O), 4.12 (dd, *J*=11.3 and 6.2 Hz, 1H, CH_2O). ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.7 (CH_2cy.), 25.6 (CH_2cy.), 35.3 (CH_2cy.), 37.0 (CH$_2$cy.), 52.0 (OCH_3), 55.0 ($CHCO_2Me$), 60.9 (OCH_2), 72.6 (HOC), 175.0 (CO_2Me). LRMS (CI) *m/z*: 202.3 (20%), 185.3 (100%), 167.3 (65%), 103.9 (30%), 99.0 (30%). IR (film, cm^{-1}): 3415, 2931, 2860, 1716, 1436, 1359, 1257, 1197, 1170, 1149, 1037, 1020. HRMS (ESI) calculated for $C_{10}H_{18}O_4Na$ ($[M+Na]^+$) 225.1103, found 225.1103 (0 ppm).

4.2.11. Methyl 3-hydroxy-2-(hydroxymethyl)-2-methyl-3-phenylpropanoate ***22***. The product was isolated using the general procedure as a colourless oil (79%) after flash chromatography on silica gel using P.E./EtOAc as eluent (65/35). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.93 (s, 1.5H, CH_3C), 1.08 (s, 1.5H, CH_3C), 3.40 (br s, 2H, OH), 3.51 (d, *J*=11.3 Hz, 0.5H, CH_2OH), 3.67–3.85 (m, 4.5H, CH_2OH and CH_3O), 5.11 (s, 0.5H, CHOH), 5.13 (s, 0.5H, CHOH), 5.28–5.40 (m, 5H, CHar.). ^{13}C NMR (75 MHz, $CDCl_3$): δ 15.1 (CCH_3), 17.1 (CCH_3), 52.1 (OCH_3), 52.3 (OCH_3), 52.4 (CCH_3), 52.8 (CCH_3), 65.9 (OCH_2), 67.1 (OCH_2), 76.5 (OCH), 78.8 (OCH), 126.3 (CHar.), 127.0 (CHar.), 127.4 (CHar.), 127.9 (CHar.), 128.0 (CHar.), 128.1 (CHar.), 139.3 (Car.), 139.7 (Car.), 176.6 (CO_2Me), 176.7 (CO_2Me). LRMS (APCI) *m/z*: 225.2 (32%), 207.1 (11%), 177.2 (100%). HRMS (ESI) calculated for $C_{12}H_{16}O_4Na$ ($[M+Na]^+$) 247.0946, found 247.0945 (0.4 ppm). IR (film, cm^{-1}): 3394, 2950, 1716, 1454, 1234, 1118, 1039, 732, 703.

4.2.12. 4-Hhydroxy-3-(hydroxymethyl)-4-phenylbutan-2-one ***25***. The product was isolated using the general procedure as a colourless oil (69%) after flash chromatography on silica gel using P.E./*i*-PrOH as eluent (85/15). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.95 (s, 1.5H, CH_3), 2.13 (s, 1.5H, CH_3), 2.87–2.94 (m, 0.5H, CHC(O)), 3.00–3.08 (m, 0.5H, CHC(O)), 3.56 (d, *J*=5.7 Hz, 1H, CH_2OH), 3.86 (d, *J*=4.4 Hz, 1H, CH_2OH), 4.91 (d, *J*=7.5 Hz, 0.5H, CHOH), 5.10 (d, *J*=6.4 Hz, 0.5H, CHOH), 7.27–7.55 (m, 5H, CHar.). ^{13}C NMR (75 MHz, $CDCl_3$): δ 30.6 (CH_3), 32.3 (CH_3), 60.7 (CHC(O)), 60.8 (CHC(O)), 61.1 (OCH_2), 61.3 (OCH_2), 73.0 (CHOH), 73.7 (CHOH), 126.0 (CHar.), 126.1 (CHar.), 127.6 (CHar.), 127.8 (CHar.), 128.4 (CHar.), 128.5 (CHar.), 130.9 (Car.), 132.3 (Car.), 210.5 (C=O), 213.2 (C=O). LRMS (CI) *m/z*: 195.1 (0.7%), 117.1 (100%), 107.0 (46%), 70.8 (31%). HRMS (ESI) calculated for $C_{11}H_{14}O_3Na$ ($[M+Na]^+$) 217.0841, found 217.0842 (0.4 ppm). IR (film, cm^{-1}): 3386, 1701, 1436, 1357, 1164, 1056, 912, 721, 694.

4.2.13. 3-Hydroxy-2-(hydroxymethyl)-3-phenylpropanenitrile ***26***. The product was isolated using the general procedure as a colourless oil (76%) after flash chromatography on silica gel using P.E./*i*-PrOH as eluent (90/10). N.B. Due to interaction in solution, peaks are widely broadened. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.95 (br s, 1H, HCN), 3.84–4.20 (br m, 2.5H, CH_2OH and CHOH), 5.04 (br m, 0.5H, CHOH), 7.30–7.60 (m, 5H, CHar.). ^{13}C NMR (75 MHz, $CDCl_3$): δ 42.7 (CHCN), 43.7(CHCN), 60.3 (OCH_2), 60.9 (OCH_2), 71.1 (OCH), 72.2 (OCH), 126.0 (CHar.), 126.5 (CHar.), 128.5 (CHar.), 128.8 (CHar.), 132.1(CHar.), 132.6 (CHar.), 140.3 (Car.), 140.6 (Car.). LRMS (CI) *m/z*: 178.1 (3%), 130.1 (18%), 107.0 (51%), 101.0 (100%). HRMS (ESI) calculated for $C_{10}H_{11}NO_2Na$ ($[M+Na]^+$) 200.0687, found 200.0681 (3.0 ppm). IR (film, cm^{-1}): 3369, 2246, 1436, 1338, 1149, 1120, 1070, 910, 723, 694.

4.2.14. 3-Hydroxy-2-(hydroxymethyl)-N-methoxy-N-methyl-3-phenylpropanamide ***27***. The product was isolated using the general procedure as a colourless oil (73%) after flash chromatography on silica gel using P.E./*i*-PrOH as eluent (85/15). ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.14 (s, 3H, CH_3N), 3.20 (br s, 1H, OH), 3.57 (s, 3H, CH_3O), 3.68–3.75 (m, 1H, CHC(O)), 4.60–4.80 (m, 3H, CH_2OH and OH), 5.07 (d, *J*=5.2 Hz, 1H, CHOH), 7.27–7.45 (m, 5H, CHar.). ^{13}C NMR (75 MHz, $CDCl_3$): δ 32.2 (NCH_3), 46.4 (HCC(O)), 61.7 (CH_2OH), 65.9 (OCH_3), 72.6 (CHOH), 126.0 (CHar.), 128.3 (CHar.), 128.7 (CHar.), 140.5 (Car.), 174.5 (C(O)). LRMS (CI) *m/z*: 240.3 (100%), 229.2 (15%), 101.1 (15%), 100.2 (45%). HRMS (ESI) calculated for $C_{12}H_{17}NO_4Na$ ($[M+Na]^+$) 262.1055, found 262.1047 (3.0 ppm). IR (film, cm^{-1}): 3350, 2923, 2850, 1633, 1448, 1419, 1384, 1178, 1110, 989.

4.2.15. Ethyl 3-cyclohexyl-3-hydroxy-2-(hydroxymethyl)-2-methylpropanoate ***29***. The product was isolated using the general procedure as a colourless oil (89%) after flash chromatography on silica gel using P.E./EtOAc as eluent (65/35). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.10–1.95 (m, 17H, CHcy., CH_3CH_2 and CH_3C), 3.16 (br s, 1H, OH), 3.50–3.55 (m, 1H, CHOH), 3.65–3.85 (m, 2H, CH_2OH), 4.10–4.25 (m, 2H, CH_3CH_2). ^{13}C NMR (75 MHz, $CDCl_3$): δ 15.4 (CH_3CH_2), 17.9 (CH_3CH_2), 20.1 (CH_3C), 26.1 (CH_2cy.), 26.3 (CH_2cy.), 26.6 (CH_2cy.), 26.7 (CH_2cy.), 31.3 (CH_2cy.), 31.6 (CH_2cy.), 40.3 (CHcy.), 40.5 (CHcy.), 50.4 (CCO_2Et), 51.4 (CCO_2Et), 61.1 (CH_2OH), 67.7 (CH_3CH_2), 68.8 (CH_3CH_2), 79.0 (CHOH), 80.4 (CHOH), 176.5 (CO_2Et), 176.6 (CO_2Et). LRMS (APCI) *m/z*: 287.0 (100%), 286.0 (55%). IR (film, cm^{-1}): 3440, 2923, 2852, 1722, 1448, 1413, 1247, 1103, 1027, 985.

4.2.16. 4-Cyclohexyl-4-hydroxy-3-(hydroxymethyl)butan-2-one ***30***. The product was isolated using the general procedure as a colourless oil (77%) after flash chromatography on silica gel using P.E./EtOAc as eluent (65/35). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.85–2.05 (m, 11H, CHcy.), 2.27 and 2.28 (s, 3H, CH_3CO), 2.72 (q, *J*=3.5 Hz, 0.5H, CHCO), 2.96 (q, *J*=4.7 Hz, 0.5H, CHCO), 3.53 (dd, *J*=7.0 and 4.1 HZ, 0.5H, CH_2OH), 3.50–4.10 (m, 2.5H, CH_2OH and CHOH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 24.9 (CH_2cy.), 25.9 (CH_2cy.), 26.1 (CH_2cy.), 26.2 (CH_2cy.), 26.4 (CH_2cy.), 29.2 (CH_3CO), 29.3 (CH_2cy.), 29.5 (CH_2cy.), 32.0 (CH_3CO), 41.2 (CHcy.), 41.9 (CHcy.), 54.9 (CHCO), 55.0 (CHCO), 60.6 (CH_2OH), 63.4 (CH_2OH), 76.1 (CHOH), 77.4 (CHOH), 207.9 (C=O), 211.7 (C=O). LRMS (CI) *m/z*: 201.0 (30%), 183.0 (20%), 70.8 (100%). IR (film, cm^{-1}): 3409, 2925, 1701, 1421, 1353, 1261, 1174, 1118, 1026, 800, 721, 694.

4.2.17. 3-Cyclohexyl-3-hydroxy-2-(hydroxymethyl)propanenitrile ***31***. The product was isolated using the general procedure as a colourless oil (87%) after flash chromatography on silica gel using P.E./EtOAc as eluent (65/35). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.90–2.05 (m, 11H, CHcy.), 2.85–3.00 (m, 1H, CHCN), 3.50–4.10 (m, 5H, CH_2OH, CHOH and OH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 25.6 (CH_2cy.), 25.9 (CH_2cy.), 26.2 (CH_2cy.), 29.0 (CH_2cy.), 29.9 (CH_2cy.), 37.7 (CHCN), 38.2 (CHCN), 41.1 (CHcy.), 42.0 (CHcy.), 60.1 (CH_2OH), 61.5 (CH_2OH), 73.5 (CHOH), 74.0 (CHOH), 118.9 (CN), 119.9 (CN). LRMS (APCI) *m/z*: 183.9 (40%), 165.9 (100%). IR (film, cm^{-1}): 3398, 2925, 2852, 2244, 1448, 1062, 1047, 725.

4.2.18. 3-Cyclohexyl-3-hydroxy-2-(hydroxymethyl)-N-methoxy-N-methylpropanamide ***32***. The product was isolated using the general procedure as a colourless oil (73%) after flash chromatography on silica gel using P.E./EtOAc as eluent (55/45). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.85–2.10 (m, 11H, CHcy.), 3.18–3.25 (m, 4H, CH_3N and CHC(O)), 3.60–3.80 (m, 4H, CH_3O and CHOH), 3.92–4.10 (m, 2H, CH_2OH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 26.0 (CH_2cy.), 26.2 (CH_2cy.),

26.5 (CH_2cy.), 28.8 (CH_2cy.), 29.6 (CH_2cy.), 34.2 (NCH_3), 41.1 (*C*Hcy.), 43.8 (HCC(O)), 61.3 (CH_2OH), 61.7 (OCH_3), 76.3 (*C*HOH), 174.5 (*C*(O)). LRMS (CI) *m*/*z*: 246.0 (60%), 228.0 (100%), 209.8 (75%), 198.2 (35%). IR (film, cm^{-1}): 3438, 2923, 2852, 1631, 1390, 1176, 1101, 1022, 798.

4.2.19. 3-Hydroxy-2-(hydroxymethyl)-N-methoxy-3-(4-methoxyphenyl)-N-methylpropanamide ***33***. The product was isolated using the general procedure as a colourless oil (48%) after flash chromatography on silica gel using P.E./*i*-PrOH as eluent (80/20). ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.11 (s, 3H, CH_3N), 3.27 (m, 1H, *CH*C(O)), 3.52 (s, 3H, CH_3ON), 3.79 (s, 3H, CH_3OAr), 3.93–4.02 (m, 2H, CH_2OH), 5.17 (d, *J*=5.9 Hz, 1H, *CH*OH), 6.87 (m, 2H, *CH*Ar), 7.30 (m, 2H, *CH*Ar). ^{13}C NMR (75 MHz, $CDCl_3$): δ 31.9 (NCH_3), 49.5 (HCC(O)), 55.4 (CH_2OH), 61.6 ($COCH_3$), 62.2 ($NOCH_3$), 73.1 (*C*HOH), 113.9 (*C*HAr), 127.3 (*C*HAr), 134.1 (*C*COH), 159.2 (*C*OCH_3), 174.5 (*C*(O)). HRMS (CI) calculated for $C_{13}H_{20}NO_5$ ($[M+H]^+$) 270.13415, found 270.13472 (2.11 ppm). IR (film, cm^{-1}): 3402, 2922, 2853, 1720, 1629, 1512, 1461, 1247, 1176, 835.

4.2.20. 3-Hydroxy-2-(hydroxymethyl)-N-methoxy-N-methyl-3-(thiophen-2-yl)propanamide ***34***. The product was isolated using the general procedure as a colourless oil (55%) after flash chromatography on silica gel using P.E./*i*-PrOH as eluent (90/10). ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.13 (s, 3H, CH_3N), 3.32 (m, 1H, *CH*C(O)), 3.53 (s, 3H, CH_3O), 3.97–4.02 (m, 2H, CH_2OH), 5.46 (d, *J*=6.8 Hz, 1H, *CH*OH), 6.94–7.02 (m, 2H, *CH*Ar), 7.21–7.23 (m, 1H, *CH*S). ^{13}C NMR (75 MHz, $CDCl_3$): δ 32.1 (NCH_3), 49.8 (HCC(O)), 62.0 (CH_2OH), 69.8 (OCH_3), 70.9 (*C*HOH), 124.5 (*CH*Ar), 125.0 (*CH*Ar), 127.0 (*CH*Ar), 146.2 (*C*COH), 174.5 (*C*(O)). HRMS (CI) calculated for $C_{10}H_{16}NSO_4$ ($[M+H]^+$) 246.08000, found 246.07938 (2.52 ppm). IR (film, cm^{-1}): 3332, 2953, 1628, 1437, 1391, 1307, 1180, 1059, 986, 748.

4.3. Determination of relative configurations

The diol (0.5 mmol, 1 equiv) was dissolved in 2,2-dimethoxypropane (2 mL, 16.2 mmol, 32.4 equiv). A catalytic amount of PTSA was added and the solution was stirred overnight. Then, solid anhydrous K_2CO_3 (500 mg) was added and the reaction was stirred for 1 h. The solids were filtered, and the product was concentrated under reduced pressure.

4.3.1. Acetonide ***28***. The product was isolated as a 2/1 *trans*/*cis* mixture as a colourless oil (quantitative) after chromatography using P.E./EtOAc as eluent (90/10). ^{1}H NMR (300 MHz, $CDCl_3$): δ trans: 1.53 (s, 3H, CH_3C), 1.65 (s, 3H, CH_3C), 2.99 (s, 3H, NCH_3), 3.14 (s, 3H, OCH_3), 3.27–3.42 (m, 1H, *CH*C(O)N), 3.96 (dd, *J*=11.4 and 5.1 Hz, 1H, CH_2OH), 4.20 (t, *J*=11.4 Hz, 1H, CH_2OH), 5.23 (d, *J*=10.4 Hz, 1H, *CH*OH) 7.19–7.45 (m, 5H, *CH*ar.). Full spectral data of the cis isomer could not be determined.

4.3.2. Acetonide ***38***. The compound was isolated as a colourless oil (44%) by chromatography using P.E./ether as eluent (90/10). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.49 (s, 3H, CH_3C), 1.57 (s, 3H, CH_3C), 1.81–2.30 (m, 6H, CH_2cy.), 2.77 (dd, *J*=10.5 and 10.4 Hz, 1H, *CH*C=O), 3.95 (dt, *J*=10.7 and 3.7 Hz, 1H, *CH*O), 5.13 (d, *J*=10.3 Hz, 1H, PhC*H*O), 7.20–7.51 (m, 5H, *CH*ar.). ^{13}C NMR (75 MHz, $CDCl_3$): 19.7 (CCH_3), 22.1 (CH_2cy.), 30.1 (CCH_3), 31.9 (CH_2cy.), 42.1 ($COCH_2$cy.), 60.3 (*C*HC=O), 71.3 (*C*HO), 73.4 (PhCHO), 99.3 (*C*$(CH_3)_2$), 128.0 (*C*Har.), 128.4 (*C*Har.), 128.6 (*C*Har.), 140.5 (*C*ar.), 207.7 (*C*=O). LRMS (CI) *m*/*z*: 261, 203, 185. IR (film, cm^{-1}): 3651, 2945, 2868, 1712, 1381, 1261, 1199, 1090, 1026, 752, 698.

4.4. Application in Suzuki coupling

4.4.1. Methyl 2-benzyl-3-hydroxy-3-phenylpropanoate ***41***. A modified procedure from the literature was used.[24] A Schlenk tube was loaded with [$(Ph_3P)_3$CuF·2MeOH] (9.3 mg, 0.01 mmol, 0.02 equiv) and (*rac*)-BINAP (6.2 mg, 0.01 mmol, 0.02 equiv). The system was closed with a septum and after 3 vacuum/argon cycles, THF (2.5 mL) was added by syringe. After dissolution of the solids, methyl acrylate (45 μL, 0.5 mmol, 1 equiv) and benzaldehyde (50 μL, 0.5 mmol, 1 equiv) were added. Bis(pinacolato)diboron (152 mg, 0.6 mmol, 1.2 equiv) was then added, and the mixture was stirred for 1 h. The solvent was removed under reduced pressure and tetrakis(-triphenylphosphine) palladium (57 mg, 0.05 mmol, 0.1 equiv) and caesium fluoride (303 mg, 2 mmol, 4 equiv) were introduced in the flask. The system was closed and after 3 vacuum/argon cycles, DMF (5 mL) and iodobenzene (111 μL, 1 mmol, 2 equiv) were added by syringe. The solution was heated at 100 °C overnight and the product was isolated as separable diastereoisomers as an uncoloured foam (89%) after flash chromatography. ^{1}H NMR (300 MHz, $CDCl_3$): δ first fraction: 2.97–3.09 (br m, 4H, CH_2Ph *H*CO_2Me and O*H*), 3.43 (s, 3H, CH_3O), 5.05 (d, *J*=4.8 Hz, 1H, *CH*OH), 7.10–7.45 (m, 10H, *CH*ar.) Second fraction: 2.73 (dd, *J*=13.5 and 5.8 Hz, 1H, CH_2Ph), 2.90 (dd, *J*=13.5 and 9.7 Hz, 1H, CH_2Ph), 3.04–3.10 (m, 2H, *H*CO_2Me and O*H*), 3.53 (s, 3H, CH_3O), 4.82 (d, *J*=6.9 Hz, 1H, *CH*OH), 7.10–7.50 (m, 10H, *CH*ar.). Spectral data are identical those found in the literature.[26]

4.5. Modification of the Weinreb amide

4.5.1. 4-Hydroxy-3-(hydroxymethyl)-4-phenylbutan-2-one ***25***. The general procedure for the coupling of benzaldehyde (53 mg, 0.5 mmol), Weinreb acrylamide (57 mg, 0.5 mmol, 1 equiv) and diboron **3** (152 mg, 0.6 mmol, 1.2 equiv) was carried out in 3 mL of THF for 5 h. The flask was cooled to −78 °C and 1.56 mL of a 1.6 M methyl lithium solution in diethyl ether (2.5 mmol, 5 equiv) was added dropwise at this temperature. The reaction was stirred at this temperature for 1 h and the cooling bath was removed. 250 mg of sodium perborate (2 mmol, 4 equiv) and 3 mL water were added and the biphasic mixture was stirred at room temperature overnight. After ether extraction and standard work up, the crude reaction mixture was purified by flash chromatography on silica gel using P.E./*i*-PrOH as eluent (90/10). The desired keto-diol **25** was isolated as a light yellow oil in a 48% yield.

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