Functionalization of 4,5-Dihydrobenzo[*g*]indazoles Using Magnesium- or Zinc-Heterocyclic Intermediates

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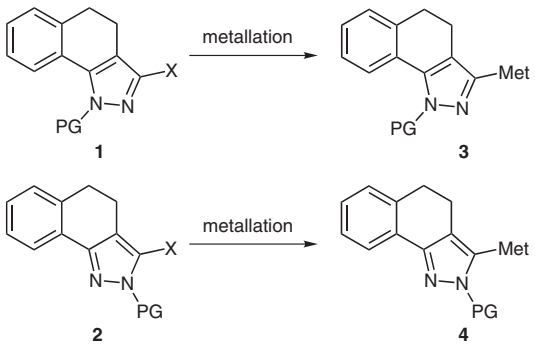
Received 4 June 2009; revised 1 July 2009

Abstract: 4,5-Dihydrobenzo[*g*]indazoles were efficiently metallated using hindered Mg- and Zn-TMP amides. Trapping of the resulting organometallic reagents with various electrophiles furnished novel C3-substituted 4,5-dihydrobenzo[*g*]indazoles.

Key words: 4,5-dihydrobenzo[*g*]indazoles, metallations, Grignard reactions, magnesium, zinc

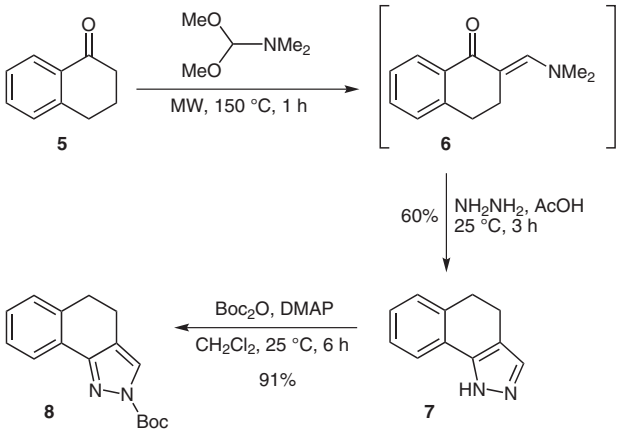
Fused pyrazoles and their derivatives are known to possess a wide range of biological activities.[1] For example, pyrazoles fused to a steroid A-ring have been reported to enhance anti-inflammatory activity.[2] Other tricyclic pyrazoles show antimicrobial, antiallergic, and nonestrogenic contraceptive activities.[3] Since steroid based pharmaceuticals often have side effects in living organisms, these nonsteroidal pyrazole derivatives may deserve attention as potential steroid analogues.[4]

Herein, we wish to report metallation procedures of heterocycles of type **1** and **2** using either an iodine–magnesium exchange (X = I) or deprotonation reactions (X = H) leading to metallated dihydrobenzo[*g*]indazoles of type **3** and **4** (Scheme 1).



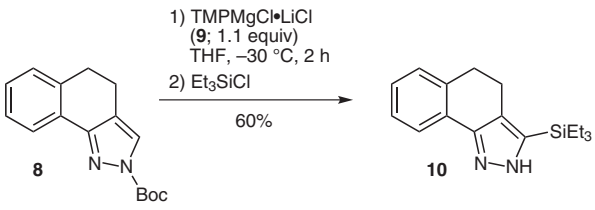
Scheme 1 Metallation of the dihydrobenzo[*g*]indazoles of type **1** and **2**

The required 4,5-dihydrobenzo[*g*]indazoles of type **1** and **2** were readily prepared from commercially available materials. The reaction of α-tetralone (**5**) with dimethylformamide dimethylacetal under microwave irradiation (150 °C, 1 h) gave the *exo*-alkylidene ketone **6**. Subsequent addition of hydrazine in acetic acid (25 °C, 3 h) furnished the desired 4,5-dihydrobenzo[*g*]indazole **7** in 60% yield. Protection of the pyrazole moiety with Boc_2O gave 4,5-dihydrobenzo[*g*]indazole-2-carboxylic acid *tert*-butyl ester (**8**) as a single isomer in 91% yield (Scheme 2).



Scheme 2 Preparation of 4,5-dihydrobenzo[*g*]indazole-2-carboxylic acid *tert*-butyl ester (**6**)

Using commercially available TMPMgCl·LiCl (**9**) base,[5,6] we were able to deprotonate **8** selectively at the C3 position of the pyrazole ring at –30 °C within two hours (Scheme 3). Reaction of the resulting magnesiated intermediate with Et_3SiCl furnished the 3-triethylsilyl-4,5-dihydrobenzo[*g*]indazole (**10**) in 60% yield. The Boc-protecting group was cleaved during the workup.

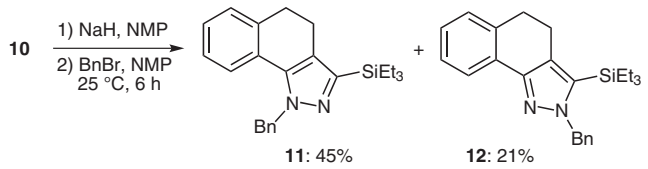


Scheme 3 Deprotonation of 4,5-dihydrobenzo[*g*]indazole-2-carboxylic acid *tert*-butyl ester (**8**) at C3 and reaction with Et_3SiCl

The silylated benzo[*g*]indazole **8** was benzylated providing a mixture of the 1-benzyl-3-triethylsilyl-4,5-dihydro-1*H*-benzo[*g*]indazole (**11**) and the 2-benzyl-3-triethylsi-

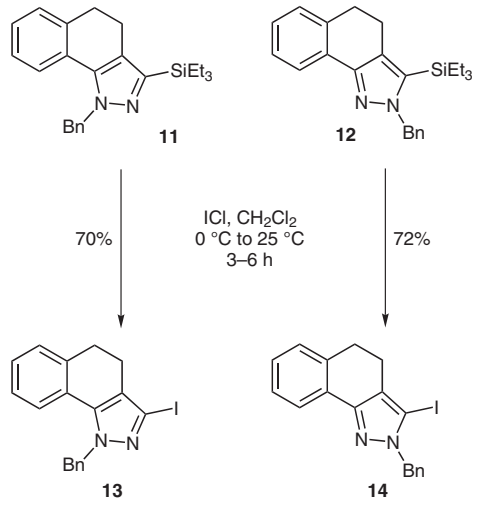
SYNTHESIS 2009, No. 21, pp 3661–3671
Advanced online publication: 23.09.2009
DOI: 10.1055/s-0029-1217008; Art ID: T11709SS

lyl-4,5-dihydro-2*H*-benzo[*g*]indazole (**12**), which could be separated by column chromatography and isolated in 45% and 21% yield, respectively (Scheme 4).



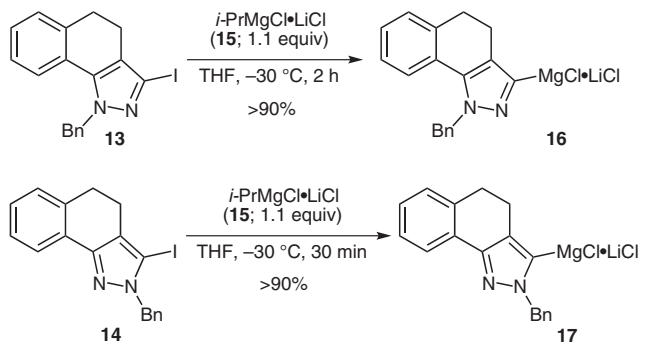
Scheme 4 Benzylation of 4,5-dihydrobenzo[*g*]indazole **8**

The silyl group of the benzo[*g*]indazoles **11** and **12** was readily converted into the corresponding heterocyclic iodides **13** and **14**, by reaction with ICl in CH_2Cl_2 (25 °C, 3–6 h) in 70–72% yields (Scheme 5).



Scheme 5 Iodination of benzo[*g*]indazoles **11** and **12** with ICl

The iodinated derivatives **13** and **14** were then magnesiated using iodine–magnesium exchange.[7] In both cases, a full conversion to the corresponding organomagnesium reagents could be achieved using commercially available *i*-PrMgCl·LiCl[8] (**15**) at –30 °C, leading to the corresponding organomagnesium species **16** and **17** (Scheme 6). Interestingly, the iodine–magnesium exchange rate of **13** was ca. four times slower than for the isomer **14**, which

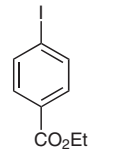
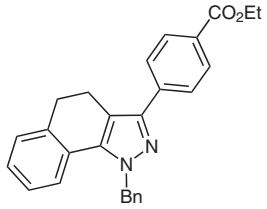
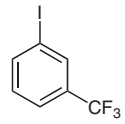
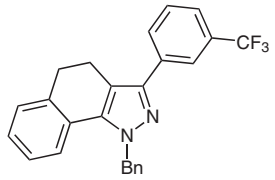
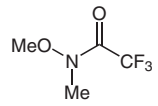
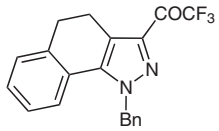
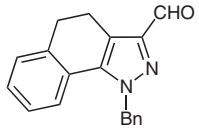
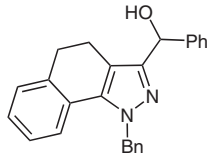
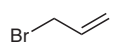
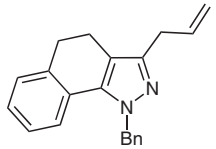


Scheme 6 Iodine–magnesium exchange on the isomeric benzo[*g*]indazoles **13** and **14**

may be indicative for the enhanced stability of **17** compared to **16**.

Trapping the magnesiated species **16** and **17** with various electrophiles, furnished a range of C3-substituted benzo[*g*]indazoles **18a–f** and **19a–d** as summarized in Tables 1 and 2, respectively. Thus, after a transmetallation of the magnesium reagent **16** with $ZnCl_2$, Negishi[9] cross-coupling reactions with aryl iodides could be carried out to furnish **18a** and **18b** in 68% and 59% yield, respectively (Table 1, entries 1 and 2). Reacting **16** with *N*-methoxy-*N*-methyltrifluoroacetamide provided the ke-

Table 1 Reactions of the 3-Magnesiated Heterocycle **16** with Electrophiles Leading to Products **18a–f**

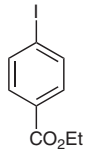
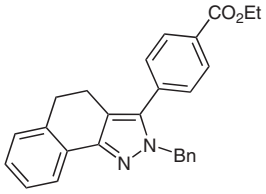
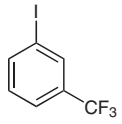
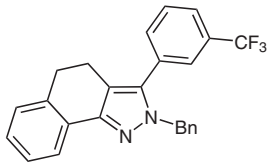
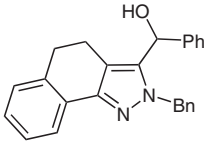
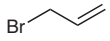
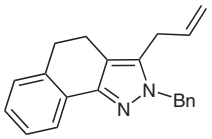
Entry	Electrophile	Product of type **18**	Yield (%)[a]
1		 **18a**	68[b]
2		 **18b**	59[b]
3		 **18c**	73
4	DMF	 **18d**	63
5	PhCHO	 **18e**	61
6		 **18f**	75[c]

[a] Isolated, analytically pure product.
[b] Obtained after transmetallation with $ZnCl_2$ (1.0 equiv) by Pd-catalyzed cross-coupling using $Pd(dba)_2$ (5 mol%) and (*o*-furyl)$_3$P (10 mol%).
[c] Transmetallation with CuCN·2LiCl (1.0 equiv).

tone **18c** in 73% yield. Trapping **16** with DMF and benzaldehyde, resulted in the formation of aldehyde **18d** and alcohol **18e** in 63% and 61% yield, respectively (entries 3–5). Transmetallation with CuCN·2LiCl[10] enabled the allylation of **16** with allyl bromide yielding **18f** in 75% yield (entry 6).

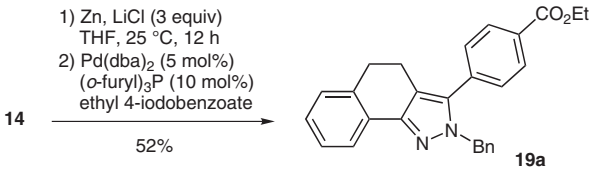
Similarly, the 3-magnesiated heterocycle **17** also underwent Negishi[9] cross-coupling reactions (after transmetallation with $ZnCl_2$) affording benzo[*g*]indazoles **19a** and **19b** in 65% and 67% yield, respectively (Table 2, entries 1 and 2). Alcohol **19c** was obtained in 68% yield after trapping the organomagnesium reagent **17** with benzaldehyde (entry 3). Allylation of **17** with allyl bromide afforded (after transmetallation with CuCN·2LiCl[10]) **19d** in 74% yield (entry 3 and 4).

Table 2 Reactions of the 3-Magnesiated Heterocycle **17** with Electrophiles Leading to Products **19a–d**

Entry	Electrophile	Product of type **19**	Yield (%)[a]
1		 **19a**	67[b]
2		 **19b**	65[b]
3	PhCHO	 **19c**	68
4		 **19d**	74[c]

[a] Isolated, analytically pure product.
[b] Obtained after transmetallation with $ZnCl_2$ (1.0 equiv) by Pd-catalyzed cross-coupling using $Pd(dba)_2$ (5 mol%) and $(o\text{-furyl})_3P$ (10 mol%).
[c] Transmetallation with CuCN·2LiCl (1.0 equiv).

The reactivity difference of the two isomeric iodides **13** and **14** became more apparent when performing a zinc insertion.[11] In the case of **14**, the insertion in the presence of LiCl was complete within 12 hours at 25 °C, leading to the corresponding zinc reagent which underwent a Negishi[9] cross-coupling furnishing **19a** in 52% yield (Scheme 7).

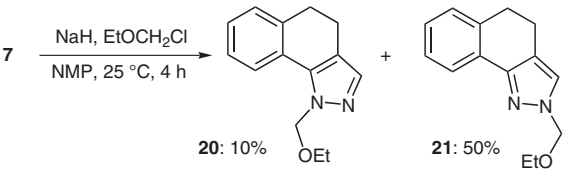


Scheme 7 Zn-insertion in compound **14** and cross-coupling with ethyl 4-iodobenzoate

However benzo[*g*]indazole **13** proved to be inert towards zinc insertion, even at higher temperatures.

Next, we have examined the metallation of benzo[*g*]indazoles of type **1** and **2** by performing deprotonation reactions using the new mixed Mg/Li[5]- and Zn/Mg/Li-amides.[12]

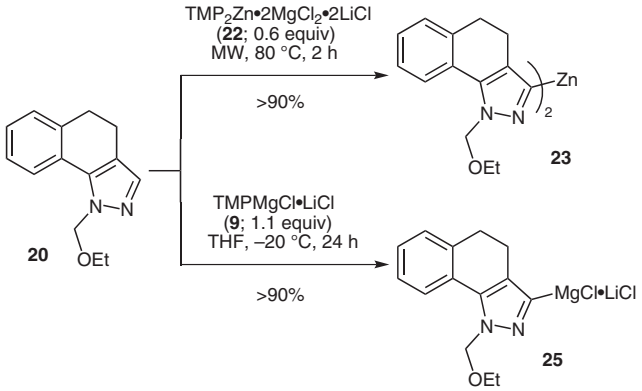
Treatment of **7** at 25 °C with NaH and reaction with $EtOCH_2Cl$ yielded 10% of 1-ethoxymethyl-4,5-dihydro-1*H*-benzo[*g*]indazole (**20**) and 50% of 2-ethoxymethyl-4,5-dihydro-2*H*-benzo[*g*]indazole (**21**), which could be readily separated by column chromatography (Scheme 8). The heterocycles **20** and **21** proved to be well suited for several directed metallations.



Scheme 8 Protection of **7** with (chloromethoxy)ethane

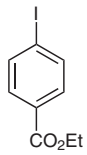
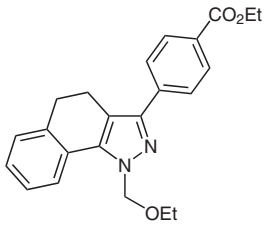
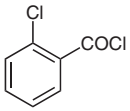
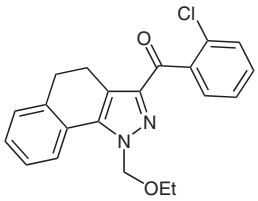
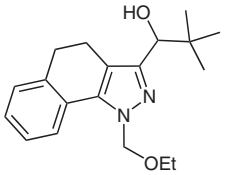
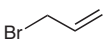
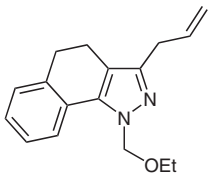
Thus, protected benzo[*g*]indazole **20** was deprotonated using $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$[12] (**22**) under microwave irradiation, leading to the zincorganometallic **23** (Scheme 9). This zinc reagent readily underwent a Negishi[9] cross-coupling with ethyl 4-iodobenzoate using $Pd(dba)_2$ (5 mol%) and $(o\text{-furyl})_3P$ (10 mol%) as catalyst providing the expected product **24a** in 62% yield (Table 3, entry 1). The reaction of **23** after transmetallation with CuCN·2LiCl[10]with an acyl chloride, afforded the expected product **24b** in 55% yield (entry 2). Magnesiation of the benzo[*g*]indazole **20** could also be performed using the base TMPMgCl·LiCl (**9**)[5] at –20 °C (Scheme 9). The magnesiated species **25** was successfully added to pivaldehyde leading to the corresponding alcohol **24c** in 60% yield (entry 3). After transmetallation with CuCN·2LiCl,[10] the organomagnesium reagent **25** reacted with allyl bromide to furnish the allylated product **24d** in 68% (entry 4).

Benzo[*g*]indazole **21**, proved more difficult to deprotonate at the C3 position. Treatment of **21** with TMPMgCl·LiCl[5] (**9**) gave only a conversion of 80% after stirring 48 hours at 25 °C. However, by using the stronger base $TMP_2Mg{\cdot}2LiCl$ (**26**)[5e,f] a full conversion to the magnesiated species **27** could be obtained within 12 hours at 0 °C (Scheme 10).

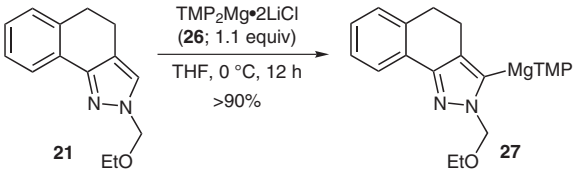


Scheme 9 Selective deprotonation of **20** at C3 using $TMP_2Mg{\cdot}2MgCl_2{\cdot}2LiCl$ (**22**) and TMPMgCl·LiCl (**9**)

Table 3 Reaction of the Metallated Species **23** and **25** with Electrophiles Leading to Products **24a–d**

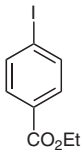
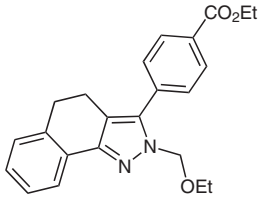
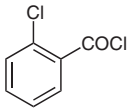
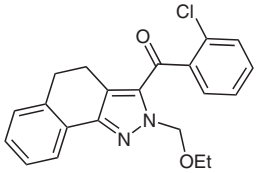
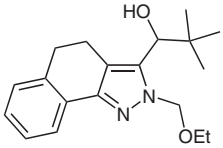
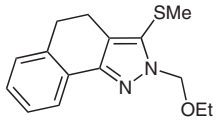
Mg or Zn reagent	Electrophile	Product of type **24**	Yield (%)[a]
23		 **24a**	62[b]
23		 **24b**	55[c]
25	*t*-BuCHO	 **24c**	60
25		 **24d**	68[c]

[a] Isolated, analytically pure product.
[b] Obtained by Pd-catalyzed cross-coupling using $Pd(dba)_2$ (5 mol%) and (*o*-furyl)$_3$P (10 mol%).
[c] Transmetallation with CuCN·2LiCl (1.0 equiv).



Scheme 10 Deprotonation of **21** at C3 using $TMP_2Mg{\cdot}2LiCl$ (**26**)

Table 4 Reaction of the Magnesiated Species **27** with Electrophiles Leading to Products **28a–d**

Entry	Electrophile	Product of type **28**	Yield (%)[a]
1			93[b]
2			60[c]
3	*t*-BuCHO		70
4	$MeSSO_2Me$		83

[a] Isolated, analytically pure product.
[b] Obtained after transmetallation with $ZnCl_2$ (1.0 equiv) by Pd-catalyzed cross-coupling using $Pd(dba)_2$ (5 mol%) and (*o*-furyl)$_3$P (10 mol%).
[c] Transmetallation with CuCN·2LiCl (1.0 equiv).

The organomagnesium reagent **27** underwent after transmetallation with $ZnCl_2$, a Negishi[9] cross-coupling reaction furnishing **28a** in 93% yield (Table 4, entry 1). Transmetallation of **27** with CuCN·2LiCl[10] enabled an acylation reaction with 2-chlorobenzoyl chloride and gave the ketone **28b** in 60% yield (entry 2). Reaction of **27** with pivaldehyde furnished the C3-substituted benzo[*g*]indazole **28c** in 70% yield (entry 3). Finally, the reaction of **27** with methanethiosulfonic acid *S*-methyl ester gave the expected product **28d** in 83% yield (entry 4).

In conclusion, we have reported metallation procedures of dihydrobenzo[*g*]indazoles of type **1** and **2** at the C3 position. The use of an iodine–magnesium exchange or direct metallations using TMPMgCl·LiCl (**9**), $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**22**) or $TMP_2Mg{\cdot}2LiCl$ (**26**) proved to be complementary. Further applications of these metallation methods to other polycyclic heterocycles are currently underway in our laboratories.

Unless otherwise indicated, all reactions were carried out with magnetic stirring and in flame-dried glassware under argon. Syringes used to transfer reagents and solvent were purged with argon prior to use. Reactions were monitored by gas chromatography (GC and GC-MS) or TLC. TLC was performed with aluminum plates covered with SiO_2 (Merck 60, F-254) and visualized either by UV detection or submerging in $KMnO_4$ solution (1.5 g $KMnO_4$, 10 g K_2CO_3, and 1.25 mL of aq 10% NaOH in 200 mL H_2O). Column chromatography was performed using Merck silica gel 60 (40–63 μm 230–400 mesh ASTM from Merck). NMR spectra were recorded in $CDCl_3$ or C_6D_6 and chemical shifts (δ) are reported in parts per million (ppm). GCs were recorded on Hewlett-Packard 6890 or 5890 Series II (Hewlett Packard, 5% phenylmethylpolysiloxane; length: 10 m, diameter: 0.25 mm; film thickness: 0.25 μm). *i*-PrMgCl·LiCl solutions were obtained from Chemetall as 14% solutions (in THF), and were titrated with I_2 prior to use.

4,5-Dihydro-1*H*-benzo[*g*]indazole (7)[13]

α-Tetralone (5.4 mL, 40 mmol) and dimethylformamide dimethylacetal (10.8 mL, 80 mmol) were dissolved in DMF (50 mL) and the reaction mixture was heated under microwave irradiation at 150 °C (200 W) for 60 min. To the dark red solution was then added AcOH (200 mL) and hydrazine hydrate (64% aq solution, 4 mL). The mixture was stirred at 25 °C for 3 h. The completion of the reaction was checked by GC analysis of the reaction aliquots. Most of the AcOH was then removed by evaporation. The mixture was quenched with aq sat. 50% $NaHCO_3$ (300 mL) and then extracted with toluene (3 × 300 mL). The combined organic phases were first washed with aq $NaHCO_3$ until neutral pH was obtained, then with H_2O (300 mL), and was finally dried (Na_2SO_4). After evaporation of the solvent, the residue was recrystallized from heptane to yield yellow crystals (4.1 g, 60%); mp 126–128 °C.

IR (Diamond ATR): 3142 (m), 2927 (m), 1469 (m), 1435 (m), 1382 (w), 1320 (w), 1169 (w), 1097 (w), 1066 (m), 954 (m), 887 (w), 789 (s), 767 (s), 736 (s), 716 (s), 652 (w), 609 cm^{-1} (m).

^1H NMR (300 MHz, C_6D_6): δ = 8.05 (d, $J_{H,H}$ = 7.1 Hz, 1 H), 7.13–7.03 (m, 3 H), 6.98 (s, 1 H), 2.65 (t, $J_{H,H}$ = 7.3 Hz, 2 H), 2.45 (t, $J_{H,H}$ = 7.3 Hz, 2 H).

^{13}C NMR (75 MHz, C_6D_6): δ = 146.5, 137.0, 130.0, 130.0 128.7, 127.6, 127.2, 122.6, 116.1, 30.1, 19.5.

MS (EI, 70 eV): *m*/*z* (%) = 171 (9), 170 (M^+, 100), 169 (63), 155 (2), 143 (27), 142 (27), 139 (3), 115 (21), 89 (5), 70 (4).

HRMS (EI): *m*/*z* calcd for $C_{11}H_{10}N_2$: 170.0844; found: 170.0836.

***tert*-Butyl 4,5-Dihydrobenzo[*g*]indazole-2-carboxylate (8)**

4,5-Dihydro-2*H*-benzo[*g*]indazole (**7**; 4.3 g, 25 mmol) was dissolved in CH_2Cl_2 (50 mL). Di-*tert*-butyl dicarbonate (7.0 g, 33 mmol) and DMAP (611 mg, 5 mmol) were added at 25 °C and the reaction mixture was stirred for 6 h. The completion of the reaction was checked by TLC and the excess of the unreacted di-*tert*-butyl dicarbonate was removed by adding diethylenediamine. The mixture was quenched with H_2O (100 mL) and extracted with Et_2O (3 × 100 mL). The combined organic phases were washed with H_2O (100 mL) and brine (100 mL), and dried (Na_2SO_4). After evaporation of the solvent, the residue was purified by flash chromatography (silica gel, pentane–Et_2O, 9:1) to give pale yellow crystals (840 mg, 91%); mp 75–76 °C.

IR (Diamond ATR): 2970 (w), 2938 (w), 1737 (s), 1450 (m), 1412 (m), 1356 (s), 1251 (s), 1149 (s), 959 (s), 845 (m), 764 (m), 719 cm^{-1} (m).

^1H NMR (400 MHz, $CDCl_3$): δ = 8.03–8.01 (m, 1 H), 7.79 (dd, $J_{H,H}$ = 1.1 Hz, 1 H), 7.28–7.19 (m, 3 H), 2.91 (t, $J_{H,H}$ = 7.2 Hz, 2 H), 2.76 (t, $J_{H,H}$ = 7.2 Hz, 2 H), 1.63 (s, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 152.5, 148.0, 137.7, 128.8, 128.3, 128.3, 126.9, 126.5, 123.8, 119.7, 84.7, 29.1, 28.0, 19.1.

MS (EI, 70 eV): *m*/*z* (%) = 270 (M^+, 7), 171 (10), 170 (100), 169 (56), 143 (24), 141 (19), 115 (17), 57 (13), 41 (11).

HRMS (EI): *m*/*z* calcd for $C_{16}H_{18}N_2O_2$: 270.1368; found: 270.1371.

3-(Triethylsilyl)-4,5-dihydro-2*H*-benzo[*g*]indazole (10)[13]

A flame-dried flask was flushed with argon and charged with **8** (1.35 g, 5 mmol) and THF (2 mL). The solution was cooled at –30 °C and TMPMgCl·LiCl (**9**; 5 mL, 1.1 M, 5.5 mmol) was added dropwise. The deprotonation was followed by GC analysis of reaction aliquots previously quenched with I_2. After 2 h, the deprotonation was complete and Et_3SiCl (904 mg, 6 mmol) was added at –30 °C. The reaction mixture was allowed to warm up to 25 °C. After completion of the reaction, the mixture was quenched with 50% aq sat. $NaHCO_3$ (50 mL) and extracted with Et_2O (3 × 50 mL). The combined organic phases were washed with H_2O (50 mL) and brine (50 mL), and dried (Na_2SO_4). After evaporation of the solvent, the residue was purified by flash chromatography (silica gel, pentane–Et_2O, 1:1) to give a white solid (815 mg, 60%); mp 125–126 °C.

IR (Diamond ATR): 2952 (w), 1738 (s), 1436 (w), 1377 (w), 1216 (m), 1064 (m), 995 (m), 891 (w), 769 (m), 723 cm^{-1} (s).

^1H NMR (600 MHz, $CDCl_3$): δ = 7.90 (d, $J_{H,H}$ = 7.6 Hz, 1 H), 7.29–7.19 (m, 3 H), 2.96 (t, $J_{H,H}$ = 7.4 Hz, 2 H), 2.84 (t, $J_{H,H}$ = 7.2 Hz, 2 H), 1.01 (t, $J_{H,H}$ = 8.1 Hz, 9 H), 0.88 (q, $J_{H,H}$ = 7.8 Hz, 6 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 148.7, 136.6, 135.3, 130.0, 128.1, 127.2, 126.7, 124.2, 122.5, 30.0, 20.5, 7.3, 3.3.

MS (EI, 70 eV): *m*/*z* (%) = 286 (4), 285 (16), 284 (M^+, 73), 256 (15), 255 (50), 228 (17), 227 (100), 199 (41), 170 (10), 128 (3), 114 (8), 100 (10), 59 (7).

HRMS (EI): *m*/*z* calcd for $C_{17}H_{24}N_2Si$: 284.1709; found: 284.1704.

1-Benzyl-3-triethylsilyl-4,5-dihydro-1*H*-benzo[*g*]indazole (11) and 2-Benzyl-3-triethylsilyl-4,5-dihydro-2*H*-benzo[*g*]indazole (12)

A flame-dried flask was flushed with argon and charged with **10** (3.12 g, 11 mmol) and NMP (20 mL). At 25 °C, NaH 60% in oil (480 mg, 12 mmol) was added and the mixture was stirred until no gas emission occurred. After approximately 2 h, benzyl bromide (2.2 g, 13 mmol) was added and the reaction mixture was stirred for 6 h. The completion of the reaction was checked by GC analysis, which showed that the 2 regioisomers were formed in a 2:1 ratio (**11**/**12**). The crude mixture was quenched with H_2O (100 mL) and extracted with Et_2O (3 × 100 mL). The combined organic phases were washed with H_2O (100 mL) and brine (100 mL), and dried (Na_2SO_4). After evaporation of the solvent, the two regioisomers were separated by flash chromatography (silica gel, pentane–Et_2O, 8:2). In the first fraction benzoindazole **11** was isolated as a pale yellow oil in 44% yield (1.8 g) whereas **12** was isolated as a pale yellow oil in the second fraction in 21% yield (860 mg).

1-Benzyl-3-triethylsilyl-4,5-dihydro-1*H*-benzo[*g*]indazole (11)

IR (Diamond ATR): 2952 (w), 2873, 1739 (s), 1454 (w), 1334 (m), 1276 (m), 1253 (m), 1154 (m), 1002 (m), 974 (w), 864 (w), 763 (m), 725 (s), 694 cm^{-1} (s).

^1H NMR (600 MHz, $CDCl_3$): δ = 7.38–7.36 (m, 1 H), 7.32–7.29 (m, 2 H), 7.26–7.23 (m, 2 H), 7.12–7.08 (m, 4 H), 5.70 (s, 2 H), 2.88 (t, $J_{H,H}$ = 7.4 Hz, 2 H), 2.77 (t, $J_{H,H}$ = 7.4 Hz, 2 H), 1.03 (t, $J_{H,H}$ = 7.9 Hz, 9 H), 0.89 (q, $J_{H,H}$ = 7.9 Hz, 6 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 145.7, 138.0, 137.7, 137.5, 128.7, 128.5, 127.4, 127.2, 126.9, 126.7, 126.2, 126.1, 122.2, 54.6, 31.2, 21.1, 7.5, 3.8.

MS (EI, 70 eV): *m*/*z* (%) = 375 (26), 374 (M^+, 79), 373 (10), 347 (18), 346 (64), 345 (62), 318 (17), 317 (56), 290 (12), 289 (44), 287 (12), 284 (20), 283 (78), 256 (19), 255 (79), 253 (11), 228 (13), 227 (55), 226 (14), 225 (17), 199 (15), 198 (18), 197 (22), 195 (9), 170 (20), 169 (11), 167 (12), 143 (8), 115 (20), 110 (8), 92 (8), 91 (100), 87 (14), 59 (18).

HRMS (ESI): *m*/*z* calcd for $C_{24}H_{30}N_2Si$: 374.2178; found: 375.2253 $[M + H]^+$.

2-Benzyl-3-triethylsilyl-4,5-dihydro-2*H*-benzo[*g*]indazole (12)

IR (Diamond ATR): 2952 (m), 2874 (w), 1737 (s), 1454 (w), 1334 (m), 1248 (s), 1154 (s), 1001 (m), 957 (w), 892 (w), 840 (w), 723 (s), 695 cm^{-1} (s).

^1H NMR (600 MHz, $CDCl_3$): δ = 7.88 (d, $J_{H,H}$ = 7.7 Hz, 1 H), 7.27–7.18 (m, 6 H), 6.96 (d, $J_{H,H}$ = 7.0 Hz, 2 H), 5.49 (s, 2 H), 2.96 (t, $J_{H,H}$ = 7.3 Hz, 2 H), 2.87 (t, $J_{H,H}$ = 7.6 Hz, 2 H), 0.87 (t, $J_{H,H}$ = 7.8 Hz, 9 H), 0.73 (q, $J_{H,H}$ = 7.5 Hz, 6 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 147.9, 138.8, 136.2, 135.9, 130.0, 128.4, 128.0, 127.1, 127.1, 127.0, 126.8, 125.9, 122.5, 55.9, 30.0, 21.1, 7.2, 3.7.

MS (EI, 70 eV): *m*/*z* (%) = 376 (6), 375 (23), 374 (M^+, 24), 346 (30), 345 (100), 317 (6), 287 (6), 197 (6), 172 (9), 91 (31), 59 (17).

HRMS (ESI): *m*/*z* calcd for $C_{24}H_{30}N_2Si$: 374.2178; found: 375.2257 $[M + H]^+$.

1-Benzyl-3-iodo-4,5-dihydro-1*H*-benzo[*g*]indazole (13)

A dry flask was flushed with argon and charged with **11** (748 mg, 2 mmol) and CH_2Cl_2 (2 mL). ICl (390 mg, 2.4 mmol) was added to the solution at 0 °C. The completion of the reaction was checked by GC-analysis of reaction aliquots. After 3 h, the mixture was quenched with aq sat. $Na_2S_2O_3$ (50 mL) and extracted with Et_2O (3 × 50 mL). The combined organic phases were washed with H_2O (50 mL) and brine (50 mL), and dried (Na_2SO_4). After evaporation of the solvent the crude mixture was purified by flash chromatography (silica gel, pentane–Et_2O, 9:1) to yield 70% (540 mg) of **13** as a white solid; mp 119–121 °C.

IR (Diamond ATR): 2932 (w), 1450 (w), 1409 (m), 1358 (w), 1307 (w), 1150 (w), 1083 (m), 907 (m), 763 (m), 726 (s), 694 cm^{-1} (s).

^1H NMR (300 MHz, $CDCl_3$): δ = 7.36–7.26 (m, 5 H), 7.21–7.10 (m, 4 H), 5.64 (s, 2 H), 2.92 (t, $J_{H,H}$ = 7.4 Hz, 2 H), 2.62 (t, $J_{H,H}$ = 7.4 Hz, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 139.3, 137.9, 136.8, 129.0, 128.9, 128.1, 127.6, 126.9, 126.2, 126.1, 124.3, 122.5, 95.7, 55.1, 30.5, 20.9.

MS (EI, 70 eV): *m*/*z* (%) = 388 (2), 387 (16), 386 (M^+, 100), 385 (29), 384 (2), 294 (4), 260 (5), 259 (24), 258 (5), 257 (4), 232 (2), 193 (3), 168 (3), 143 (3), 140 (4), 139 (6), 129 (3), 127 (2), 115 (2), 91 (63).

HRMS (EI): *m*/*z* calcd for $C_{18}H_{15}IN_2$: 386.0280; found: 386.0276.

2-Benzyl-3-iodo-4,5-dihydro-2*H*-benzo[*g*]indazole (14)

A dry flask was flushed with argon and charged with **12** (380 mg, 1 mmol) and CH_2Cl_2 (1 mL). ICl (194 mg, 1.1 mmol) was added to the solution at 0 °C. The completion of the reaction was checked by GC-analysis of reaction aliquots. After 6 h, the mixture was quenched with aq sat. $Na_2S_2O_3$ (50 mL) and extracted with Et_2O (3 × 50 mL). The combined organic phases were washed with H_2O (50 mL) and brine (50 mL), and dried (Na_2SO_4). After evaporation of the solvent the crude mixture was purified by flash chromatography (silica gel, pentane–Et_2O, 9:1) to yield 72% (277 mg) of **14** as a pale yellow solid; mp 96–98 °C.

IR (Diamond ATR): 2913 (m), 2877 (m), 1474 (w), 1456 (w), 1373 (w), 1358 (w), 1320 (m), 1237 (m), 1068 (s), 1005 (m), 843 (m), 772 (m), 736 (s), 722 (s), 698 cm^{-1} (s).

^1H NMR (600 MHz, $CDCl_3$): δ = 7.84 (d, $J_{H,H}$ = 7.7 Hz, 1 H), 7.32–7.30 (m, 2 H), 7.27–7.21 (m, 6 H), 5.45 (s, 2 H), 2.96 (t, $J_{H,H}$ = 7.4 Hz, 2 H), 2.65 (t, $J_{H,H}$ = 7.4 Hz, 2 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 149.5, 136.8, 136.6, 129.3, 128.6, 128.4, 127.7, 127.7, 127.2, 126.9, 123.8, 122.1, 81.0, 55.5, 29.2, 20.6.

MS (EI, 70 eV): *m*/*z* (%) = 386 (M^+, 1), 296 (29), 295 (25), 294 (100), 293 (20), 259 (46), 230 (2), 217 (5), 203 (17), 168 (2), 140 (3), 115 (3), 91 (85), 65 (7).

HRMS (EI): *m*/*z* calcd for $C_{18}H_{15}IN_2$: 386.0280; found: 386.0276.

1-(Ethoxymethyl)-4,5-dihydro-1*H*-benzo[*g*]indazole (20) and 2-(Ethoxymethyl)-4,5-dihydro-2*H*-benzo[*g*]indazole (21)

A flame-dried flask was flushed with argon and charged with 4,5-dihydro-2*H*-benzo[*g*]indazole (**7**; 1.7 g, 10 mmol) and NMP (10 mL). At 25 °C, NaH 60% in oil (450 mg, 11 mmol) was added and the mixture was stirred until no gas emission occurred. After approximately 30 min, (chloromethoxy)ethane (1.1 g, 12 mmol) was added and the mixture was stirred for 4 h at 25 °C. The completion of the reaction was checked by GC analysis, which showed that the 2 regioisomers were formed in a 1:5 ratio (**20/21**). The crude mixture was quenched with H_2O (100 mL) and extracted with Et_2O (3 × 100 mL). The combined organic phases were washed with H_2O (100 mL) and brine (100 mL), and dried (Na_2SO_4). After evaporation of the solvent, the two regioisomers were separated by flash chromatography (silica gel, pentane–Et_2O, 9:1). In the first fraction benzo[*g*]indazole **20** was isolated in 10% yield (230 mg) as yellow oil, whereas **21** was isolated in the second fraction in 50% yield (1.1 g) as a yellow oil.

1-(Ethoxymethyl)-4,5-dihydro-1*H*-benzo[*g*]indazole (20)

IR (Diamond ATR): 2975 (w), 2937 (w), 1707 (w), 1514 (w), 1466 (m), 1448 (m), 1382 (m), 1303 (m), 1262 (w), 1231 (w), 1161 (w), 1089 (s), 1017 (m), 984 (m), 891 (m), 845 (m), 784 (s), 763 (s), 734 (s), 695 (s), 627 cm^{-1} (m).

^1H NMR (600 MHz, $CDCl_3$): δ = 7.86 (d, $J_{H,H}$ = 7.8 Hz, 1 H), 7.38 (s, 1 H), 7.34–7.29 (m, 2 H), 7.24–7.21 (m, 1 H), 5.64 (s, 2 H), 3.70 (q, $J_{H,H}$ = 7.0 Hz, 2 H), 2.89 (t, $J_{H,H}$ = 7.4 Hz, 2 H), 2.71 (t, $J_{H,H}$ = 7.4 Hz, 2 H), 1.21 (t, $J_{H,H}$ = 7.0 Hz, 3 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 138.6, 137.5, 136.2, 128.6, 127.6, 127.1, 126.9, 123.7, 119.3, 79.2, 64.2, 30.5, 19.7, 14.9.

MS (EI, 70 eV): *m*/*z* (%) = 228 (M^+, 11), 192 (14), 184 (24), 183 (100), 169 (12), 165 (8), 143 (4), 142 (5), 128 (5), 127 (5), 115 (11), 101 (8), 83 (4), 74 (6), 69 (5), 59 (12), 57 (7), 55 (5), 45 (6), 44 (7), 43 (6), 41 (5).

HRMS (EI): *m*/*z* calcd for $C_{14}H_{16}N_2O$: 228.1263; found: 228.1261.

2-(Ethoxymethyl)-4,5-dihydro-2*H*-benzo[*g*]indazole (21)

IR (Diamond ATR): 2976 (w), 2933 (w), 1470 (m), 1439 (w), 1423 (w), 1330 (m), 1234 (m), 1141 (m), 1093 (s), 991 (m), 892 (m), 794 (m), 764 (s), 736 (m), 716 (s), 681 (w), 651 cm^{-1} (w).

^1H NMR (600 MHz, $CDCl_3$): δ = 7.88 (d, $J_{H,H}$ = 7.5 Hz, 1 H), 7.34 (s, 1 H), 7.27–7.19 (m, 3 H), 5.44 (s, 2 H), 3.58 (q, $J_{H,H}$ = 7.0 Hz, 2 H), 2.93 (t, $J_{H,H}$ = 7.3 Hz, 2 H), 2.77 (t, $J_{H,H}$ = 7.4 Hz, 2 H), 1.18 (t, $J_{H,H}$ = 7.0 Hz, 3 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 148.8, 136.7, 129.6, 128.3, 127.5, 126.8, 126.3, 122.4, 117.9, 80.5, 64.6, 29.5, 19.2, 14.9.

MS (EI, 70 eV): *m*/*z* (%) = 229 (13), 228 (M^+, 95), 184 (100), 183 (81), 181 (12), 170 (19), 169 (51), 168 (13), 143 (15), 142 (19), 140 (11), 139 (11), 128 (14), 127 (12), 116 (14), 115 (37), 59 (13).

HRMS (EI): *m*/*z* calcd for $C_{14}H_{16}N_2O$: 228.1263; found: 228.1261.

Iodine–Magnesium Exchange on 1-Benzyl-3-iodo-4,5-dihydro-1*H*-benzo[*g*]indazole (13); General Procedure 1 (GP1)

A flame-dried round-bottomed flask equipped with a magnetic stirring bar, an argon inlet, and a rubber septum was charged with **13** (386 mg, 1.0 mmol) dissolved in THF (1 mL). *i*-PrMgCl·LiCl (**15**; 1.0 mL, 1.1 M in THF, 1.1 mmol) was added slowly at –30 °C and the resulting mixture was stirred for 2 h. The completion of the exchange reaction was checked by GC-analysis of reaction aliquots. The freshly prepared organomagnesium reagent **16** was either transmetallated with $ZnCl_2$ (1.0 mL, 1.0 M, 1.0 mmol) and used in a Negishi cross-coupling with the corresponding iodides, or transmetallated with CuCN·2LiCl (1.0 mmol, 1.0 M, 1 mL) for subsequent allylation. When used directly, the corresponding electrophile (1.2 mmol) was added at –30 °C and the reaction mixture was slowly allowed to warm up to 25 °C. The consumption of the magnesium reagent was checked by GC analysis, using tetradecane as internal standard. After completion of the reaction, the mixture was quenched with aq sat. NH_4Cl [50 mL; in the presence of copper, 25% aq NH_3 (50 mL) was also added to the mixture] and extracted with Et_2O (3 × 50 mL). The combined organic extracts were dried (Na_2SO_4), filtered, and concentrated in vacuum. Purification by column chromatography afforded the desired C3-functionalized 4,5-dihydro-1*H*-benzo[*g*]indazoles **18a–f**.

4-(1-Benzyl-4,5-dihydro-1*H*-benzo[*g*]indazol-3-yl)benzoic Acid Ethyl Ester (18a)

According to GP1, the 3-magnesiated heterocycle **16** (1 mmol) was transmetallated with $ZnCl_2$ (1 mL, 1.0 M, 1 mmol) and stirred for 30 min at –30 °C. Ethyl 4-iodobenzoate (331 mg, 1.2 mmol) was dissolved in THF (1 mL) and mixed with $Pd(dba)_2$ (28 mg, 0.05 mmol) and (*o*-furyl)$_3$P (23 mg, 0.10 mmol). This mixture was added to the zinc reagent at –30 °C and the mixture was slowly allowed to warm up to 25 °C. After purification by column chromatography (silica gel, pentane–Et_2O, 9:1), **18a** was isolated as a white solid (277 mg, 68%); mp 118–119 °C.

IR (Diamond ATR): 2981 (m), 1709 (s), 1611 (m), 1449 (m), 1364 (m), 1270 (s), 1099 (s), 1018 (m), 857 (m), 776 (m), 721 (s), 695 cm^{-1} (m).

^1H NMR (400 MHz, $CDCl_3$): δ = 8.14 (d, $J_{H,H}$ = 8.6 Hz, 2 H), 7.86 (d, $J_{H,H}$ = 8.6 Hz, 2 H), 7.35–7.26 (m, 5 H), 7.21–7.15 (m, 4 H), 5.73 (s, 2 H), 4.41 (q, $J_{H,H}$ = 7.2 Hz, 2 H), 2.99–2.93 (m, 4 H), 1.42 (t, $J_{H,H}$ = 7.2 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.5, 146.1, 139.7, 138.1, 137.4, 137.1, 129.8, 129.1, 128.8, 128.7, 127.6, 127.5, 126.9, 126.8, 126.1, 122.3, 116.7, 60.9, 54.8, 30.9, 20.6, 14.3.

MS (EI, 70 eV): *m*/*z* (%) = 409 (24), 408 (M^+, 100), 407 (91), 406 (33), 393 (4), 379 (7), 363 (6), 331 (10), 317 (6), 303 (3), 289 (4), 259 (7), 244 (4), 216 (6), 215 (12), 91 (50).

HRMS (EI): *m*/*z* calcd for $C_{27}H_{24}N_2O_2$: 408.1838; found: 408.1826.

1-Benzyl-3-[3-(trifluoromethyl)phenyl]-4,5-dihydro-1*H*-benzo[*g*]indazole (18b)

According to GP1, the 3-magnesiated heterocycle **16** (1 mmol) was transmetallated with $ZnCl_2$ (1 mL l, 1.0 M, 1 mmol) and stirred for 30 min at –30 °C. 1-Iodo-3-trifluoromethylbenzene (327 mg, 1.2 mmol) was dissolved in THF (1 mL) and mixed with $Pd(dba)_2$ (28 mg, 0.05 mmol) and (*o*-furyl)$_3$P (23 mg, 0.10 mmol). This mixture was added to the zinc reagent at –30 °C and the mixture was slowly allowed to warm up to 25 °C. After purification by column chromatography (silica gel, pentane–Et_2O, 9:1), **18b** was isolated as a white solid (238 mg, 59%); mp 81–83 °C.

IR (Diamond ATR): 1452 (m), 1325 (s), 1316 (s), 1156 (s), 1122 (s), 1073 (w), 913 (m), 807 (m), 736 (m), 727 (s), 700 cm^{-1} (s).

^1H NMR (400 MHz $CDCl_3$): δ = 8.07 (s, 1 H), 7.98–7.96 (m, 1 H), 7.69–7.49 (m, 3 H), 7.36–7.27 (m, 4 H), 7.23–7.17 (m, 4 H), 5.75 (s, 2 H), 2.97 (s, 4 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 145.8, 139.8, 137.5, 137.1, 134.4, 130.9 (q, $J_{C,F}$ = 32.3 Hz), 130.4, 129.0, 128.9, 128.8, 127.7, 127.5, 126.9, 126.1, 126.1, 124.6 (q, $J_{C,F}$ = 3.7 Hz), 124.2 (q, $J_{C,F}$ = 272.3 Hz), 124.0 (q, $J_{C,F}$ = 3.7 Hz), 122.4, 118.7, 54.8, 30.9, 20.5.

MS (EI, 70 eV): *m*/*z* (%) = 406 (5), 405 (24), 404 (M^+, 100), 403 (80), 402 (19), 401 (5), 389 (5), 385 (4), 327 (18), 314 (4), 313 (15), 312 (3), 285 (3), 283 (6), 259 (11), 215 (3), 214 (12), 141 (4), 115 (3), 92 (6), 91 (66), 65 (6), 57 (3), 44 (19), 43 (3).

HRMS (EI): *m*/*z* calcd for $C_{25}H_{19}F_3N_2$: 404.1500; found: 404.1490.

1-(1-Benzyl-4,5-dihydro-1*H*-benzo[*g*]indazol-3-yl)-2,2,2-trifluoroethanone (18c)

According to GP1, the 3-magnesiated heterocycle **16** (1 mmol) was reacted with 2,2,2-trifluoro-*N*-methoxy-*N*-methylacetamide (189 mg, 1.2 mmol) at –30 °C. The mixture was slowly allowed to warm up to 25 °C. After purification by column chromatography (silica gel, pentane–Et_2O, 9:1), **18c** was isolated as a white solid (260 mg, 73%); mp 105–107 °C.

IR (Diamond ATR): 2981 (w), 1705 (s), 1498 (m), 1432 (m), 1320 (m), 1195 (s), 1141 (s), 1019 (m), 957 (s), 887 (s), 760 (m), 726 (s), 693 cm^{-1} (m).

^1H NMR (300 MHz, $CDCl_3$): δ = 7.39–7.30 (m, 5 H), 7.24–7.15 (m, 4 H), 5.78 (s, 2 H), 3.11 (t, $J_{H,H}$ = 7.6 Hz, 2 H), 2.95 (t, $J_{H,H}$ = 7.5 Hz, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 176.4 (q, $J_{C,F}$ = 36.1 Hz), 140.4, 140.0, 137.6, 135.5, 129.1, 129.1, 128.5, 128.0, 127.0, 126.2, 125.4, 124.7, 122.5, 116.4 (q, $J_{C,F}$ = 290.7 Hz), 56.0, 29.9, 19.7.

MS (EI, 70 eV): *m*/*z* (%) = 357 (15), 356 (M^+, 67), 355 (18), 287 (16), 279 (12), 266 (6), 265 (36), 264 (7), 259 (8), 195 (4), 168 (13), 143 (4), 139 (5), 92 (10), 91 (100), 83 (5), 71 (6), 69 (5), 65 (10), 57 (7), 44 (15), 41 (5).

HRMS (EI): *m*/*z* calcd for $C_{20}H_{15}F_3N_2O$: 356.1136; found: 356.1133.

1-Benzyl-4,5-dihydro-1*H*-benzo[*g*]indazole-3-carbaldehyde (18d)

According to GP1, the 3-magnesiated heterocycle **16** (1 mmol) was reacted with DMF (0.08 mL, 1.5 mmol) at –30 °C. The mixture was slowly allowed to warm up to 25 °C. After purification by column chromatography (silica gel, pentane–Et_2O, 9:1), **18d** was isolated as a white solid (181 mg, 63%); mp 99–101 °C.

IR (Diamond ATR): 1738 (s), 1686 (s), 1496 (w), 1439 (m), 1365 (m), 1217 (m), 1159 (w), 1017 (m), 833 (m), 791 (s), 766 (s), 725 (s), 704 (m), 693 cm^{-1} (m).

^1H NMR (400 MHz, $CDCl_3$): δ = 10.09 (s, 1 H), 7.38–7.28 (m, 5 H), 7.23–7.14 (m, 4 H), 5.73 (s, 2 H), 3.07 (t, $J_{H,H}$ = 7.5 Hz, 2 H), 2.92 (t, $J_{H,H}$ = 7.5 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 187.8, 146.3, 140.5, 137.9, 135.9, 129.0, 128.2, 127.9, 126.9, 126.2, 125.9, 122.3, 120.5, 55.6, 30.1, 19.3.

MS (EI, 70 eV): *m*/*z* (%) = 289 (18), 288 (M^+, 91), 287 (13), 260 (6), 259 (26), 211 (9), 198 (11), 197 (82), 196 (17), 170 (7), 169 (58), 142 (8), 139 (8), 115 (12), 91 (100) 89 (6), 65 (17), 43 (24).

HRMS (EI): *m*/*z* calcd for $C_{19}H_{16}N_2O$: 288.1263; found: 288.1258.

(1-Benzyl-4,5-dihydro-1*H*-benzo[*g*]indazol-3-yl)phenylmethanol (18e)

According to GP1, the 3-magnesiated heterocycle **16** (1 mmol) was reacted with benzaldehyde (127 mg, 1.2 mmol) at –30 °C. The mix-

ture was slowly allowed to warm up to 25 °C. After purification by column chromatography (silica gel, pentane–Et_2O, 8:2) **18e** was isolated as a pale yellow oil (223 mg, 61%).

IR (Diamond ATR): 2980 (m), 1496 (m), 1453 (m), 1382 (m), 1326 (m), 1261 (w), 1163 (m), 1122 (m), 764 (m), 724 (s), 695 cm^{-1} (s).

^1H NMR (400 MHz, $CDCl_3$): δ = 7.46 (d, $J_{H,H}$ = 7.0 Hz, 2 H), 7.36–7.31 (m, 4 H), 7.28–7.21 (m, 4 H), 7.15–7.08 (m, 4 H), 5.96 (d, $J_{H,H}$ = 3.8 Hz, 1 H), 5.63 (s, 2 H), 3.43 (br s, 1 H), 2.77 (t, $J_{H,H}$ = 7.4 Hz, 2 H), 2.41 (t, $J_{H,H}$ = 7.3 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 149.7, 142.6, 139.6, 137.6, 137.3, 128.8, 128.7, 128.3, 127.5, 127.5, 126.8, 126.8, 126.6, 126.2, 122.2, 115.8, 70.8, 54.6, 30.6, 19.2.

MS (EI, 70 eV): *m*/*z* (%) = 367 (26), 366 (M^+, 100), 365 (8), 350 (12), 349 (14), 348 (21), 347 (31), 275 (25), 273 (10), 271 (8), 259 (22), 258 (8), 257 (25), 256 (7), 244 (7), 229 (11), 197 (7), 183 (11), 169 (19), 115 (7), 105 (21), 92 (8), 91 (98), 77 (12), 65 (7).

HRMS (EI): *m*/*z* calcd for $C_{25}H_{22}N_2O$: 366.1732; found: 366.1725.

3-Allyl-1-benzyl-4,5-dihydro-1*H*-benzo[*g*]indazole (18f)

According to GP1, the 3-magnesiated heterocycle **16** (1 mmol) was transmetallated with CuCN·2LiCl (1.0 mL, 1.0 M, 1 mmol). After stirring for 15 min at –30 °C, it was reacted with allyl bromide (144 mg, 1.2 mmol). The mixture was slowly allowed to warm up to 25 °C. After purification by column chromatography (silica gel, pentane–Et_2O, 9:1), **18f** was isolated as a pale yellow oil (225 mg, 75%).

IR (Diamond ATR): 2980 (m), 1639 (w), 1486 (m), 1453 (m), 1158 (w), 912 (m), 760 (m), 728 (s), 694 cm^{-1} (s).

^1H NMR (400 MHz, $CDCl_3$): δ = 7.33–7.22 (m, 5 H), 7.17–7.09 (m, 4 H), 6.08–5.98 (m, 1 H), 5.61 (s, 2 H), 5.15–5.06 (m, 2 H), 3.46 (td, $J_{H,H}$ = 6.2, 1.6 Hz, 2 H), 2.89 (t, $J_{H,H}$ = 7.4 Hz, 2 H), 2.64 (t, $J_{H,H}$ = 7.4 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 146.0, 138.7, 137.6, 137.6, 135.7, 128.8, 128.7, 127.3, 127.2, 127.2, 126.8, 126.1, 122.2, 117.0, 115.6, 54.3, 31.5, 30.9, 19.2.

MS (EI, 70 eV): *m*/*z* = 301 (22), 300 (M^+, 100), 299 (68), 285 (9), 271 (4), 259 (8), 257 (8), 223 (15), 210 (7), 209 (38), 207 (7), 183 (10), 181 (8), 168 (6), 165 (7), 152 (4), 127 (4), 115 (7), 91 (59), 65 (7), 44 (9).

HRMS (EI): *m*/*z* calcd for $C_{21}H_{20}N_2$: 300.1626; found: 300.1620.

Iodine–Magnesium Exchange on 2-Benzyl-3-iodo-4,5-dihydro-2*H*-benzo[*g*]indazole (14); General Procedure 2 (GP2)

A flame-dried round-bottomed flask equipped with a magnetic stirring bar, an argon inlet, and a rubber septum was charged with **14** (386 mg, 1.0 mmol) dissolved in THF (1 mL). *i*-PrMgCl·LiCl (**15**; 1.0 mL, 1.1 M in THF, 1.1 mmol) was added slowly at –30 °C and the resulting mixture was stirred for 30 min. The completion of the exchange reaction was checked by GC analysis of reaction aliquots. The freshly prepared organomagnesium reagent **17** was either transmetallated with $ZnCl_2$ (1.0 mL, 1.0 M, 1.0 mmol) and used in a Negishi cross-coupling with the corresponding iodides, or transmetallated with CuCN·2LiCl (1 mL, 1.0 M, 1.0 mmol) for subsequent allylation. When used directly, the corresponding electrophile was added at –30 °C and the reaction mixture was slowly allowed to warm up to 25 °C. The consumption of the magnesium reagent was checked by GC analysis, using tetradecane as internal standard. After completion of the reaction, the mixture was quenched with aq sat. NH_4Cl [20 mL; in the presence of copper, 25% aq NH_3 (20 mL) was also added to the mixture] and extracted with Et_2O (3 × 50 mL). The combined organic extracts were dried (Na_2SO_4), filtered, and concentrated in vacuum. Purification by column chromatography afforded the desired C3-functionalized 4,5-dihydro-2*H*-benzo[*g*]indazoles **19a–d**.

4-(2-Benzyl-4,5-dihydro-2*H*-benzo[*g*]indazol-3-yl)benzoic Acid Ethyl Ester (19a)

According to GP2, the 3-magnesiated heterocycle **17** (1 mmol) was transmetallated with $ZnCl_2$ (1 mL, 1.0 M, 1 mmol) and stirred for 30 min at –30 °C. Ethyl 4-iodobenzoate (331 mg, 1.2 mmol) was dissolved in THF (1 mL) and mixed with $Pd(dba)_2$ (28 mg, 0.05 mmol) and (*o*-furyl)$_3$P (23 mg, 0.10 mmol). This mixture was added to the zinc reagent at –30 °C and the mixture was slowly allowed to warm up to 25 °C. After purification by column chromatography (silica gel, pentane–Et_2O, 9:1), **19a** was isolated as a white solid (273 mg, 67%); mp 95–96 °C.

IR (Diamond ATR): 2930 (w), 2831 (w), 1722 (s), 1612 (m), 1475 (m), 1436 (m), 1362 (m), 1310 (m), 1267 (s), 1101 (s), 1027 (m), 1008 (m), 864 (m), 770 (s), 728 (s), 701 cm^{-1} (s).

^1H NMR (400 MHz, $CDCl_3$): δ = 8.05 (d, $J_{H,H}$ = 8.3 Hz, 2 H), 7.93 (d, $J_{H,H}$ = 7.4 Hz, 1 H), 7.33 (d, $J_{H,H}$ = 8.1 Hz, 2 H), 7.30–7.20 (m, 6 H), 7.06 (d, $J_{H,H}$ = 7.4 Hz, 2 H), 5.37 (s, 2 H), 4.35 (q, $J_{H,H}$ = 7.2 Hz, 2 H), 2.96 (t, $J_{H,H}$ = 7.3 Hz, 2 H), 2.73 (t, $J_{H,H}$ = 7.3 Hz, 2 H), 1.40 (t, $J_{H,H}$ = 7.1 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.1, 147.0, 137.8, 136.7, 135.6, 133.6, 129.3, 128.8, 128.8, 128.1, 127.6, 127.3, 126.5, 126.4, 125.8, 125.7, 121.4, 115.4, 60.2, 52.5, 28.6, 18.4, 13.3.

MS (EI, 70 eV): *m*/*z* (%) = 409 (23), 408 (M^+, 100), 407 (48), 378 (7), 331 (8), 317 (10), 289 (6), 259 (15), 215 (12), 149 (4), 115 (4), 91 (30).

HRMS (EI): *m*/*z* calcd for $C_{27}H_{24}N_2O_2$: 408.1838; found: 408.1826.

2-Benzyl-3-(3-trifluoromethylphenyl)-4,5-dihydro-2*H*-benzo[*g*]indazole (19b)

According to GP2, the 3-magnesiated heterocycle **17** (1 mmol) was transmetallated with $ZnCl_2$ (1 mL, 1.0 M, 1mmol) and stirred for 30 min at –30 °C. 1-Iodo-3-trifluoromethylbenzene (327 mg, 1.2 mmol) was dissolved in THF (1 mL) and mixed with $Pd(dba)_2$ (28 mg, 0.05 mmol) and (*o*-furyl)$_3$P (23 mg, 0.10 mmol). This mixture was added to the zinc reagent at –30 °C and the mixture was slowly allowed to warm up to 25 °C. After purification by column chromatography (silica gel, pentane–Et_2O, 9:1), **19b** was isolated as a yellow oil (263 mg, 65%).

IR (Diamond ATR): 1496 (w), 1455 (w), 1331 (s), 1319 (s), 1168 (m), 1124 (s), 1073 (m), 1025 (w), 806 (w), 775 (w), 730 (s), 701 cm^{-1} (s).

^1H NMR (400 MHz, $CDCl_3$): δ = 7.96 (d, $J_{H,H}$ = 7.5 Hz, 1 H), 7.65 (d, $J_{H,H}$ = 7.7 Hz, 1 H), 7.55–7.42 (m, 3 H), 7.33–7.22 (m, 6 H), 7.80, (d, $J_{H,H}$ = 7.5 Hz, 2 H), 5.35 (s, 2 H), 2.97 (t, $J_{H,H}$ = 7.3 Hz, 2 H), 2.72 (t, $J_{H,H}$ = 7.2 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 147.8, 138.2, 137.5, 136.5, 132.5, 131.1 (q, $J_{C,F}$ = 32.4 Hz), 131.1, 129.7, 129.2, 128.6, 128.3, 127.6, 127.5, 126.9, 126.7, 126.1 (q, $J_{C,F}$ = 3.8 Hz), 125.1 (q, $J_{C,F}$ = 3.5 Hz), 123.8 (q, $J_{C,F}$ = 272.6 Hz), 122.4, 116.4, 53.6, 29.6, 19.3.

MS (EI, 70 eV): *m*/*z* (%) = 406 (3), 405 (23), 404 (M^+, 100), 403 (48), 402 (5), 389 (2), 385 (3), 329 (3), 328 (12), 315 (5), 314 (16), 285 (2), 283 (3), 260 (3), 259 (15), 216 (4), 215 (10), 213 (2), 142 (3), 115 (5), 92 (5), 91 (60), 89 (2), 65 (4), 44 (2).

HRMS (EI): *m*/*z* calcd for $C_{25}H_{19}F_3N_2$: 404.1500; found: 404.1490.

(2-Benzyl-4,5-dihydro-2*H*-benzo[*g*]indazol-3-yl)phenylmethanol (19c)

According to GP2, the 3-magnesiated heterocycle **17** (1 mmol) was reacted with benzaldehyde (127 mg, 1.2 mmol) at –30 °C. The mixture was slowly allowed to warm up to 25 °C. After purification by

column chromatography (silica gel, pentane–Et_2O, 8:2), **19c** was isolated as a pale yellow oil (249 mg, 68%).

IR (Diamond ATR): 1496 (w), 1453 (m), 1438 (m), 1290 (m), 1124 (w), 1097 (w), 1025 (m), 728 (s), 696 cm^{-1} (s).

^1H NMR (400 MHz, $CDCl_3$): δ = 8.19 (d, $J_{H,H}$ = 7.4 Hz, 1 H), 7.25–7.21 (m, 2 H), 7.13–6.94 (m, 11 H), 5.80 (s, 1 H), 5.21 (d, $J_{H,H}$ = 4.5 Hz, 2 H), 4.54 (br s, 1 H), 2.62–2.49 (m, 2 H), 2.45–2.38 (m, 1 H), 2.25–2.15 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 148.0, 141.7, 141.6, 140.5, 138.0, 136.7, 130.3, 128.6, 128.5, 128.5, 127.6, 127.5, 127.4, 127.0, 126.4, 122.9, 116.1, 67.0, 53.7, 29.6, 19.4.

MS (EI, 70 eV): *m*/*z* (%) = 367 (22), 366 (M^+, 100), 365 (5), 364 (8), 350 (5), 349 (5), 348 (11), 347 (15), 276 (5), 275 (29), 273 (3), 271 (6), 260 (4), 259 (17), 258 (3), 257 (9), 229 (6), 228 (4), 197 (9), 169 (5), 115 (4), 105 (10), 92 (4), 91 (49), 77 (4).

HRMS (EI): *m*/*z* calcd for $C_{25}H_{22}N_2O$: 366.1732; found: 366.1731.

3-Allyl-2-benzyl-4,5-dihydro-2*H*-benzo[*g*]indazole (19d)

According to GP2, the 3-magnesiated heterocycle **17** (1 mmol) was transmetallated with CuCN·2LiCl (1.0 mL, 1.0 M, 1 mmol). After stirring for 15 min at –30 °C, it was reacted with allyl bromide (144 mg, 1.2 mmol). The mixture was slowly allowed to warm up to 25 °C. After purification by column chromatography (silica gel, pentane–Et_2O, 9:1), **19d** was isolated as a pale yellow solid (222 mg, 74%); mp 61–62 °C.

IR (Diamond ATR): 2942 (w), 1738 (s), 1640 (w), 1485 (m), 1456 (m), 1379 (m), 1319 (m), 1207 (m), 917 (m), 765 (m), 736 (s), 699 cm^{-1} (m).

^1H NMR (400 MHz, $CDCl_3$): δ = 7.90 (d, $J_{H,H}$ = 7.6 Hz, 1 H), 7.32–7.18 (m, 6 H), 7.13–7.11 (m, 2 H), 5.81–5.71 (m, 1 H), 5.36 (s, 2 H), 5.07–4.97 (m, 2 H), 3.28 (td, $J_{H,H}$ = 5.8 = 1.6 Hz, 2 H), 2.95 (t, $J_{H,H}$ = 7.4 Hz, 2 H), 2.68 (t, $J_{H,H}$ = 7.2 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 147.1, 137.5, 136.5, 135.5, 133.4, 130.1, 128.6, 128.2, 127.4, 127.1, 126.7, 126.5, 122.1, 116.5, 115.5, 53.2, 29.6, 28.6, 18.9.

MS (EI, 70 eV): *m*/*z* (%) = 301 (23), 300 (M^+, 100), 299 (37), 298 (6), 285 (8), 271 (10), 259 (13), 258 (4), 257 (10), 223 (18), 210 (7), 209 (34), 207 (6), 183 (6), 181 (6), 178 (4), 168 (5), 165 (7), 152 (5), 115 (7), 92 (6), 91 (62), 83 (4), 65 (8), 44 (15).

HRMS (EI): *m*/*z* calcd for $C_{21}H_{20}N_2$: 300.1626; found: 300.1622.

Deprotonation of 1-Ethoxymethyl-4,5-dihydro-1*H*-benzo[*g*]indazole (20) Using $TMP_2Zn·2MgCl_2·2LiCl$ (22); General Procedure (GP3)

A dry and argon flushed 10 mL pressurized vial, equipped with a magnetic stirring bar, was charged with **20** (228 mg, 1.0 mmol) dissolved in THF (1 mL). The zinc base **22** (1.5 mL, 0.4 M in THF, 0.6 mmol) was added and the reaction mixture was heated using a Discover BenchMate® Microwave system at 80 °C and 200 W for 2 h. The completion of the metallation was checked by GC analysis of reaction aliquots quenched with I_2 in anhyd THF. After complete metallation and cooling to 25 °C, the organozinc reagent **23** was either used directly in a Negishi cross-coupling reaction or was cooled to –20 °C and transmetallated with CuCN·2LiCl (1.0 mL, 1.0 M in THF, 1.0 mmol) to react with an acyl chloride. The consumption of the zinc reagent was checked by GC analysis, using tetradecane as internal standard. After completion of the reaction, the mixture was quenched with aq sat. NH_4Cl [20 mL; in the presence of copper, 25% aq NH_3 (20 mL) was also added to the mixture] and extracted with Et_2O (3 × 50 mL). The combined organic extracts were dried (Na_2SO_4), filtered, and concentrated in vacuum. Purification by column chromatography afforded the desired C3-functionalized 4,5-dihydro-1*H*-benzo[*g*]indazoles **24a**,**b**.

4-(1-Ethoxymethyl-4,5-dihydro-1*H*-benzo[*g*]indazol-3-yl)benzoic Acid Ethyl Ester (24a)

According to GP3, the 3-zincated heterocycle **23** (1 mmol) was transmetallated with $ZnCl_2$ (1mL, 1.0 M, 1 mmol) and stirred for 10 min at 25 °C. Ethyl 4-iodobenzoate (331 mg, 1.2 mmol) was dissolved in THF (1 mL) and mixed with $Pd(dba)_2$ (28 mg, 0.05 mmol) and (*o*-furyl)$_3$P (23 mg, 0.10 mmol). This mixture was added to the zinc reagent at 25 °C. After purification by column chromatography (silica gel, pentane–Et_2O, 9:1), **24a** was isolated as a white solid (233 mg, 62%); mp 114–116 °C.

IR (Diamond ATR): 1707 (s), 1611 (m), 1444 (w), 1387 (w), 1366 (w), 1277 (s), 1228 (w), 1178 (w), 1112 (m), 1085 (s), 1020 (m), 862 (m), 806 (w), 780 (m), 765 (m), 722 (s), 706 (m), 650 cm^{-1} (w).

^1H NMR (600 MHz, $CDCl_3$): δ = 8.11 (d, $J_{H,H}$ = 8.1 Hz, 2 H), 7.93 (d, $J_{H,H}$ = 7.7 Hz, 1 H), 7.80 (d, $J_{H,H}$ = 8.3 Hz, 2 H), 7.36–7.32 (m, 2 H), 7.28–7.26 (m, 1 H), 5.71 (s, 2 H), 4.40 (q, $J_{H,H}$ = 7.2 Hz, 2 H), 3.76 (q, $J_{H,H}$ = 7.0 Hz, 2 H), 2.93 (s, 4 H), 1.41 (t, $J_{H,H}$ = 7.1 Hz, 3 H), 1.23 (t, $J_{H,H}$ = 7.0 Hz, 3 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 166.5, 146.2, 140.3, 137.9, 137.3, 129.9, 129.4, 128.5, 127.9, 127.3, 127.0, 126.9, 123.9, 117.3, 79.5, 64.4, 61.0, 30.6, 20.5, 14.9, 14.4.

MS (EI, 70 eV): *m*/*z* (%) = 376 (M^+, 5), 332 (30), 331 (100), 303 (13), 258 (4), 216 (4), 143 (3), 115 (3).

HRMS (EI): *m*/*z* calcd for $C_{23}H_{24}N_2O_3$: 376.1787; found: 376.1777.

(2-Chlorophenyl)(1-ethoxymethyl-4,5-dihydro-1*H*-benzo[*g*]indazol-3-yl)methanone (24b)

According to GP3, the 3-zincated heterocycle **23** (1 mmol) was transmetallated with CuCN·2LiCl (1 mL, 1.0 M, 1.0 mmol) at –20 °C. After stirring for 15 min at –20 °C, it was reacted with 2-chlorobenzoyl chloride (209 mg, 1.2 mmol). The mixture was slowly allowed to warm up to 25 °C. After purification by column chromatography (silica gel, pentane–Et_2O, 9:1), **24b** was isolated as a pale yellow solid (219 mg, 55%); mp 132–134 °C.

IR (Diamond ATR): 2980 (w), 2931 (w), 2880 (w), 1648 (m), 1589 (w), 1435 (m), 1356 (w), 1309 (w), 1274 (w), 1193 (w), 1162 (w), 1111 (m), 1090 (s), 1057 (m), 958 (m), 892 (m), 807 (m), 757 (s), 735 cm^{-1} (s).

^1H NMR (600 MHz, $CDCl_3$): δ = 7.89 (d, $J_{H,H}$ = 7.7 Hz, 1 H), 7.55 (d, $J_{H,H}$ = 7.5 Hz, 1 H), 7.45–7.39 (m, 2 H), 7.36–7.32 (m, 3 H), 7.29–7.26 (m, 1 H), 5.64 (s, 2 H), 3.67 (q, $J_{H,H}$ = 7.0 Hz, 2 H), 3.07 (t, $J_{H,H}$ = 7.6 Hz, 2 H), 2.94 (t, $J_{H,H}$ = 7.4 Hz, 2 H), 1.19 (t, $J_{H,H}$ = 7.0 Hz, 3 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 190.3, 145.3, 140.6, 139.0, 137.5, 131.7, 131.1, 130.0, 129.8, 128.7, 128.3, 127.2, 126.2, 126.1, 123.7, 122.5, 80.0, 64.5, 30.0, 19.8, 14.8.

MS (EI, 70 eV): *m*/*z* (%) = 368 (14), 367 (10), 366 (M^+, 41), 324 (19), 323 (30), 322 (55), 321 (71), 310 (9), 309 (31), 308 (17), 307 (52), 306 (9), 293 (11), 287 (21), 286 (9), 285 (25), 272 (10), 227 (8), 216 (9), 215 (20), 197 (24), 195 (15), 184 (15), 183 (96), 182 (10), 181 (34), 169 (17), 154 (9), 141 (33), 139 (100), 115 (14), 113 (11), 111 (32), 75 (10).

HRMS (EI): *m*/*z* calcd for $C_{21}H_{19}ClN_2O_2$: 366.1135; found: 366.1129.

Deprotonation of 1-Ethoxymethyl-4,5-dihydro-1*H*-benzo[*g*]indazole (20) Using TMPMgCl·LiCl (9); General Procedure (GP4)

A flame-dried round-bottomed flask equipped with a magnetic stirring bar, an argon inlet, and a rubber septum was charged with **20** (228 mg, 1.0 mmol) dissolved in THF (1 mL). TMPMgCl·LiCl (**9**; 1.1 mL, 1.1 M in THF, 1.0 mmol) was added slowly at –20 °C and the resulting mixture was stirred for 24 h. The completion of the ex-

change reaction was checked by GC analysis of reaction aliquots quenched with I_2 in anhyd THF. After complete metallation, the organomagnesium reagent **25** was either reacted directly with electrophiles or transmetallated with CuCN·2LiCl (1.0 mL, 1.0 M in THF, 1.0 mmol) to undergo a subsequent allylation. The consumption of the magnesium reagent was checked by GC analysis, using tetradecane as internal standard. After completion of the reaction, the mixture was quenched with aq sat. NH_4Cl [20 mL; in the presence of copper, 25% aq NH_3 (20 mL) was also added to the mixture] and extracted with Et_2O (3 × 50 mL). The combined organic extracts were dried (Na_2SO_4), filtered, and concentrated in vacuum. Purification by column chromatography afforded the desired C3-functionalized 4,5-dihydro-1*H*-benzo[*g*]indazoles **24c**,**d**.

1-(1-Ethoxymethyl-4,5-dihydro-1*H*-benzo[*g*]indazol-3-yl)-2,2-dimethylpropan-1-ol (24c)

According to GP4, the 3-magnesiated heterocycle **25** (1 mmol) was reacted with pivaldehyde (103 mg, 1.2 mmol) at –20 °C. The mixture was slowly allowed to warm up to 25 °C. After purification by column chromatography (silica gel, pentane–Et_2O, 8:2), **24c** was isolated as a pale yellow oil (161 mg, 60%).

IR (Diamond ATR): 3258 (m), 2923 (s), 2854 (s), 1476 (m), 1458 (m), 1447 (m), 1358 (m), 1310 (w), 1296 (w), 1260 (w), 1173 (w), 1070 (s), 1008 (s), 930 (w), 897 (w), 828 (m), 782 (m), 766 (m), 737 (m), 716 (w), 652 cm^{-1} (w).

^1H NMR (600 MHz, $CDCl_3$): δ = 7.86 (d, $J_{H,H}$ = 7.5 Hz, 1 H), 7.33–7.29 (m, 2 H), 7.24–7.23 (m, 1 H), 5.66–5.58 (m, 2 H), 4.45 (s, 1 H), 3.70 (q, $J_{H,H}$ = 7.0 Hz, 2 H), 2.87 (t, $J_{H,H}$ = 7.2 Hz, 2 H), 2.70–2.64 (m, 2 H), 1.21 (t, $J_{H,H}$ = 7.0 Hz, 3 H), 0.96 (s, 9 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 148.6, 139.3, 137.6, 130.1, 128.5, 127.8, 127.2, 123.9, 117.4, 79.0, 76.0, 64.2, 36.9, 30.6, 25.8, 20.2, 15.0.

MS (EI, 70 eV): *m*/*z* (%) = 314 (M^+, 12), 258 (15), 257 (19), 212 (13), 211 (100), 199 (10), 59 (61).

HRMS (EI): *m*/*z* calcd for $C_{19}H_{26}N_2O_2$: 314.1994; found: 314.1986.

3-Allyl-1-ethoxymethyl-4,5-dihydro-1*H*-benzo[*g*]indazole (24d)

According to GP4, the 3-magnesiated heterocycle **25** (1 mmol) was transmetallated with CuCN·2LiCl (1 mL, 1.0 M, 1.0 mmol) at –20 °C. After stirring for 15 min at –20 °C, it was reacted with allyl bromide (144 mg, 1.2 mmol). The mixture was slowly allowed to warm up to 25 °C. After purification by column chromatography (silica gel, pentane–Et_2O, 9:1), **24d** was isolated as a white solid (182 mg, 68%).

IR (Diamond ATR): 2976 (w), 2933 (w), 2896 (w), 1483 (m), 1446 (m), 1368 (w), 1310 (m), 1263 (w), 1222 (w), 1169 (w), 1088 (s), 1017 (m), 934 (m), 912 (s), 835 (m), 759 (s), 734 (m), 700 cm^{-1} (m).

^1H NMR (400 MHz, C_6D_6): δ = 8.06 (d, $J_{H,H}$ = 7.6 Hz, 1 H), 7.14–7.12 (m, 1 H), 7.08–7.01 (m, 2 H), 6.13–6.03 (m, 1 H), 5.41 (s, 2 H), 5.14–5.03 (m, 2 H), 3.62 (t, $J_{H,H}$ = 7.0 Hz, 2 H), 3.44 (td, $J_{H,H}$ = 6.5, 1.6 Hz, 2 H), 2.65 (t, $J_{H,H}$ = 7.4 Hz, 2 H), 2.41 (t, $J_{H,H}$ = 7.4 Hz, 2 H), 0.99 (t, $J_{H,H}$ = 7.0 Hz, 3 H).

^{13}C NMR (100 MHz, C_6D_6): δ = 146.1, 139.3, 137.4, 136.3, 128.8, 128.0, 127.6, 127.4, 124.1, 117.7, 115.5, 79.2, 64.3, 31.8, 30.9, 19.5, 15.0.

MS (EI, 70 eV): *m*/*z* (%) = 268 (M^+, 7), 261 (3), 225 (3), 224 (23), 223 (100), 222 (2), 221 (7), 210 (2), 209 (4), 207 (3), 196 (4), 195 (4), 183 (3), 181 (5), 169 (3), 168 (3), 165 (3), 154 (3), 142 (2), 128 (2), 115 (4).

HRMS (EI): *m*/*z* calcd for $C_{17}H_{20}N_2O$: 268.1576; found: 268.1575.

Deprotonation of 2-Ethoxymethyl-4,5-dihydro-2*H*-benzo[*g*]indazole (21) Using TMP_2Mg·2LiCl (26); General Procedure 5 (GP5)

A flame-dried round-bottomed flask equipped with a magnetic stirring bar, an argon inlet, and a rubber septum was charged with **21** (228 mg, 1.0 mmol), dissolved in THF (1 mL). TMP_2Mg·2LiCl (**26**; 1.8 mL, 0.6 M in THF, 1.1 mmol) was added slowly at 0 °C and the resulting mixture was stirred for 12 h. The completion of the exchange reaction was checked by GC-analysis of reaction aliquots quenched with I_2 in anhyd THF. After complete metallation, the organomagnesium reagent **27** was either reacted directly with electrophiles or transmetallated with CuCN·2LiCl (1.0 mL, 1.0 M in THF, 1.0 mmol) to undergo a subsequent allylation. Transmetallation with $ZnCl_2$ (1.0 mL, 1.0 M, 1.0 mmol) was necessary before performing a Negishi cross-coupling. The consumption of the magnesium reagent was checked by GC analysis, using tetradecane as internal standard. After completion of the reaction, the mixture was quenched with aq sat. NH_4Cl (20 mL) [in the presence of copper, 25% aq NH_3 (20 mL) was also added to the mixture] and extracted with Et_2O (3 × 50 mL). The combined organic extracts were dried (Na_2SO_4), filtered, and concentrated in vacuum. Purification by column chromatography afforded the desired C3-functionalized 4,5-dihydro-2*H*-benzo[*g*]indazoles **28a**–**d**.

4-(2-Ethoxymethyl-4,5-dihydro-2*H*-benzo[*g*]indazol-3-yl)benzoic Acid Ethyl Ester (28a)

According to GP5, the 3-magnesiated heterocycle **27** (1 mmol) was transmetallated with $ZnCl_2$ (1 mL, 1.0 M, 1 mmol) and stirred for 30 min at 0 °C. Ethyl 4-iodobenzoate (331 mg, 1.2 mmol) was dissolved in THF (1 mL) and mixed with $Pd(dba)_2$ (28 mg, 0.05 mmol) and (*o*-furyl)$_3$P (23 mg, 0.10 mmol). This mixture was added to the zinc reagent at 0 °C, and the mixture was allowed to slowly warm up to 25 °C. After purification by column chromatography (silica gel, pentane–Et_2O, 9:1), **28a** was isolated as a white solid (350 mg, 93%); mp 118–120 °C.

IR (Diamond ATR): 2927 (m), 1718 (s), 1610 (m), 1438 (m), 1367 (w), 1304 (w), 1271 (s), 1220 (w), 1170 (w), 1099 (s), 1076 (s), 1027 (m), 995 (w), 864 (m), 831 (m), 771 (s), 732 (s), 704 cm^{-1} (s).

^1H NMR (600 MHz, $CDCl_3$): δ = 8.16 (d, $J_{H,H}$ = 8.1 Hz, 2 H), 7.94 (d, $J_{H,H}$ = 7.5Hz, 1 H), 7.65 (d, $J_{H,H}$ = 8.3 Hz, 2 H), 7.31–7.28 (m, 1 H), 7.24–7.23 (m, 2 H), 5.44 (s, 2 H), 4.41 (q, $J_{H,H}$ = 7.2 Hz, 2 H), 3.73 (q, $J_{H,H}$ = 7.0 Hz, 2 H), 2.95 (t, $J_{H,H}$ = 7.2 Hz, 2 H), 2.78 (t, $J_{H,H}$ = 7.3 Hz, 2 H), 1.41 (t, $J_{H,H}$ = 7.1 Hz, 3 H), 1.21 (t, $J_{H,H}$ = 7.0 Hz, 3 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 166.2, 148.1, 139.1, 136.8, 134.1, 130.3, 129.9, 129.3, 129.2, 128.4, 127.9, 126.9, 122.7, 117.0, 78.3, 64.7, 61.2, 29.5, 19.6, 15.0, 14.3.

MS (EI, 70 eV): *m*/*z* (%) = 376 (M^+, 5), 334 (5), 333 (31), 332 (100), 303 (10), 289 (2), 273 (1), 258 (4), 244 (2), 215 (6), 202 (2), 189 (1), 143 (3), 142 (2), 128 (2), 115 (3), 97 (1), 59 (1).

HRMS (EI): *m*/*z* calcd for $C_{23}H_{24}N_2O_3$: 376.1787; found: 376.1789.

(2-Chlorophenyl)(2-ethoxymethyl-4,5-dihydro-2*H*-benzo[*g*]indazol-3-yl)methanone (28b)

According to GP5, the 3-magnesiated heterocycle **27** (1 mmol) was transmetallated with CuCN·2LiCl (1 mL, 1.0 M, 1.0 mmol) at –20 °C. After stirring for 15 min at –20 °C, it was reacted with 2-chlorobenzoyl chloride (209 mg, 1.2 mmol). The mixture was slowly allowed to warm up to 25 °C. After purification by column chromatography (silica gel, pentane–Et_2O, 9:1), **28b** was isolated as a pale yellow solid (220 mg, 60%); mp 97–98 °C.

IR (Diamond ATR): 1658 (s), 1590 (w), 1426 (s), 1320 (w), 1281 (m), 1235 (w), 1093 (s), 1057 (m), 1031 (m), 915 (s), 836 (m), 760 (s), 735 (s), 643 cm^{-1} (m).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.92 (d, $J_{H,H}$ = 7.7 Hz, 1 H), 7.47–7.38 (m, 4 H), 7.27 (t, $J_{H,H}$ = 7.5 Hz 1 H), 7.21 (t, $J_{H,H}$ = 7.4 Hz 1 H), 7.15 (d, $J_{H,H}$ = 7.5 Hz, 1 H), 5.93 (s, 2 H), 3.65 (q, $J_{H,H}$ = 7.0 Hz, 2 H), 2.74 (t, $J_{H,H}$ = 7.4 Hz, 2 H), 2.14 (t, $J_{H,H}$ = 7.4 Hz, 2 H), 1.19 (t, $J_{H,H}$ = 7.0 Hz, 3 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 185.0, 148.1, 139.0, 136.0, 135.4, 131.9, 131.3, 130.3, 129.0, 128.6, 128.2, 128.1, 127.3, 127.0, 124.1, 122.6, 80.1, 64.8, 28.7, 19.9, 15.0.

MS (EI, 70 eV): *m*/*z* (%) = 366 (M^+, 39), 337 (17), 323 (22), 322 (18), 321 (64), 309 (34), 308 (16), 307 (22), 293 (21), 288 (15), 287 (72), 286 (14), 285 (28), 227 (17), 215 (19), 197 (29), 183 (71), 181 (26), 169 (24), 141 (30), 139 (100), 115 (15), 111 (31), 74 (14), 59 (25).

HRMS (EI): *m*/*z* calcd for $C_{21}H_{19}ClN_2O_2$: 366.1135; found: 366.1129.

1-(2-Ethoxymethyl-4,5-dihydro-2*H*-benzo[*g*]indazol-3-yl)-2,2-dimethylpropan-1-ol (28c)

According to GP5, the 3-magnesiated heterocycle **27** (1 mmol) was reacted with pivaldehyde (103 mg, 1.2 mmol) at 0 °C. The mixture was slowly allowed to warm up to 25 °C. After purification by column chromatography (silica gel, pentane–Et_2O, 8:2), **28c** was isolated as a pale yellow solid (220 mg, 70%); mp 94–96 °C.

IR (Diamond ATR): 3257 (w), 2948 (w), 2482 (w), 1442 (w), 1359 (w), 1296 (m), 1244 (w), 1199 (w), 1104 (s), 1088 (s), 1063 (m), 1013 (m), 896 (w), 872 (m), 760 (m), 739 (m), 715 cm^{-1} (m).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.84 (d, $J_{H,H}$ = 7.3 Hz, 1 H), 7.26–7.24 (m, 1 H), 7.21–7.18 (m, 2 H), 5.68–5.66 (m, 1 H), 5.50–5.48 (m, 1 H), 4.71 (s, 1 H), 3.57–3.51 (m, 2 H), 2.89 (t, $J_{H,H}$ = 7.2 Hz, 2 H), 2.78–2.70 (m, 2 H), 1.12 (t, $J_{H,H}$ = 7.1 Hz, 3 H), 0.99 (s, 9 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 147.8, 139.2, 136.8, 129.6, 128.2, 127.6, 126.8, 122.4, 117.6, 80.0, 75.0, 64.6, 38.0, 29.6, 26.1, 20.8, 14.8.

MS (EI, 70 eV): *m*/*z* (%) = 314 (M^+, 3), 269 (2), 257 (7), 212 (13), 211 (100), 199 (3), 183 (4), 169 (3), 154 (1), 142 (2), 127 (1), 115 (3), 59 (5), 44 (2), 41 (2).

HRMS (EI): *m*/*z* calcd for $C_{19}H_{26}O_2N_2$: 314.1994; found: 314.2000.

2-Ethoxymethyl-3-methylsulfanyl-4,5-dihydro-2*H*-benzo[*g*]indazole (28d)

According to GP5, the 3-magnesiated heterocycle **27** (1 mmol) was reacted with methanethiosulfonic acid *S*-methyl ester (152 mg, 1.2 mmol) at 0 °C. The mixture was slowly allowed to warm up to 25 °C. After purification by column chromatography (silica gel, pentane–Et_2O, 8:2), **28d** was isolated as a yellow oil (227 mg, 83%).

IR (Diamond ATR): 2929 (w), 1472 (m), 1438 (m), 1296 (m), 1278 (m), 1240 (m), 1098 (s), 1068 (s), 1028 (w), 973 (w), 892 (w), 825 (m), 772 (s), 726 (s), 685 cm^{-1} (w).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.88 (d, $J_{H,H}$ = 7.3 Hz, 1 H), 7.29–7.20 (m, 3 H), 5.64 (s, 2 H), 3.64 (t, $J_{H,H}$ = 7.0 Hz, 2 H), 2.96 (t, $J_{H,H}$ = 7.4 Hz, 2 H), 2.82–2.77 (m, 2 H), 2.34 (s, 3 H), 1.17 (t, $J_{H,H}$ = 7.0 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 148.2, 136.8, 132.1, 129.1, 128.4, 128.0, 126.9, 122.7, 122.5, 67.9, 64.5, 29.2, 19.5, 19.3, 15.0.

MS (EI, 70 eV): *m*/*z* (%) = 275 (3), 274 (M^+, 20), 231 (7), 230 (24), 229 (100), 227 (9), 216 (5), 215 (13), 197 (14), 187 (4), 184 (2), 183 (14), 182 (10), 181 (18), 171 (14), 169 (10), 168 (9), 156 (6), 154 (6), 153 (4), 152 (3), 142 (5), 141 (3), 140 (5), 139 (4), 128 (12), 127 (8), 117 (3), 116 (4), 115 (8), 89 (4), 59 (6), 43 (2).

HRMS (EI): *m*/*z* calcd for $C_{15}H_{18}N_2OS$: 274.1140; found: 274.1133.

Acknowledgment

We thank the Fond der Chemischen Industrie, the ERC (European Research Council), the DFG for financial support, Boehringer-Ingelheim (Vienna) Evonik (Frankfurt), Chemetall (Frankfurt), and BASF (Ludwigshafen) for the generous gift of chemicals.

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