Practical Method for the Rhodium-Catalyzed Addition of Aryl- and Alkenylboronic Acids to Aldehydes

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Abstract: The arylation or alkenylation of aldehydes with boronic acids is conveniently effected by a catalyst system comprising $RhCl_3 \cdot 3H_2O$ (1 mol %), the sterically hindered imidazolium salt **2** (1 mol %), and a base. The *N*-heterocyclic carbene **6** derived from **2** is believed to be the actual ligand to the catalytically active rhodium species formed *in situ*. The method is compatible with various functional groups in both reaction partners and follows a non-chelation controlled pathway in additions to the Garner aldehyde **23**.

Introduction

Although the addition of carbon nucleophiles to aldehydes is usually a facile process, limits are encountered where *functionalized* organometallic reagents are required. Since organomagnesium and organolithium derivatives, which are most frequently used for this purpose, tolerate only few electrophilic groups on themselves,[1] there remains ample room for further methodological advancements. In spite of the progress that has been achieved by using functionalized organozinc, copper, chromium, tin, manganese, and related organometallic species,[1] recent publications describing the addition of arylboronic acid derivatives to aldehydes in the presence of catalytic amounts of Rh(I) and phosphine additives deserve particular mention.[2–6] These methods combine a high efficiency with a reasonable tolerance towards polar substituents in the substrates and benefit from the stability and ready accessibility of the required boron derivatives. It is believed that the reaction involves a transmetallation of the boronic acid with formation of an organorhodium(I) species which is nucleophilic enough to transfer its aryl substituent to an aldehyde. Originally, $Rh(acac)(coe)_2$ (coe = cyclooctene) or $Rh(acac)(CO)_2$ in combination with bidentate phosphine ligands such as dppb [1,4-bis(diphenylphosphino)butane] or dppf [1,1′-bis(diphenylphosphino)ferrocene] have been recommended for the *in situ* preparation of the yet elusive catalyst.[2,4] Later on, however, it was noticed that sterically hindered and strongly basic monodentate phosphines, preferentially $P(t\text{-}Bu)_3$ or PCy_3, lead to better results.[3]

This finding has attracted our attention because of our excellent experience with *N*-heterocyclic carbenes (NHC's) as superior surrogates for the air-sensitive and rather expensive PCy_3. NHC's constitute a class of ligands that exhibits pronounced σ-donor but very poor π-acceptor properties.[7] They are easily generated from the corresponding imidazolium salts and have been employed with considerable success in various catalytic transformations involving the turn-over of an electron-rich transition metal template. In particular, this refers to olefin metathesis[8–10] and palladium-catalyzed cross-coupling reactions.[11,12] Described below is the successful extension of this concept to the rhodium-catalyzed addition of organoboron compounds to aldehydes which is significantly upgraded in practical terms if carried out in the presence of the sterically hindered imidazolium salt **2**.

Results and Discussion

The data summarized in Table 1 show the efficiency of $Rh(acac)(coe)_2$ (3 mol %)[3] in combination with different ligands or ligand precursors (3 mol % each) in catalyzing the addition of phenylboronic acid to *p*-methoxybenzaldehyde in basic medium (Scheme 1). As can be seen, the imidazolium chlorides **1** and **2** bearing bulky aromatic substituents on their N-atoms gave excellent results, whereas the corresponding imidazolium salts **3** and **4** containing *N*-alkyl groups turned out to be less efficient.[13] Imidazolium salts

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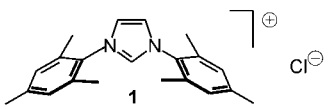
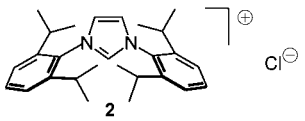
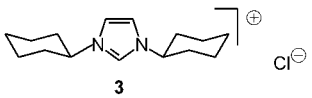
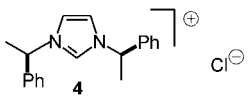
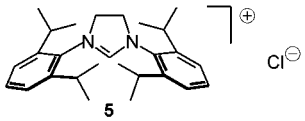
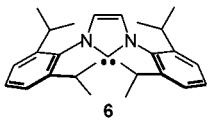
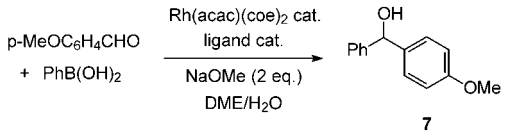
are known to generate NHC's in the presence of non-nucleophilic bases; therefore, a control experiment using free carbene **6** as the additive has been carried out (entry 8). The reaction took the expected course affording alcohol **7** in 55% yield. Although this result suggests that carbenes are in fact involved as the actual donor ligands to the rhodium center in all of these reactions, it is particularly fortunate from the preparative point of view that the *in situ* release of this ligand from the imidazolium salt **2** and base followed by its interception by the admixed rhodium pre-catalyst leads to significantly better results than the use of isolated **6** (cf. entries 4/8). Furthermore, it was found that compound **2** delivering an "unsaturated" carbene gives better results than the use of the corresponding dihydroimidazolium salt **5** that furnishes an even more basic "saturated" NHC (entry 7).

Table 1. Screening of different additives in the rhodium-catalyzed addition of phenylboronic acid to *p*-methoxybenzaldehyde depicted in Scheme 1.

Entry	Additive	Time (h)	Yield (%)
1	$P(t\text{-}Bu)_3$	16	79[3]
2	PCy_3	16	83[3]
3	 **1**	2.5	80
4	 **2**	1.5	77
5	 **3**	12	32
6	 **4**	11	65
7	 **5**	5	56
8	 **6**	4.5	55



Scheme 1.

A survey of different bases showed that K_2CO_3 (15%, 4 h) and Et_3N (11%, 8 h) are inappropriate, likely because they are unable to generate the NHC *in situ* by deprotonation of **2**, whereas all stronger bases such as aqueous NaOH (90%, 6 h), NaOMe (77%, 1.5 h), KO*t*-Bu (83%, 1 h), Cs_2CO_3 (50%, 3.5 h) and even TBAF (67%, 14 h) gave product **7** in reasonable to excellent yields.

Next, various rhodium and other transition metal complexes have been screened for catalytic activity (Table 2). We were pleased to learn that the replacement of Rh(acac)(coe)$_2$[3] – a compound that is not commercially available – by simple, robust and fully air-stable salts such as $[Rh(OAc)_2]_2$ or $RhCl_3 \cdot 3\,H_2O$ increases the overall efficiency. Use of the latter results in the shortest reaction time and the highest yield even if the catalyst loading is reduced to 1 mol % (entry 4). This screening, however, has also revealed that rhodium is rather unique in catalyzing the addition reaction. None of the other late transition metal salts that have been tested showed any appreciable activity. This includes different cobalt salts as well as $IrCl_3 \cdot n\,H_2O$, i.e. the elements located above and below rhodium in the periodic table (entry 5, footnote b).

The results summarized above lead to an optimized and very user-friendly procedure for the addition of arylboronic acids to aldehydes which is distinguished by its high efficiency, a low catalyst loading, short reaction times, mild conditions (50–80 °C), the use of inexpensive bases in aqueous solvents, and the fact that only fully air-stable and well accessible ingredients

Table 2. Screening of the activity of different metal salts (3 mol % each, unless stated otherwise) in combination with imidazolium chloride **2** (3 mol %) in catalyzing the addition of phenylboronic acid to *p*-methoxybenzaldehyde. All reactions were carried out in aqueous DME at 80 °C in the presence of NaOMe (2 equivalents).

Entry	Metal Salt	Time (h)	Yield (%)
1	$Rh(acac)(coe)_2$	1.5	77
2	$[RhCl(cod)]_2$	6.5	< 10
3	$[Rh(OAc)_2]_2$	0.5	79
4	$RhCl_3 \cdot 3\,H_2O$	0.2	93[a]
5	–[b]	4–21	< 5

[a] Using only 1 mol % of the rhodium salt and of the imidazolium chloride.

[b] The following metal salts showed no appreciable catalytic activity: $Pd(OAc)_2$, $PtCl_2$, $CoCl_2 \cdot 6\,H_2O$, $Co(acac)_2$, $RuCl_3 \cdot n\,H_2O$, $IrCl_3 \cdot n\,H_2O$.

Table 3. Rhodium-catalyzed addition of boronic acids to aldehydes. All reactions were carried out using $RhCl_3 \cdot 3H_2O$ (1 mol %), imidazolium chloride **2** (1 mol %), and NaOMe (1–2 equivalents) in aqueous DME at 80 °C unless stated otherwise.

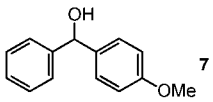
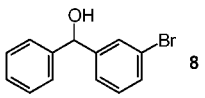
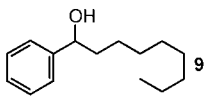
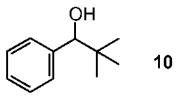
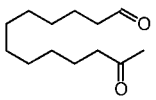
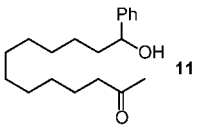
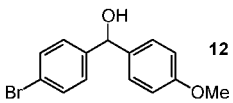
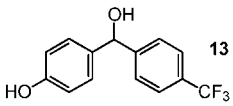
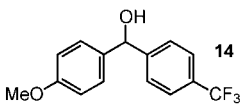
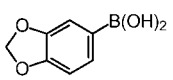
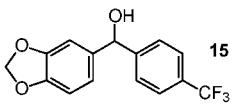
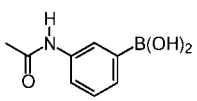
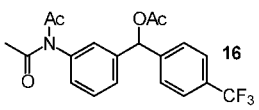
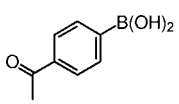
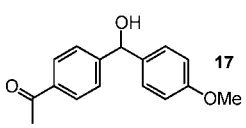
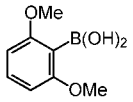
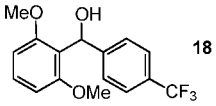
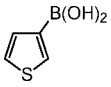
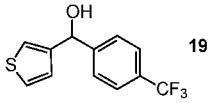
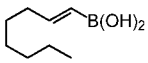
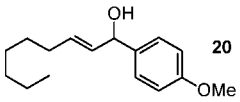
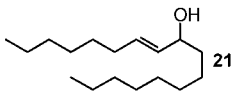
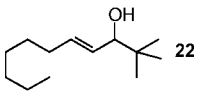
Entry	Boronic Acid	Aldehyde	Time (h)	Product	Yield (%)
1	$C_6H_5B(OH)_2$	*p*-MeO-C_6H_4CHO	0.2	 **7**	93
2		*m*-Br-C_6H_4CHO	0.8	 **8**	78
3		nonanal	0.8	 **9**	80
4		*t*-BuCHO	1.5	 **10**	66
5			2	 **11**	60
6	*p*-Br-$C_6H_4B(OH)_2$	*p*-MeO-C_6H_4CHO	6.5	 **12**	90[a]
7	*p*-HO-$C_6H_4B(OH)_2$	*p*-F_3C-C_6H_4CHO	1	 **13**	52
8	*p*-MeO-$C_6H_4B(OH)_2$	*p*-F_3C-C_6H_4CHO	2	 **14**	88
9		*p*-F_3C-C_6H_4CHO	2	 **15**	82
10		*p*-F_3C-C_6H_4CHO	1.2	 **16**	61[b]
11		*p*-MeO-C_6H_4CHO	1	 **17**	94

Table 3. (Continued)

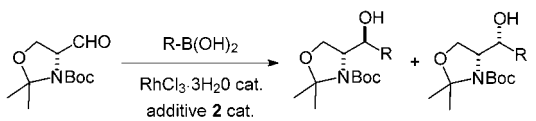
Entry	Boronic Acid	Aldehyde	Time (h)	Product	Yield (%)
12		*p*-F_3C-C_6H_4CHO	2	 **18**	99[a]
13		*p*-F_3C-C_6H_4CHO	1	 **19**	97[a]
14		*p*-MeO-C_6H_4CHO	1.5	 **20**	80
15		nonanal	2	 **21**	76[c]
16		*t*-BuCHO	1.5	 **22**	50

[a] Using 3 mol % of rhodium and ligand.
[b] The product formed was peracetylated to facilitate the work-up.
[c] Using 5 mol % of rhodium and ligand at 50 °C.

are required. The results compiled in Table 3 reveal the wide scope of this method which is compatible with acetal, amide, urethane, ether, trifluoromethyl, unprotected hydroxy as well as bromide functions in both reaction partners. Importantly, entries 5 and 11 show that the addition is highly chemoselective for aldehydes, while keto groups in either component remain unaffected. Electron-rich and electron-poor aromatic aldehydes react with similar ease, and aliphatic ones are also suitable even if they are sterically hindered (entries 4, 16). Moreover, the reaction is not limited to arylboronic acids but can also be applied to alkenylboronic acids as nucleophiles which are readily accessible by hydroboration of alkynes with catecholborane and hydrolysis of the resulting boronates (entries 14–16).[14,15] Limitations, however, were encountered with arylboronic acid derivatives bearing strongly electron-withdrawing groups. Thus, attempted addition of *p*-nitro- or *p*-cyanophenylboronic acid to benzaldehyde by means of the present catalyst system has been unsuccessful. This failure is ascribed to the reduced nucleophilicity of these compounds which makes the transmetalation to the rhodium catalyst unfavorable.

Addition reactions to the Garner aldehyde **23**[16] provide information on the stereochemical course of these rhodium-catalyzed transformations (Table 4). Gratifyingly, a very high selectivity for the *anti*-configurated product **24** was noted (entry 1), which likely originates from a non-chelation controlled pathway caused by the low affinity of the electron-rich rhodium center to the "hard" donor sites in **23**. Alcohol **24** and derivatives thereof have recently attracted at-

Table 4. Rhodium-catalyzed addition of boronic acids to the Garner aldehyde **23**.



23

24 (R = Ph)
25 (R = -CH=CH$(CH_2)_5CH_3$)

R	Yield (%)	*anti*:*syn*
Ph	71[a]	97:3
$CH_3(CH_2)_5CH$=CH-	78[b]	82:18

[a] Using 3 mol % each of $RhCl_3 \cdot 3H_2O$ and imidazolium chloride **2** at 80 °C.
[b] Using 5 mol % each of $RhCl_3 \cdot 3H_2O$ and imidazolium chloride **2** at 55 °C.

tention as sphingosine mimics[17] as well as important building blocks for drug development programs aiming at the design of selective inhibitors of protein kinase C isozymes.[18] It is worth mentioning that the selectivity for the desired *anti*-configurated isomer of **24** is significantly higher than that observed in the addition of phenylmagnesium bromide to aldehyde **23** (*anti : syn* = 83 : 17).[19] Since an unambiguous assignment of the relative stereochemistry of such compounds by NMR is hampered by the observation of rotamers in solution, the crude product mixture was recrystallized from hexane, thus affording crystals of the major isomer that were suitable for X-ray analysis. Its molecular structure in the solid state (Figure 1) confirms the *anti*-relationship between the newly formed stereocenter and the C-N bond. The 1,3-oxazolidine ring adopts a flattened twist conformation. The puckering amplitude of 0.31 Å is slightly smaller than the average of 0.36 Å calculated from a selection of 105 1,3-oxazolidine rings contained in the Cambridge Structure Database.[20] The ring nitrogen atom is planar (sum of the bond angles 359.3°) and is less than 0.01 Å from the ring mean plane. The distances of the other ring atoms from the ring mean plane are in agreement with approximate C_2 symmetry. Further analysis shows interesting crystal packing effects because an intermolecular hydrogen bond between the hydroxy proton and the ring oxygen is observed, whereas the stronger hydrogen bond acceptor carbonyl oxygen O3 only takes part in a much weaker C–H…O interaction.[21,22] However, in this case there is a competing C–H…π interaction involving the phenyl ring. In the crystal the phenyl rings between neighboring molecules form a dihedral angle of 77.2°. The shortest distance between a hydrogen atom and the phenyl ring plane is 2.70 Å.[23] Adjusting the carbon-hydrogen bond length to the value of 1.08 Å, obtained from neutron diffraction experiments, shortens this distance to 2.60 Å. The hydrogen bond pattern forms a zig-zag stack parallel to the *c* axis of the crystal, while the hydrophobic parts of the molecule separate individual stacks (Figure 2).

The addition of (*E*)-octenylboronic acid to Garner aldehyde **23** had to be carried out at lower temperature (55 °C) in order to avoid competing proto-deborylation. The reduced reaction rate was compensated for by a somewhat higher catalyst loading (5 mol %); this resulted in the formation of the desired truncated sphingosine derivative **25** in 78% yield after 2 h reaction time, although the stereochemical bias towards

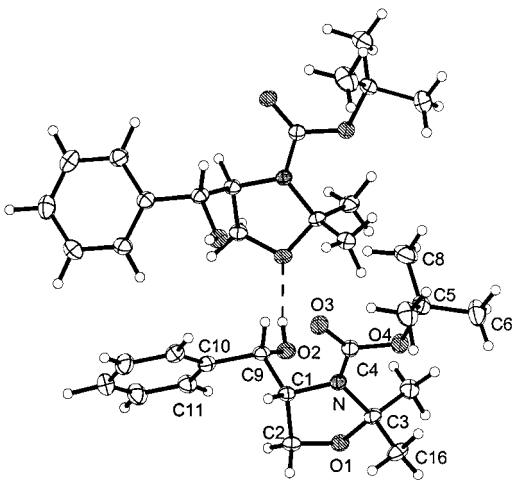


Figure 1. Molecular structure diagram of *anti*-**24** plus symmetry equivalent [i] molecule. Anisotropic displacement parameters are drawn at the 50% probability level, hydrogen atoms are drawn with an arbitrary radius. Hydrogen bonds: O(2)–H(O2) 0.88(4), H(O2)…O(1)^{i} 1.90(4), O(2)…O(1)^{i} 2.770(2) Å, ∠(O(2)H(O2)O(1)^{i}) 171(3)°; C(2)–H(2A) 1.01(2), H(2A)…O(3)^{ii} 2.58(2), C(2)…O(3)^{ii} 3.441(3) Å, ∠(C(2)H(2A)O(3)^{ii}) 142.6(17)°. Symmetry operators i) –x, $^{1}/_{2}$ + y, $^{1}/_{2}$ – z ; ii) –x + 1, –y + 1, –z + 1. The shortest C–H contacts between the phenyl rings are H(11)^{i}…C(15) 2.91 Å, H(11)^{i}…C(14) 2.93 Å.

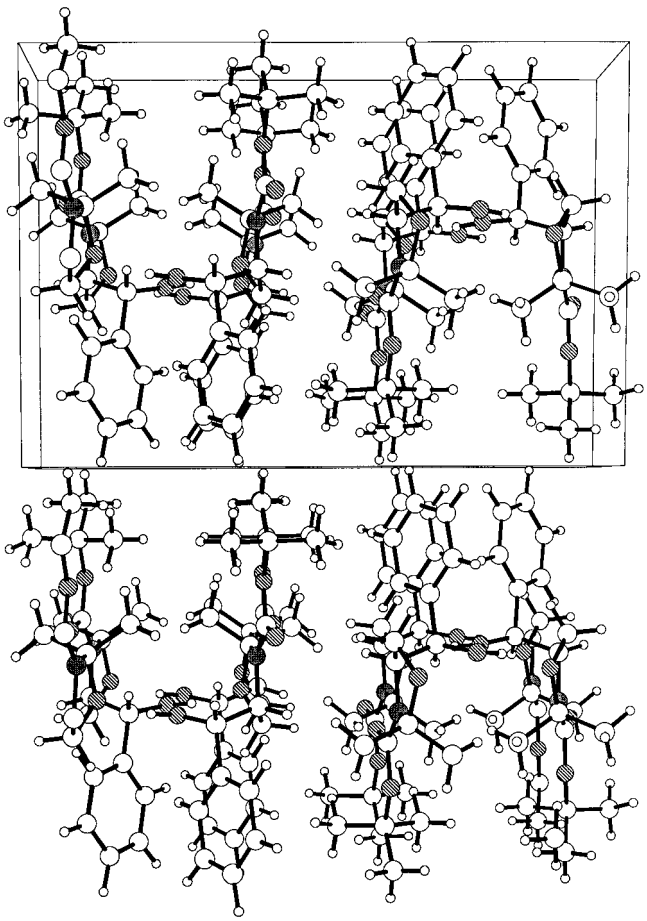


Figure 2. Crystal packing diagram of *anti*-**24** viewed along the *c* direction. The phenyl ring C–H…π herring-bone pattern is parallel to the hydroxy…O-oxazolidine hydrogen bond. The weak C–H…O bond links the stacks horizontally (*b* direction).

the *anti*-isomer is somewhat lower under these conditions (Table 4, entry 2).

Conclusion

A convenient and highly user-friendly method for the addition of aryl- or alkenylboronic acids to aldehydes is presented which employs a catalyst formed *in situ* from $RhCl_3 \cdot 3\,H_2O$ (1 mol %), the readily accessibly and fully air-stable imidazolium salt **2** (1 mol %) and inexpensive aqueous bases. The addition is highly chemoselective for aldehydes, it turned out to be compatible with many functional groups in both reaction partners, and exhibits a high preference for a non-chelation controlled pathway in reactions with Garner aldehyde. Future investigations are aiming at the development of an asymmetric version of this process and at exploiting its favorable profile in a combinatorial set-up using resin-bound reagents.

Experimental Section

General Remarks

All reactions were carried out under Ar. The DME used was purified by distillation over Na/K alloy prior to use. Flash chromatography: Merck silica gel 60 (230–400 mesh). NMR: spectra were recorded on DPX 300 spectrometer in the solvents indicated; chemical shifts (δ) are given in ppm relative to TMS, coupling constants (*J*) in Hz. IR: Nicolet Magna 750 FT-IR, wave numbers in cm^{-1}. MS (EI): Finnigan MAT 8200 (70 eV), HR-MS: Finnigan MAT 95. All arylboronic acids were purchased (Lancaster, Aldrich) and used as received. Aldehydes were distilled under reduced pressure prior to use.

Representative Procedure for the Rhodium-Catalyzed Addition of Boronic Acids to Aldehydes; (4-Methoxyphenyl)phenylmethanol (7)

Phenylboronic acid (2.40 g, 19.6 mmol), imidazolium chloride **2** (42 mg, 0.098 mmol, 1 mol %),[13a] NaOMe (0.53 g, 9.8 mmol), 4-methoxybenzaldehyde (1.33 g, 9.8 mmol) and water (10 mL) were successively added to a suspension of $RhCl_3 \cdot 3\,H_2O$ (26 mg, 0.098 mmol, 1 mol %) in DME (40 mL). The resulting mixture was heated for 30 min at 80 °C, cooled to ambient temperature, diluted with ethyl acetate (50 mL) and extracted with water. After drying over Na_2SO_4, the organic phase was evaporated and the residue was purified by flash chromatography (hexane/ethyl acetate, 6/1) thus affording the title compound as a colorless syrup that slowly crystallized upon standing at ambient temperature; yield: 1.96 g (93%); IR: ν = 3408, 3065, 3008, 2951, 2909, 2836, 1612, 1587, 1517, 1494, 1445, 1305, 1265, 1254, 1178, 1110, 1034, 1018, 1008, 841, 810, 727, 697 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.26–7.37 (m, 7H), 6.86 (d, 2H, *J* = 8.0 Hz), 5.77 (br. s, 1H, OH), 3.78 (s, 3H), 2.34 (br. s, 1H, OH); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.4, 144.8, 136.8, 128.7, 128.0, 127.6, 126.6, 114.1, 75.9, 55.5; MS: *m/z* (rel. intensity) = 214 ([M^+], 76), 213 (18), 197 (14), 137 (42), 136 (13), 135 (50), 109 (100), 108 (39), 105 (53), 94 (13), 77 (39). The analytical and spectroscopic data are in agreement with those previously reported in the literature.[24]

All other compounds were prepared analogously. The analytical and spectroscopic data of products **9**,[25] **10**,[26] **12**,[27] **14**,[28] **17**,[29] **24**,[19] were in agreement with those of authentic samples prepared according to literature procedures; the data of new compounds are compiled below.

Compound 8: IR: ν = 3219, 3059, 3027, 2884, 1692, 1569, 1493, 1454, 1418, 1313, 1180, 1091, 1039, 1024, 778, 768, 702 cm^{-1}; ^{1}H NMR (300 MHz, CD_2Cl_2): δ = 7.20–7.59 (m, 9H), 5.76 (s, 1H), 2.72 (br. s, 1H, -OH); ^{13}C NMR (75 MHz, CD_2Cl_2): δ = 146.8, 143.8, 130.7, 130.4, 129.7, 128.9, 128.2, 126.8, 125.5, 122.8, 75.7; MS: *m/z* (rel. intensity) = 264/262 ([M^+], 20), 185 (19), 183 (32), 165 (12), 107 (13), 106 (11), 105 (100), 79 (27), 78 (25), 77 (44), 76 (10), 51 (15); anal.: calcd. for $C_{13}H_{11}BrO$: C, 59.3; H 4.2; found: C, 59.22; H, 4.08.

Compound 11: IR: ν = 3480, 3088, 3028, 2922, 2847, 1703, 1604, 1495, 1464, 1452, 1404, 1372, 1357, 1334, 1244, 1163, 1108, 1083, 1055, 1032, 758, 701 cm^{-1}; ^{1}H NMR (300 MHz, CD_2Cl_2): δ = 7.24–7.35 (m, 5H), 4.63 (dd, 1H, *J* = 6.2, 5.8 Hz), 2.39 (t, 2H, *J* = 7.3 Hz), 2.19 (br. s, 1H, OH), 2.08 (s, 3H), 1.50–1.74 (m, 4H), 1.27 (br. m, 14H); ^{13}C NMR (75 MHz, CD_2Cl_2): δ = 209.3, 145.8, 128.6, 127.6, 126.2, 74.7, 44.0, 39.7, 29.9, 29.8, 29.7, 29.5, 26.2, 24.2; MS: *m/z* (rel. intensity) = 290 ([M^+], 12), 184 (12), 107 (100), 91 (13), 79 (35), 77 (14), 71 (33), 59 (12), 58 (32), 43 (34), 41 (10); anal.: calcd. for $C_{19}H_{30}O_2$: C, 78.6; H, 10.4; found: C, 78.78; H, 10.44.

Compound 13: IR: ν = 3387, 3193, 3027, 2897, 1613, 1601, 1511, 1452, 1421, 1334, 1238, 1222, 1175, 1163, 1122, 1105, 1007, 859, 836, 818 cm^{-1}; ^{1}H NMR (300 MHz, THF-d_8): δ = 8.17 (br, 1H, OH); 7.55 (s, 4H), 7.13 (d, 2H, *J* = 8.5 Hz), 6.66 (d, 2H, *J* = 8.5 Hz), 5.68 (s, 1H), 4.80 (br. s, 1H, OH); ^{13}C NMR (75 MHz, THF-d_8): δ = 158.0, 151.6, 136.7, 129.2 (q, *J* = 32 Hz), 128.7, 127.6, 125.6, 125.5 (q, *J* = 269 Hz), 115.8, 75.4; MS: *m/z* (rel. intensity) = 268 ([M^+], 54), 267 (11), 173 (40), 145 (18), 123 (43), 122 (14), 121 (32), 95 (100), 94 (15), 77 (16); anal.: calcd. for $C_{14}H_{11}F_3O$: C, 62.7; H, 4.1; found: C, 62.57; H, 4.04.

Compound 15: IR: ν = 3359, 2896, 1619, 1504, 1489, 1444, 1327, 1248, 1164, 1124, 1067, 1040, 1017, 930, 853, 811, 785, 764 cm^{-1}; ^{1}H NMR (300 MHz, CD_2Cl_2): δ = 7.53 (AB, 4H, *J* = 8.3 Hz), 6.76–6.86 (m, 3H), 5.93 (m, 2H), 5.78 (s, 1H), 2.61 (br. s, 1H, OH); ^{13}C NMR (75 MHz, CD_2Cl_2): δ = 148.4, 147.7, 137.9, 129.4 (q, *J* = 32 Hz), 126.9, 125.7, 124.9 (q, *J* = 270 Hz), 120.5, 108.4, 107.4, 101.7, 75.7; MS: *m/z* (rel. intensity) = 296 ([M^+], 100), 279 (13), 197 (10), 173 (32), 152 (11), 151 (39), 149 (22), 145 (19), 127 (10), 123 (88), 121 (10), 93 (63), 65 (25); anal.: calcd. for $C_{15}H_{11}F_3O_3$: C, 60.8; H, 3.7; found: C, 60.76; H, 3.73.

Compound 16: IR: ν = 3080, 3020, 2993, 2941, 1750, 1719, 1690, 1622, 1607, 1590, 1486, 1423, 1371, 1329, 1248, 1223, 1167, 1120, 1069, 1031, 1017, 984, 928, 861, 707 cm^{-1}; ^{1}H NMR (300 MHz, CD_2Cl_2): δ = 7.12–7.66 (m, 8H), 6.91 (s, 1H), 2.22 (s, 6H), 2.17 (s, 3H); ^{13}C NMR (75 MHz, CD_2Cl_2): δ = 173.0, 170.0, 144.3, 141.9, 140.4, 130.4 (q, *J* = 32 Hz), 130.3, 129.1, 127.7, 125.9, 124.5 (q, *J* = 270 Hz), 75.8, 27.1, 21.1; MS: *m/z* (rel. intensity) = 393 ([M^+], 15), 351 (65), 291 (75), 250 (32), 181 (53), 43 (100); anal.: calcd. for $C_{20}H_{18}F_3NO_4$: C, 61.1; H, 4.6; found: C, 61.28; H, 4.53.

Compound 18: IR: ν = 3570, 3475, 3002, 2968, 2941, 2840,

1617, 1594, 1477, 1459, 1437, 1417, 1329, 1245, 1221, 1168, 1130, 1111, 1068, 1033, 1016, 873, 841, 783, 766, 731 cm^{-1}; ^1H NMR (300 MHz, CD_2Cl_2): δ = 7.52 (AB, 4H, *J* = 8.5 Hz), 7.28 (t, 1H, *J* = 8.5 Hz), 6.65 (d, 2H, *J* = 8.5 Hz), 6.33 (br. d, 1H, *J* = 11.3 Hz), 4.31 (br. d, 1H, *J* = 11.3 Hz), 3.80 (s, 6H); ^{13}C NMR (75 MHz, CD_2Cl_2): δ = 158.0, 149.9, 129.7, 128.5 (q, *J* = 32 Hz), 126.2, 125.1, 124.9 (q, *J* = 270 Hz), 119.3, 104.9, 68.2, 56.1 (2×); MS: *m/z* (rel. intensity) = 313 (16), 312 ([M^+], 94), 295 (17), 294 (85), 293 (10), 279 (11), 263 (15), 173 (21), 168 (12), 167 (100), 165 (24), 159 (16), 151 (19), 149 (29), 145 (22), 139 (23), 137 (24), 135 (20), 127 (16), 122 (17), 107 (25), 77 (16); anal.: calcd. for $C_{16}H_{15}F_3O_3$: C, 61.5; H, 4.8; found: C, 61.57; H, 4.84.

Compound 19: IR: ν = 3347, 3108, 2882, 1620, 1417, 1327, 1165, 1125, 1067, 1016, 854, 838, 790, 761, 710 cm^{-1}; ^1H NMR (300 MHz, CD_2Cl_2): δ = 7.57 (AB, 4H, *J* = 8.1 Hz), 7.32 (dd, 1H, *J* = 3.0, 5.1 Hz), 7.21 (dd, 1H, *J* = 1.0, 3.0 Hz), 6.99 (dd, 1H, *J* = 1.0, 5.0 Hz), 5.93 (s, 1H), 2.71 (br. s, 1H, OH); ^{13}C NMR (75 MHz, CD_2Cl_2): δ = 148.0, 145.2, 129.8 (q, *J* = 32 Hz), 127.0, 126.5, 125.8, 124.7 (q, *J* = 270 Hz), 122.4, 72.3; MS: *m/z* (rel. intensity) = 258 ([M^+], 58), 225 (14), 173 (32), 145 (21), 127 (14), 113 (24), 112 (15), 111 (38), 85 (100); anal.: calcd. for $C_{12}H_9F_3OS$: C, 55.8; H, 3.5; found: C, 55.90; H, 3.51.

Compound 20: IR: ν = 3373, 2998, 2956, 2926, 2855, 1667, 1611, 1586, 1512, 1465, 1442, 1302, 1248, 1173, 1038, 968, 831 cm^{-1}; ^1H NMR (300 MHz, CD_2Cl_2): δ = 7.28 (d, 2H, *J* = 6.8 Hz), 6.88 (d, 2H, *J* = 6.8 Hz), 5.65–5.74 (m, 2H), 5.08 (d, 1H, *J* = 4.9 Hz), 3.79 (s, 3H), 2.03–2.11 (m, 3H), 1.28–1.40 (m, 8H), 0.91 (t, 3H, *J* = 7.0 Hz); ^{13}C NMR (75 MHz, CD_2Cl_2): δ = 159.4, 136.4, 133.1, 132.4, 127.7, 114.0, 74.9, 55.6, 32.6, 32.1, 29.5, 29.3, 23.0, 14.3; MS: *m/z* (rel. intensity): 248 ([M^+], 35), 247 (11), 217 (10), 164 (13), 163 (100), 150 (49), 137 (26), 135 (60), 121 (47), 109 (33), 108 (18), 77 (14), 55 (39); anal.: calcd. for $C_{16}H_{24}O_2$: C, 77.4; H, 9.7; found: C, 77.67; H, 9.93.

Compound 21: IR: ν = 3348, 2956, 2925, 2855, 1670, 1637, 1466, 1378, 1306, 1055, 1004, 967, 723 cm^{-1}; ^1H NMR (300 MHz, CD_2Cl_2): δ = 5.59 (dt, 1H, *J* = 6.1, 15.4 Hz), 5.54 (ddt, 1H, *J* = 1.3, 6.7, 15.4 Hz), 3.98 (q, 1H, *J* = 6.7 Hz), 2.02 (q, 2H, *J* = 6.5 Hz), 1.28–1.51 (m, 22H), 0.88 (t, 6H, *J* = 6 Hz); ^{13}C NMR (75 MHz, CD_2Cl_2): δ = 133.8, 132.1, 73.4, 37.9, 32.6, 32.3, 32.1, 30.0, 29.7, 29.6, 29.2, 26.1, 25.9, 23.1, 23.0, 14.3; MS: *m/z* (rel. intensity) = 254 ([M^+], 3), 169 (20), 156 (11), 141 (99), 123 (22), 96 (12), 81 (41), 71 (24), 69 (13), 67 (26), 58 (13), 57 (100); anal.: calcd. for $C_{17}H_{34}O$: C, 80.2; H, 13.5; found: C, 80.41; H, 13.30.

Compound 22: IR: ν = 3429, 2956, 2927, 2857, 1667, 1478, 1464, 1393, 1379, 1363, 1098, 1037, 997, 970 cm^{-1}; ^1H NMR (300 MHz, CD_2Cl_2): δ = 5.60 (dt, 1H, *J* = 6.8, 15.4 Hz), 5.49 (ddt, 1H, *J* = 1.1, 7.2, 15.4 Hz), 3.65 (d, 1H, *J* = 7.2 Hz), 2.04 (q, 2H, *J* = 6.7 Hz), 1.47 (br. s, 1H, OH), 1.27–1.38 (m, 8H), 0.86–0.91 (m, 12H); ^{13}C NMR (75 MHz, CD_2Cl_2): δ = 133.9, 130.4, 81.3, 35.0, 32.8, 32.1, 30.0, 29.2, 25.9, 23.0, 14.3; MS: *m/z* (rel. intensity) = 198 ([M^+], 1), 141 (41), 123 (15), 81 (30), 67 (16), 57 (100); anal.: calcd. for $C_{13}H_{26}O$: C, 78.7; H, 13.2; found: C, 78.96; H, 13.08.

Compound *anti*-25: $[\alpha]_D^{20}$ = 2.1° (*c* 0.73, CH_2Cl_2); IR: ν = 3443, 2977, 2959, 2928, 2873, 2857, 1700, 1478, 1457, 1390, 1366, 1256, 1175, 1098, 1071, 1052, 966, 849, 767 cm^{-1}; ^1H NMR (300 MHz, CD_2Cl_2): δ = 5.70 (dt, 1H, *J* = 6.2, 15.5 Hz), 5.43 (ddt, 1H, *J* = 1.3, 6.2, 15.5 Hz), 3.80–4.20 (br. m, 4H), 2.03 (q, 2H, *J* = 6.5 Hz), 1.26–1.51 (m, 23H), 0.88 (t, 3H, *J* = 6 Hz); ^{13}C NMR (75 MHz, CD_2Cl_2): δ = 133.3, 128.9, 94.8, 81.2, 74.4, 65.4, 62.8, 32.7, 32.1, 29.5, 29.3, 28.5, 26.5, 24.8, 23.0, 14.2; MS: *m/z* (rel. intensity) = 341 ([M^+], 1), 200 (31), 144 (26), 100 (72), 57 (100); anal.: calcd. for $C_{19}H_{35}NO_4$: C, 66.8; H, 10.3; found: C, 66.59; H, 10.15.

X-Ray Crystallographic Study of *anti*-24

$C_{17}H_{25}NO_4$, M = 307.38 g · mol^{-1}, colorless, crystal dimensions 0.50 × 0.25 × 0.05 mm, monoclinic $P2_1/c$ (no. 14), at 100 K a = 12.7491(8), b = 18.2535(12), c = 7.4578(4) Å, β = 99.750(2), V = 1710.48(18) $Å^3$, Z = 4, ρ = 1.194 Mg · m^{-3}, μ = 0.084 mm^{-1}, λ = 0.71073 Å. X-ray diffraction data were collected using a Nonius KappaCCD diffractometer employing ω-scans to cover reciprocal space up to 33.14° θ with 99.8% completeness, integration of raw data yielded a total of 17533 reflections, merged into 6510 unique reflections with R_{int} = 0.1900 after applying Lorentz, polarization and absorption corrections. The structure was solved by direct method using SHELXS-97,[30] and atomic positions and displacement parameters were refined using full matrix least-squares based on F^2 using SHELXL-97.[30] Refinement of 299 parameters using all reflections converged at R = 0.0836, wR = 0.2376, highest residual electron density peak 0.698 $Å^3$. Crystallographic data (excluding structure factors) have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-159665. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [Fax: (+44) 1223–336–033; E-mail: deposit@ccdc.cam.ac.uk].

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