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Hydrogenation of BF_2 complexes with 1,3-dicarbonyl ligands

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ABSTRACT

The catalytic hydrogenation (H_2, Pd/C) of a set of BF_2 complexes with a 1,3-dicarbonyl structural unit leading to monocarbonyl compounds has been studied. The transformation presented is general for the aryl-substituted derivatives and occurs under mild conditions (H_2, 1 bar, 25 °C) in methanol or THF.

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1. Introduction

The catalytic hydrogenation of 1,2- and 1,3-diketo derivatives employing a variety of catalysts, including copper, nickel, cobalt, platinum, palladium and other metals, has been well documented.[1] The early investigations of Pd-catalyzed hydrogenations revealed a strong connection between the preparation of the palladium-on-carbon catalyst and the structure–reactivity dependence of the carbonyl compound on the outcome of the reaction.[2] The difference between aliphatic and aromatic carbonyls is marked, and catalyst preference differs. The hydrogenation of aromatic carbonyls occurs mainly by conversion to the benzyl alcohols. When hydrogenolysis is desired it is facilitated by strong acids and elevated temperature.[3] To the best of our knowledge, no examples of the reduction of BF_2 complexes derived from 1,3-dicarbonyls had been reported at the outset of our study. However, their preparation proved facile, as might have been anticipated on the basis of the isolation of these complexes derived from 1,3-diketones.[4] Such BF_2 complexes are very often recognized as intermediates in the boron trifluoride-catalyzed acylation of ketones with anhydrides.[5] The best procedure for their preparation is the treatment of methylene chloride or toluene solutions of the corresponding 1,3-dicarbonyls with 1.5–2.0 equiv of boron trifluoride etherate at room temperature.[6] Using this method, crystalline BF_2 complexes are obtained in excellent yields. Until now a hydrolysis to the parent 1,3-dicarbonyl compounds was the only studied chemistry of these species. Recently, we reported on the transformations of **1** and **5** using a variety of nitrogen nucleophiles, providing enaminones, β-ketoamides and nitrogen heterocycles.[6a,c,d] Additionally, at the same time, Christoffers et al. reported on β-diketonatoboron difluorides as intermediates in an asymmetric Michael reaction.[6b] Furthermore, our methodology was recently applied by Garcia-Garibay et al. for the synthesis of (+) and (−)-α-cuparenone.[7]

2. Results and discussion

Herein, we demonstrate the reactivity of structurally different (alkyl-, aryl-, alkoxy- and alkylamino-substituted) BF_2 complexes with 1,3-dicarbonyl ligands under catalytic hydrogenation conditions, enabling a facile approach towards the corresponding mono carbonyl compounds. The initial experiments to determine the optimal reaction conditions were carried out on 1,3-diketonatoboron difluorides **1a** and **1b** (Scheme 1). The treatment of **1a** with H_2 (1 bar) in MeOH or THF solutions at room temperature in the presence of Pd (10% on carbon) resulted, after 24 h, in the complete deoxygenation of substrate **1a**, thus giving 1,3-diphenylpropane (**2a**) in an excellent yield. The same procedure applied to the methyl and *n*-butyl analogues **1b** and **1c** yielded the corresponding alcohols **2b** and **2c** as the sole products.

1a; R = Ph
1b; R = Me
1c; R = *n*-Bu

2a; R = Ph, R^1 = H; 88%
2b; R = Me, R^1 = OH; 98%
2c; R = *n*-Bu, R^1 = OH; 71%

Scheme 1. Catalytic hydrogenation of BF_2 complexes **1**.

Recent publications on the reductive deoxygenation of ketoamides and esters involved SmI_2 additives[8] and $Ru_3(CO)_{12}$,[9] providing monocarbonyl compounds together with the corresponding hydroxy and dihydroxy derivatives. As shown in Table 1, we applied our conditions to 1,3-ketoamide and ester substrates. Under the described reaction conditions the difluoroboron complex **5a** undergoes the same β-deoxygenation process, giving a synthetically useful building block, **6a**.[10] To establish whether investigated BF_2

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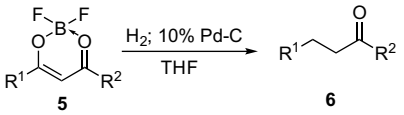
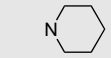
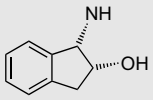
Table 1
Hydrogenation of various BF_2 complexes **4**

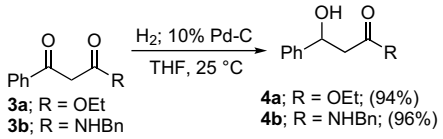


5 **6**

Compounds **5** and **6**	R^1	R^2	Yield[a]
a	C_6H_5	OEt	66
b	4-$MeOC_6H_4$	OEt	83
c	C_6H_5	NH*i*-Pr	88
d	C_6H_5	NEt_2	92
e[b]	C_6H_5	$NHCH_2CH{=}CH_2$	92
f[b]	4-$MeOC_6H_4$	$NHCH_2CH{=}CH_2$	89
g	C_6H_5		87
h	C_6H_5	NHBn	91
i	C_6H_5		89

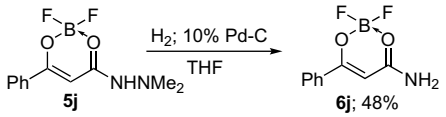
[a] Yields of isolated products are given.
[b] 2-Propene unit is also hydrogenated resulting in R^2=NH*n*-Pr, **6e** and **6f**.

chelates show different reactivity comparing to 1,3-diketo derivatives, we have performed the control experiment employing a treatment of ethyl 3-oxo-3-phenylpropanoate (**3a**) and *N*-benzyl-3-oxo-3-phenylpropanamide (**3b**) under the same reaction conditions.



Scheme 2. Catalytic hydrogenation of **3a** and **3b**.

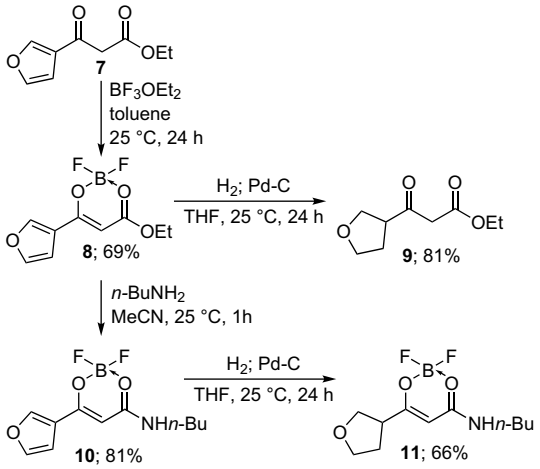
The hydrogenation resulted in the formation of ethyl 3-hydroxy-3-phenylpropanoate (**4a**, 94%) and *N*-benzyl-3-hydroxy-3-phenylpropanamide (**4b**, 96%), respectively (Scheme 2).[11] These results are different from that discussed by Hirota et al.,[12] wherein deoxygenated products were obtained using Pd/C as a catalyst. On the other hand, benzoyl–benzyl transformations may not always be straightforward processes,[13] especially when other functional groups, such as benzyl moiety, as in our case (Table 1, example **h** and **i**), are present. However, the above control experiments, testing two different 1,3-dicarbonyls, confirmed the enhanced reactivity of BF_2 complexes compared to the uncoordinated 1,3-ketoesters and 1,3-ketoamides. Further, we examined if we could extend this methodology to BF_2 complexes derived from β-ketoamides. The latter have been prepared using the methodology, recently described by us and Christoffers et al., starting from the corresponding β-ketoester–BF_2 complexes and alkyl amines.[6b–d] Under standard reaction conditions (1 bar H_2, 10% Pd/C, THF, 25 °C, 5–24 h) **5c** underwent a smooth reduction, forming the corresponding amide **6c** in a good yield. As shown in Table 1, this hydrogenation procedure can be successfully applied to a range of amido BF_2 complexes bearing different substituents, thus forming the corresponding 3-arylpropanamides **6c**–**6i** in excellent yields. Additionally, with the examples **5e** and **5f**, a simultaneous reduction of the allylamino moiety occurred (Table 1, example **e** and **f**). As is evident from the literature, **6i** has been the subject of numerous patent applications in connection with indinavir and indinavir-like compounds. Asymmetric alkylations and aminations of chiral amide cuprates derived from **6i** were achieved in excellent yields and



Scheme 3. Catalytic hydrogenation of hydrazido derivative **3j**.

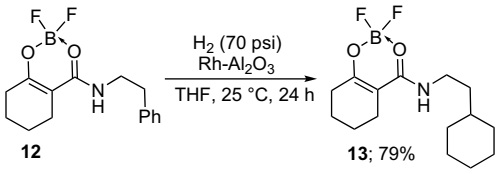
stereoselectivity.[14] Herein, we describe an alternative approach to **6i**, starting with the β-ketoester–BF_2 complex **5i**. It is worth mentioning that under the applied reaction conditions (H_2, 1 bar, THF, 25 °C, 5–24 h) no hydrogenolysis of the benzylic moiety in **6h** and **6i** is observed. The hydrazido derivative **5j** underwent a N–N cleavage reaction, resulting in the formation of the amido product **6j**, with the –O–B(F_2)–O= moiety retained (Scheme 3).

In addition, substrates **8** and **10**, containing the furan-3-yl moiety, were readily reduced to tetrahydrofuranyl derivatives without affecting the 1,3-dicarbonyl moiety. The isolated BF_2 amido complex **11** showed, under the conditions of the reaction workup, a greater stability than the initially reduced ester analogue of **8**, which led to ethyl 3-oxo-3-(tetrahydrofuran-3-yl)propanoate (**9**) as the final product (Scheme 4).



Scheme 4. Catalytic hydrogenation of 3-furanyl derivatives.

We also turned our attention to the amido complex **12**. After several attempts to obtain the reduction product we changed the catalyst from Pd/C to Rh/Al_2O_3 and applied a longer reduction time and higher H_2 pressures. In the latter case, only the reduction of the phenyl ring occurred, leaving the –O–B(F_2)–O= structural unit intact (Scheme 5).



Scheme 5. Catalytic hydrogenation of **12**.

The examples **10** and **12**[6d] seem to open up the possibility of employing certain BF_2 complexes as protecting groups in the 1,3-dicarbonyl chemistry.

3. Conclusions

In summary, we have presented a new transformation of 1,3-dicarbonyl–BF_2 chelates under very mild reaction conditions using

a H_2, Pd/C catalyst. This reaction was demonstrated on a series of aryl-substituted derivatives and it was found to be, to a certain extent, substrate dependent. The method could produce several industrially and pharmaceutically important substances in a straightforward manner. The experiments revealed that the –O–BF_2–O═ moiety can be applied in certain cases as a protecting group for 1,3-dicarbonyls under the appropriate reaction conditions.

4. Experimental

4.1. General methods

Solvents and starting compounds were obtained from commercial sources (Fluka, Sigma and Aldrich). Light petroleum refers to the fraction with the boiling point 40–60 °C. TLC was carried out on Fluka silica-gel TLC-cards. All mps were determined on a hot stage apparatus and are uncorrected. IR spectra were recorded on a BioRad FTS 3000MX instrument. NMR spectra were recorded on a Bruker Avance 300 DPX spectrometer at 302 K. Chemical shifts are reported in δ ppm, referenced to an internal TMS standard for ^{1}H NMR, chloroform-*d* (δ 77.0), DMSO-d_6 (δ 39.5) for ^{13}C NMR. Microanalyses were performed on a Perkin–Elmer 2400 series II CHNS/O analyser. Mass spectra and high-resolution mass measurements were performed on a VG-Analytical Autospec EQ instrumet.

4.2. General procedure for the hydrogenation of BF_2 complexes

The BF_2 complex (1 mmol) in THF (10 mL) was added to 10% Pd/C (100 mg), or Rh/Al_2O_3 (50 mg) in the case of **12**, and the mixture was hydrogenated for 5–24 h at room temperature and 1 bar, or 4.83 bar (70 psi) in the case of **12**. The suspension was filtered through a pad of Celite and washed with MeOH (100 mL). The solvent was removed under a reduced pressure, and the residue was purified by silica gel column chromatography to give pure products.

*4.2.1. 1,3-Diphenylpropane (**2a**)*[15a]

Preparation of the title compound according to the general procedure described above gave, after purification on SiO_2 (EtOAc/petroleum ether=1:7), 172 mg (88%) of a colourless oil. R_f=0.61 (EtOAc/petroleum ether=1:7). IR (NaCl-plates): 3062, 3026, 2932, 2856, 1601, 1495, 1453, 1080, 1028, 745, 698 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.88–1.98 (m, 2H, –$CH_2CH_2CH_2$–), 2.62 (t, J=7.5 Hz, 4H, –$CH_2CH_2CH_2$–), 7.12–7.27 (m, 10H, –*Ph*).

*4.2.2. Phenylbutan-2-ol (**2b**)*[15b]

Purification on SiO_2 (EtOAc/petroleum ether=3:5) gave 147 mg (98%) of a yellowish oil. R_f=0.54 (EtOAc/petroleum ether=3:5). IR (NaCl-plates): 3367, 3027, 2966, 2928, 1603, 1495, 1454, 1373, 1126, 1055, 745, 699 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.21 (d, J=6.0 Hz, 3H, –CH_3), 1.71–1.79 (m, –CH_2CH(OH)CH_3), 1.82–1.85 (br s, 1H), 2.65–2.87 (m, 2H, PhCH_2–), 3.61–3.69 (m, 1H, –CH_2CH(OH)CH_3), 7.18–7.33 (m, 5H, –*Ph*).

*4.2.3. 1-Phenyheptan-3-ol (**2c**)*[15c]

The crude material obtained was purified on SiO_2 (EtOAc/petroleum ether=1:5) to give 137 mg (71%) of **2c** as a colourless oil. R_f=0.21 (EtOAc/petroleum ether=1:5). IR (NaCl-plates): 3391, 2931, 2859, 1547, 1455, 1032, 993, 745, 699 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.93 (t, J=7.0 Hz, 3H, –CH_3), 1.34–1.51 (series of m, 7H, –CH(OH)(CH_2)$_3$), 1.74–1.84 (m, 2H, –CH_2CH(OH)–), 2.65–2.80 (m, 2H, PhCH_2–), 3.75–3.86 (m, 1H, –CH_2CH(OH)CH_2–), 7.14–7.30 (m, 5H, –*Ph*).

4.3. General procedure for the preparation of BF_2 complexes

To a solution of the corresponding amine (1.3 mmol) in MeCN (5 mL), 2,2-difluoro-4-ethoxy-1,3,2-dioxaborinane **5b** (1.0 mmol) was added at room temperature. The reaction mixture was stirred at room temperature for 1 h. After the reaction was complete, the reaction mixture was concentrated in vacuo and the residue was treated with Et_2O (10 mL) and filtered off yielding pure product.

*4.3.1. [N-Allyl-3-(hydroxy-κO)-3-(4-methoxyphenyl)-acrylamidato-κO′](difluoro)boron (**5f**)*

A yellowish solid (197 mg, 70%). R_f=0.18 (EtOAc/petroleum ether=3:5). IR (KBr): 3387, 3022, 1616, 1531, 1506, 1436, 1335, 1268, 1234, 1180, 934, 837, 785, 651 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.83 (s, 3H, –OCH_3), 4.03–4.06 (m, 2H, –CH═CH_2), 5.20–5.30 (m, 2H, –NHCH_2–), 5.76–5.91 (m, 1H, –CH═CH_2), 5.87 (s, 1H, PhC(O)═CHCONH–), 6.66 (t, J=5.5 Hz, 1H, –NH–), 6.86 (AA′XX′, J=8.5 Hz, 2H, –*Ph*), 7.80 (AA′XX′, J=8.5 Hz, 2H, –*Ph*). ^{13}C NMR (300 MHz, $CDCl_3$): δ 43.2, 55.4, 114.0, 118.5, 129.0, 131.5, 163.1, 168.9 (t, J=2.5 Hz), 172.4 (t, J=1.5 Hz). MS (CI) m/z (%): 281 (M^+, 25), HRMS calcd for $C_{13}H_{14}BF_2NO_3$: 281.1035; found: 281.1040. Elemental analysis calcd for $C_{13}H_{14}BF_2NO_3$: C, 55.55; H, 5.02; N, 4.98. Found: C, 55.78; H, 4.98; N, 5.09.

*4.3.2. (1R,2S)-Difluoro{3-(hydroxy-κO)-N-[2-hydroxy-2,3-dihydro-1H-inden-1-yl]-3-phenylacrylamidato-κO′}boron (**5i**)*

To a solution of (1*S*,2*R*)-1-aminoindan-2-ol (150 mg, 1 mmol) in MeCN (5 mL), 2,2-difluoro-4-ethoxy-1,3,2-dioxaborinane **5a** (246 mg, 1.1 mmol) was added at room temperature. The reaction mixture was stirred at room temperature for 1 h. After the reaction was complete, the reaction mixture was concentrated in vacuo and the residue was purified by flash chromatography (EtOAc/petroleum ether=3:5) yielding a white solid (220 mg, 64%). Mp=141.5–144.0 °C. R_f=0.25 (EtOAc/petroleum ether=3:5). $[\alpha]_D^{20}$ −98.0 (*c* 5.0, Me_2CO). IR (KBr): 3563, 3355, 1708, 1611, 1526, 1489, 1458, 1299, 1234, 1070, 1030, 770 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.54 (br s, 1H, –OH), 2.89 (dd, J=17.0, 2.0 Hz, 1H, –OHCHCH_2–), 3.12 (dd, J=17.0, 5.0 Hz, 1H, –OHCHCH_2–), 4.58 (ddd, J=7.5, 5.0, 2.0 Hz, 1H, –(NH)CHCH(OH)CH_2–), 5.37 (dd, J=7.5, 5.0 Hz, 1H, –(NH)CHCH(OH)CH_2–), 5.96 (s, 1H, PhC(O)═CHCONH–), 7.14–7.28 (m, 5H, –*Ph*), 7.31–7.38 (m, 2H, –NH, and –*Ar*–), 7.42–7.50 (m, 1H, –*Ar*–), 7.79–7.84 (m, 2H, –*Ar*–). ^{13}C NMR (300 MHz, DMSO-d_6): δ 39.7, 58.5, 72.9, 84.5, 124.7, 125.4, 127.0, 127.6, 128.6, 128.9, 132.4, 132.7, 138.3, 139.6 169.1 (t, J=2.5 Hz), 172.9 (t, J=1.5 Hz). MS (EI) m/z (%): 343 (M^+, 25). Elemental analysis calcd for $C_{18}H_{16}BF_2NO_3$: C, 63.01; H, 4.70; N, 4.08. Found: C, 62.94; H, 4.71; N, 4.08.

*4.3.3. Ethyl 3-phenylpropanoate (**6a**)*[15d]

Purification on SiO_2 (EtOAc/petroleum ether=3:5) gave 117 mg (66%) of a yellowish oil. R_f=0.26 (EtOAc/petroleum ether=1:35). IR (NaCl-plates): 3029, 2982, 2936, 1735, 1497, 1450, 1373, 1152, 1039, 748, 700 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.22 (t, J=7.0 Hz, 3H, –OCH_2CH_3), 2.58–2.64 (t, J=7.5 Hz, 2H, –$CH_2CH_2CO_2$Et), 2.95 (t, J=7.5 Hz, 2H, –$CH_2CH_2CO_2$Et), 4.12 (q, J=7.0 Hz, 2H, –OCH_2CH_3), 7.16–7.30 (m, 5H, –*Ph*).

*4.3.4. Ethyl 3-(4-methoxyphenyl)propanoate (**6b**)*[15e]

Purification on SiO_2 (EtOAc/petroleum ether=1:35) gave 173 mg (83%) of a yellow oil. R_f=0.35 (EtOAc/petroleum ether=1:35). IR (KBr): 2982, 1731, 1613, 1584, 1246, 1175 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.24 (t, J=7.0 Hz, 3H, –OCH_2CH_3), 2.59 (t, J=7.5 Hz, 2H, –$CH_2CH_2CO_2$Et), 2.90 (t, J=7.5 Hz, 2H, –$CH_2CH_2CO_2$Et), 3.80 (s, 3H, –OCH_3), 4.13 (q, J=7.0 Hz, 2H, –OCH_2CH_3), 6.82 (AA′XX′, J=8.5 Hz, 2H, –*Ph*), 7.12 (AA′XX′, J=8.5 Hz, 2H, –*Ph*).

4.3.5. *N*-Isopropyl-3-phenylpropanamide (**6c**)[15f]

Purification on SiO_2 (EtOAc/petroleum ether=1:1) gave 168 mg (88%) of a white solid. Mp=83.0–86.5 °C. $Mp_{(lit.)}$=89–90 °C. R_f=0.31 (EtOAc/petroleum ether=1:1). IR (KBr): 3301, 2968, 1639, 1544, 1452, 1379, 1233, 1173, 982, 750, 700 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.06 (d, J=6.5 Hz, 6H, –CH(CH_3)$_2$), 2.42 (t, J=8.0 Hz, 2H, –CH_2CO–), 2.95 (t, J=7.5 Hz, 2H, PhCH_2–), 3.96–4.10 (m, 1H, –NH CH(CH_3)$_2$), 5.16 (br s, 1H, –NH–), 7.18–7.32 (m, 5H).

4.3.6. *N*,*N*-Diethyl-3-phenylpropanamide (**6d**)[15g]

Purification on SiO_2 (EtOAc/petroleum ether=3:5) gave 188 mg (92%) of a yellowish oil. R_f=0.28 (EtOAc/petroleum ether=3:5). IR (NaCl-plates): 2970, 2933, 1642, 1454, 1431, 1265, 1138, 1076, 701 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.07–1.13 (m, 6H, –N(CH_2CH_3)$_2$), 2.56–2.62 (m, 2H, –CH_2CO–), 2.96–3.01 (m, 2H, PhCH_2–), 3.22 (t, J=7.0 Hz, 2H, –N(CH_2CH_3)$_2$), 3.37 (t, J=7.0 Hz, 2H, –N(CH_2CH_3)$_2$), 7.16–7.31 (m, 5H, –Ph).

4.3.7. 3-Phenyl-*N*-propylpropanamide (**6e**)[15h]

Purification on SiO_2 (EtOAc/petroleum ether=3:5) gave 176 mg (92%) of a white solid. Mp=46.5–49.0 °C. $Mp_{(lit.)}$=52–54 °C. R_f=0.23 (EtOAc/petroleum ether=3:5). IR (KBr): 3301, 2962, 2932, 2870, 1644, 1548, 1231, 1155, 749, 700 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 0.85 (t, J=7.5 Hz, 3H, –NHCH$_2$CH$_2$CH_3), 1.44 (dt, J=7.0, 7.0 Hz, 2H, –NHCH$_2$CH_2CH$_3$), 2.46 (t, J=8.0 Hz, 2H, –CH_2CO–), 2.96 (t, J=7.5 Hz, 2H, PhCH_2–), 3.16 (dt, J=7.0, 7.0 Hz, 2H, –NHCH_2CH$_2$CH$_3$), 5.45 (br s, 1H, –NH–), 7.16–7.30 (m, 5H, –*Ph*).

4.3.8. 3-(4-Methoxyphenyl)-*N*-propylpropanamide (**6f**)

Purification on SiO_2 (CH_2Cl_2) gave 197 mg (89%) of a colourless oil. R_f=0.25 (CH_2Cl_2). IR (NaCl-plates): 3296, 2957, 1638, 1541, 1508, 1242, 1026, 813 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 0.58 (t, J=7.5 Hz, 3H, –NHCH$_2$CH$_2$CH_3), 1.45 (dt, J=7.0, 7.0 Hz, 2H, –NHCH$_2$CH_2CH$_3$), 2.42 (t, J=7.0 Hz, 2H, –CH_2CO–), 2.90 (t, J=7.0 Hz, 2H, PhCH_2–), 3.13–3.20 (m, 2H, –NHCH_2CH$_2$CH$_3$), 3.78 (s, 3H, –OCH_3), 5.41 (br s, 1H, –NH–), 6.81 (AA′XX′, J=8.5 Hz, 2H, –*Ph*), 7.11 (AA′XX′, J=8.5 Hz, 2H, –*Ph*). ^{13}C NMR ($CDCl_3$): δ 11.3, 22.8, 30.9, 38.8, 41.2, 55.2, 113.9, 129.3, 133.0, 158.0, 172.1. MS (CI) m/z (%): 221 (M^+, 63). HRMS calcd for $C_{13}H_{19}NO_2$: 221.1416; found: 221.1420.

4.3.9. 1-(3-Phenylpropanoyl)piperidine (**6g**)[15i]

Purification on SiO_2 (EtOAc/petroleum ether=3:5) gave 188 mg (87%) of a colourless oil. R_f=0.23 (EtOAc/petroleum ether=3:5). IR (NaCl-plates): 2934, 2855, 1639, 1441, 1379, 1251, 1218, 1024, 750, 701 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.39–1.61 (m, 6H, piperidine –CH_2–), 2.57–2.62 (t, J=7.5 Hz, 2H, –CH_2CO–), 2.93–2.98 (t, J=7.5 Hz, 2H, PhCH_2–), 3.30 (t, J=5.5 Hz, 2H, piperidine –CH_2–), 3.54 (t, J=5.5 Hz, 2H, piperidine –CH_2–), 7.13–7.29 (m, 5H, –*Ph*).

4.3.10. *N*-Benzyl-3-phenylpropanamide (**6h**)[15j]

Purification on SiO_2 (EtOAc/petroleum ether=1:1) gave 266 mg (91%) of a white solid. Mp=83.0–86 °C. $Mp_{(lit.)}$=83–84 °C. R_f=0.20 (EtOAc/petroleum ether=1:1). IR (KBr): 3291, 1639, 1544, 1497, 1450, 1067, 1030 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 2.50 (t, J=7.5 Hz, 2H, PhCH_2–), 2.98 (t, J=7.5 Hz, 2H, –CH_2CO–), 4.37 (d, J=6.0 Hz, 2H, –NHCH_2Ph), 5.75 (br s, 1H, –NHCH$_2$Ph), 7.11–7.32 (m, 10H, 2×–*Ph*).

4.3.11. (1*S*,2*R*)-*N*-(2-Hydroxy-2,3-dihydro-1*H*-inden-1-yl)3-phenylpropanamide (**6i**)

Purification on SiO_2 (EtOAc/petroleum ether=3:5) gave 250 mg (89%) of a white solid. Mp=159–161 °C. R_f=0.15 (EtOAc/petroleum ether=3:5). IR (NaCl-plates): 3443, 3306, 3218, 1646, 1616, 1551, 1452, 1196, 1049, 735 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 2.52–2.68 (m, 2H, –CH_2CO–), 2.87 (dd, J=16.5, 2.0 Hz, 1H, –CH(OH)CH_2–), 3.03 (t, J=7.5 Hz, 2H, PhCH_2–), 3.11 (dd, J=16.5, 5.0 Hz, 1H, –CH(OH)CH_2–),4.49 (dt, J=5.0, 2.0 Hz, 1H, –(NH)CHCH(OH)CH$_2$–), 5.33 (dd, J=8.5, 5.0 Hz, 1H, –(NH)CHCH(OH)CH$_2$–), 5.95 (d, J=8.0 Hz, 1H, –NH–), 7.02–7.05 (m, 1H, –*Ar*–), 7.14–7.34 (m, 8H, –*Ph* and –*Ar*–). ^{13}C NMR (300 MHz, $CDCl_3$): δ 31.9, 38.6, 39.5, 57.5, 73.5, 124.4, 125.2, 126.4, 127.1, 128.2, 128.5, 128.6, 139.9, 140.4, 140.7, 172.7. MS (EI) m/z (%): 282 (MH^+, 35). Elemental analysis calcd for $C_{18}H_{19}NO_2$: C, 76.84; H, 6.81; N, 4.98. Found: C, 76.98; H, 6.82; N, 4.92.

4.3.12. Difluoro[3-(hydroxy-κO)-3-phenylacrylamidato-κO′] boron (**6j**)[6d]

Purification on SiO_2 (MeOH/CH_2Cl_2=1:20) gave 101 mg (48%) of a white solid. Mp=187.5–190.0 °C. $Mp_{(lit.)}$=186.5–188.5 °C. R_f=0.30 (MeOH/CH_2Cl_2=1:20). IR (KBr): 3471, 3372, 1656, 1609, 1525, 1487, 1368, 1030, 986, 772, 687 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 6.06 (s, 1H, PhC(O)=CHCONH$_2$), 7.50–7.63 (m, 3H, –*Ph*), 7.81–7.85 (m, 2H, –*Ph*), 9.21 (br s, 2H, PhC(O)=CHCONH_2).

4.3.13. [Ethyl 3-(3-furyl)-3-(hydroxy-κO)acrylatato-κO′](difluoro)boron (**8**)

A solution of 1,3-diketoester **7** (477 mg, 2.6 mmol) in dry toluene (10 mL) was treated with $BF_3 \cdot OEt_2$ (5.2 mmol, 2.0 equiv). The solution was left at 25 °C for 24 h and then concentrated in vacuo. The crude material was suspended in Et_2O (5 mL) and filtered off, yielding a pure product (415 mg, 69%) as white solid. Mp=141.5–144.0 °C. R_f=0.55 (EtOAc/petroleum ether=3:5). IR (KBr): 3458, 1616, 1541, 1416, 1393, 1345, 1260, 1163, 1071, 1007, 901, 868, 789 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.44 (t, J=7.0 Hz, 3H, –CH_3), 4.55 (q, J=7.0 Hz, 2H. –CH_2–), 5.66 (s, 1H, C(O)=CHCO–), 6.68 (dd, J=1.5, 1.0 Hz, 1H, furan-4-*H*), 7.49 (dd, J=1.5, 1.5 Hz, 1H, furan-5-*H*), 8.13 (dd, J=1.5, 1.0 Hz, 1H, furan-2-*H*). ^{13}C NMR (300 MHz, DMSO-d_6): δ 14.0, 66.0, 83.5, 107.9, 121.9, 144.7, 147.2, 174.4 (t, J=2.0 Hz), 175.3 (t, J=1.5 Hz). MS (EI) m/z (%): 230 (M^+, 33), 136 (50), 95 (100). HRMS calcd for $C_9H_9BF_2O_4$: 230.0562; found: 230.0569. Elemental analysis calcd for $C_9H_9BF_2O_4$: C, 47.00; H, 3.94. Found: C, 46.86; H, 4.06.

4.3.14. Ethyl 3-oxo-3-(tetrahydrofuran-2-yl)propanoate (**9**)

Purification on SiO_2 (EtOAc/petroleum ether=3:5) gave 169 mg (81%) of a colourless oil. R_f=0.39 (EtOAc/petroleum ether=3:5). IR (NaCl-plates): 2982, 2872, 1744, 1716, 1645, 1468, 1027, 917 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.27 (q, J=7.0 Hz, 3H, –CH_3), 2.10–2.17 (m, 2H, –CH_2–), 3.31–3.42 (m, 1H, –CH–), 3.53 (s, 2H, –COCH_2CO–), 3.74–3.96 (m, 2H, –OCH_2CH$_2$–), 3.93 (d, J=6.5 Hz, 2H, –OCH_2CH–), 4.20 (q, J=7.0 Hz, 2H, –CH_2CH$_3$). ^{13}C NMR (300 MHz, $CDCl_3$): δ 14.0, 28.8, 48.4, 51.0, 61.4, 68.2, 69.1, 166.8, 202.3. MS (CI) m/z (%): 209 (M+Na^+, 90). HRMS calcd for $C_9H_{14}O_4Na$: 209.0790; found: 209.0790.

4.3.15. [*N*-Butyl-3-(3-furyl)-3-(hydroxy-κO)acrylamidato-κO′](difluoro)boron (**10**)

To a solution of *n*-butylamine (376 mg, 5.2 mmol) in MeCN (5 mL), 2,2-difluoro-4-alkoxy-1,3,2-dioxaborinane **8** (912 mg, 4.0 mmol) was added at room temperature. The reaction mixture was stirred at room temperature for 1 h. After the reaction was complete, the reaction mixture was concentrated in vacuo and the residue was purified by flash chromatography (EtOAc/petroleum ether=1:5) yielding a white solid (822 mg, 80%). Mp=72.0–75.0 °C. R_f=0.27 (EtOAc/petroleum ether=3:5). IR (KBr): 3375, 2959, 1634, 1535, 1379, 1339, 1164, 1007, 870, 787, 737 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 0.93 (t, J=7.5 Hz, 3H, –CH_3), 1.32–1.69 (m, 4H, –CH_2CH_2–), 3.43–3.49 (m, 2H, –NHCH_2–), 5.59 (s, 1H, –CO=CHCO–), 6.45 (br s, 1H, –NH–), 6.59–6.60 (m, 1H, furan-4-*H*), 7.41–7.42 (m, 1H, furan-5-*H*), 7.99–8.00 (m, 1H, furan-2-*H*). ^{13}C NMR (300 MHz, DMSO-d_6): δ 13.5, 19.8, 30.9, 40.8, 84.7, 107.8, 122.1, 144.2, 145.4, 167.2 (t, J=2.5 Hz), 168.6 (t, J=1.5 Hz). MS (EI) m/z (%): 257 (M^+, 59), 215 (29), 185 (64), 95 (100). Elemental analysis calcd for $C_{11}H_{14}BF_2NO_3$: C, 51.40; H, 5.49; N, 5.45. Found: C, 51.69; H, 5.60; N, 5.38.

4.3.16. [N-Butyl-3-(hydroxy-κO)-3-(tetrahydrofuran-2-yl)acrylamidato-κO′](difluoro)boron (**11**)

Purification on SiO_2 (EtOAc/petroleum ether=3:5) gave 172 mg (66%) of a white solid. Mp=39.5–43.0 °C. R_f=0.42 (MeOH/CH_2Cl_2=1:20). IR (KBr): 3370, 2962, 2937, 2876, 1620, 1540, 1443, 1331, 1150, 1049, 912, 793 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 0.92–0.96 (m, 3H, –CH_3), 1.31–1.43 (m, 2H, –CH_2–), 1.53–1.64 (m, 2H, –CH_2–), 2.10–2.23 (m, 2H, –CH_2–), 3.00–3.14 (m, 1H, –CH–), 3.22–3.46 (m, 2H, –NHCH_2–), 3.80–4.00 (m, 4H, –CH_2OCH_2–), 5.32 (s, 1H, –CO=CHCO–), 6.70 (br s, 1H, –NH–). ^{13}C NMR (300 MHz, $CDCl_3$): δ 13.5, 19.8, 30.5, 30.8, 40.7, 45.1, 68.3, 70.7, 86.4, 168.5 (t, J=2.5 Hz), 180.1 (t, J=1.5 Hz). MS (EI) m/z (%): 261 (M^+, 2), 242 (91), 218 (63), 69 (100), 57 (37). HRMS calcd for $C_{11}H_{18}NO_3BF_2$: 261.1348; found: 261.1353.

4.3.17. [N-(2-Cyclohexylethyl)-2-(hydroxy-κO)cyclohex-1-ene-1-carboxamidato-κO′](difluoro)boron (**13**)

Purification on SiO_2 (EtOAc/petroleum ether=3:5) gave 236 mg (79%) of a white solid. Mp=99.5–102.0 °C. R_f=0.38 (EtOAc/petroleum ether=3:5). IR (NaCl): 3380, 2924, 2849, 1638, 1541, 1447, 1419, 1254, 1200, 884, 747 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 0.85–1.00 (m, 2H, cyclohexane-CH_2), 1.12–1.34 (m, 6H, cyclohexane-CH_2), 1.47–1.55 (m, 2H, –NHCH$_2$CH_2–), 1.67–1.76 (m, 8H, cyclohexane-CH_2), 2.10–2.16 (m, 2H, –CH$_2$C(O)=C(CO)CH_2–), 2.33–2.38 (m, 2H, –CH_2C(O)=C(CO)CH$_2$–), 3.45–3.52 (sim m, 2H, –NHCH_2–), 6.04 (br s, 1H, –NH–). ^{13}C NMR (300 MHz, DMSO-d_6): δ 20.9, 21.4, 21.8, 26.0, 26.3, 30.5, 33.0, 35.2, 36.4, 39.1, 94.1, 168.0, 174.9. MS (EI) m/z (%): 299 (M^+, 64), 203 (70), 173 (100), 125 (36), 55 (39). HRMS calcd for $C_{15}H_{24}NO_2BF_2$: 299.1868; found 299.1877. Elemental analysis calcd for $C_{15}H_{24}NO_2BF_2$: C, 60.22; H, 8.09; N, 4.68. Found: C, 60.46; H, 8.20; N, 4.55.

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