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Design and synthesis of a new indazole library: direct conversion of *N*-methoxy-*N*-methylamides (Weinreb amides) to 3-keto and 3-formylindazoles

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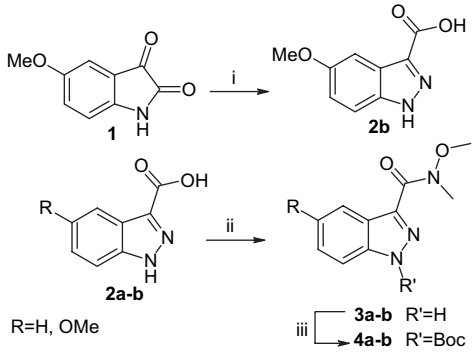
Abstract—Nucleophilic addition of Grignard or lithiated reagents on the new Weinreb amides **3** and **4** afforded efficiently the corresponding ketones and allowed the design and synthesis of a new indazole library. These 3-ketoindazoles were obtained by a direct and original conversion of *N*-methoxy-*N*-methylamides with good yields. Furthermore, the reduction of **3** with $LiAlH_4$ furnished the corresponding aldehydes as a versatile and efficient pathway to 3-formylindazoles.

1. Introduction

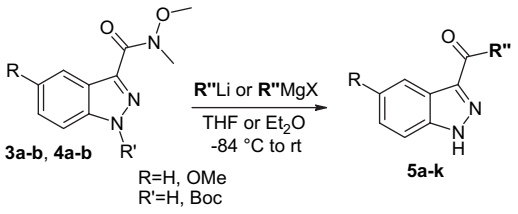
Weinreb et al. have discovered that *N*-methoxy-*N*-methylamides (commonly named Weinreb amides) could be combined with both Grignard and lithiated reagents, and were important valuable carbonyl equivalents.[1] The stable metal-chelated tetrahedral intermediates which were formed resisted further nucleophilic attack, and did not produce tertiary alcohols even with a large excess of organometallic compound.[2] Use of these Weinreb amides became one of the most straightforward methods for the preparation of ketones and aldehydes.[3]

Thus in a study devoted to develop mild and flexible strategies to design new indazole libraries and synthesize heterocyclic scaffolds to prepare new valuable building blocks in medicinal chemistry,[4] we devised an efficient method for the synthesis of various 1-(1*H*-indazol-3-yl)ketones. An in-depth survey of the literature did not show such a study.[5] For example, 3-acylindazoles were obtained from the halogen–metal exchange starting from 3-bromoindazole with very poor yields,[5c] from the easeless Knochel's methodology with cuprates starting from 3-iodoindazoles,[5f] or recently using hazardous diazo substances.[5i]

With this in mind, we decided to synthesize original Weinreb amides **3a**,**b** and **4a**,**b** (Scheme 1), which were then treated with lithium and magnesium nucleophiles (Scheme 2).



Scheme 1. Reagents: (i) (1) NaOH aq (1.03 equiv), 50 °C; (2) $NaNO_2$ aq (1 equiv), H_2SO_4 concd, 0 °C; (3) $SnCl_2 \cdot 2H_2O$ (2.4 equiv), HCl concd, 98%; (ii) NH(OMe)Me·HCl (1.1 equiv), pyridine (2.2 equiv), then EDC (2 equiv), pyridine (2 equiv), THF, rt, 68–84%; (iii) $(Boc)_2O$ (2 equiv), TEA (1.1 equiv), DMAP (cat.), CH_2Cl_2, rt, 58–98%.



Scheme 2.

Herein we would like to report the convergent synthetic approach to new indazoles by direct conversion of Weinreb amides to ketones.

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2. Results and discussion

Weinreb amides **3a**,**b** and **4a**,**b** were obtained starting from the 3-carboxylic indazoles **2a**,**b**. Carboxylic acid **2a** was commercially available, and compound **2b** was obtained by treatment of 5-methoxyisatine **1** with aqueous sodium hydroxide, then aqueous sodium nitrite in sulfuric acid.[6,7] Finally the intermediate diazonium salt was reduced with a cooled solution of tin(II) chloride dihydrate in hydrochloric acid to give the corresponding carboxylic acid **2b** in 98% yield (Scheme 1 and Table 1). *N*-Methoxy-*N*-methylamides are usually prepared from commercially available *N*,*O*-dimethyl-hydroxylamine hydrochloride and an acid chloride or another activated derivative. Our preliminary attempts to transform the acids **2a**,**b** to the corresponding Weinreb amides were performed using dicyclohexylcarbodiimide (DCC), the most important of coupling agents.[8] The desired products were obtained after purification by column chromatography but the yields were lower than 55%. In order to improve these yields, we decided to use 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC). The basic advantage of EDC is the water-solubility of the resulting-urea avoiding further purifications.[9] Thus, the coupling reaction with *N*,*O*-dimethyl-hydroxylamine hydrochloride, EDC and pyridine as base in THF at room temperature furnished the Weinreb amides **3a** and **3b** in 84 and 68% yields, respectively. This method was already easily scaled up for the synthesis of multigram amounts (>10 g) of compound **3a**, whose structure has been confirmed by X-ray analysis.[10]

Table 1. Synthesis of the protected Weinreb amides **4**

	2 (%)	**3** (%)	**4** (%)
R=H (**a**)	Com.	84	98
R=OMe (**b**)	98	68	58

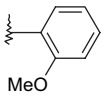
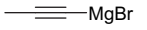
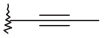
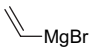
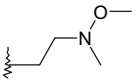
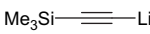
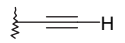
Com.: commercially available.

Subsequent protection of the indazole nucleus with *tert*-butyloxycarbonyl (Boc), in the presence of triethylamine (TEA) and a catalytic amount of dimethylaminopyridine (DMAP) in dichloromethane,[11] afforded the protected compounds **4a** and **4b** in 98 and 58% yields, respectively (Scheme 1 and Table 1). For the latter, ^{1}H NMR and ^{13}C NMR experiments were specially interesting. The protons of the *N*-methyl at δ 3.39 ppm, and the carbons of the *N*-methyl and the *N*-methoxy of protected amide **4a** at δ 33.1 and δ 61.6 ppm, respectively, appeared as a broad singlet. For the compound **4b**, the H_4 on indazole nucleus at δ 7.54 ppm, and the carbon of the *N*-methoxy at δ 61.2 ppm also appeared as a broad singlet. These results seemed to be the outcome of a slow conformational process often seen with amide structures and were confirmed by the use of a high temperature NMR technique. Indeed the broad singlet became a narrow peak.

To examine the usefulness of these Weinreb amides **3a**,**b** and **4a**,**b**, various organometallic reagents were used to give the ketones **5a**–**k** (Scheme 2 and Table 2).

The first attempt was realized with bromobenzene and magnesium turnings in ether to generate in situ phenylmagnesium bromide, and protected amide **4a**. In fact only deprotected compound **5a** was isolated in 70% yield (Table 2, entry 1). Finally the Boc protected group did not seem to be necessary since the reaction loaded with unprotected amide **3a** gave the compound **5a** in 92% yield (Table 2, entry 2). The same reaction was carried out with 5-methoxy derivatives **3b** and **4b** to afford compound **5b** in 40 and 46% yields, respectively (Table 2, entries 4 and 5). These poor results were due to the fact that the amide **3b** was slightly soluble in THF or Et_2O, and the Boc protecting group didn't really improve the solubility of the compound **4b**.

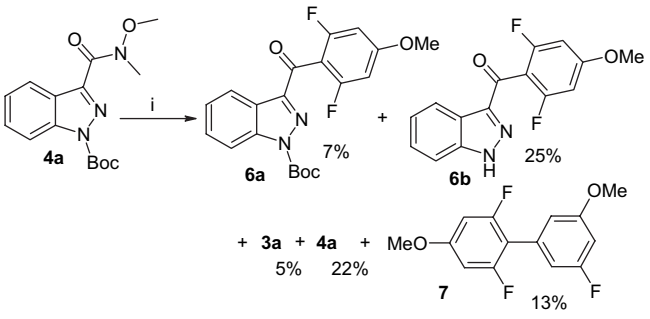
Table 2. Synthesis of 3-ketoindazoles **5a**–**k**

	Reactant	R″Li/R″MgX	Equiv	R″	Product (%)
1	**4a**	PhMgBr	5		**5a** (70)
2	**3a**	PhMgBr	5		**5a** (92)
3	**3a**	PhLi	5		**5a** (85)
4	**3b**	PhMgBr	5		**5b** (40)
5	**4b**	PhMgBr	5		**5b** (46)
6	**3a**	2-MeO–PhMgBr	5		**5c** (57)
7	**3a**	*i*-PrMgCl	5		**5d** (81)
8	**3b**	*i*-PrMgCl	5		**5e** (30)
9	**3a**	MeMgBr	5		**5f** (82)
10	**3a**	*n*-BuLi	5		**5g** (37)
11	**3a**		6		**5h** (62)
12	**3a**		5		**5i** (8)
13	**3a**		6		**5j** (37)
14	**3a**		7		**5k** (23)

We decided to perform the reactions at −84 °C in THF or Et_2O with 5 equiv of the Grignard or lithiated reagents for an important reason: an excess of organometallic reagent must be necessary because of the acidity of the indazolyl NH proton, which is inevitably the first to be removed. To compare the reactivity of the amide **3a** with lithiated species, compound **5a** was obtained after reaction with phenyllithium in 85% yield (Table 2, entry 3). 2-Methoxyphenylmagnesium bromide gave the indazole **5c** in 57% yield (Table 2, entry 6). With *iso*-propylmagnesium chloride, amides **3a** and **3b** provided compounds **5d** and **5e** in 81 and 30% yields, respectively (Table 2, entries 7 and 8). Methylmagnesium bromide and *n*-butyllithium afforded the corresponding indazoles **5f** and **5g** in 82 and 37% yields, respectively (Table 2, entries 9 and 10). Lithium phenylacetylide was generated in situ at low temperature in THF with

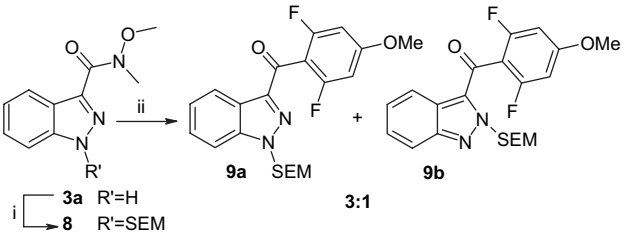
6 equiv of phenylacetylene and 6 equiv of *n*-butyllithium. The Weinreb amide **3a** was then added to give the desired compound **5h** in 62% yield (Table 2, entry 11). But with 1-propynylmagnesium bromide, amide **3a** provided compound **5i** in only 8% yield (Table 2, entry 12). The reaction of Weinreb amide **3a** with vinylmagnesium bromide (6 equiv) and lithium (trimethylsilyl)acetylide (7 equiv) did not afford the expected products (Table 2, entries 13 and 14). In the first case, it is well known that the addition of vinyl Grignard reagent to Weinreb amide generally led to the vinyl ketone in poor yields. The reason is that the synthesized product mainly reacts in a Michael addition with the released *N*,*O*-dimethyl-hydroxylamine.[12] After the quenching procedure, the vinyl ketone was not detected and the β-amino-ketone **5j** was obtained in 37% yield. In the second case, surprisingly no desired product was detected even before the quenching procedure, only the desilylated compound **5k** was obtained in 23% yield. It was a direct pathway to access terminal alkynes.

Next our efforts for the obtention of the ketoindazoles focused on the introduction of the 2,6-difluoroanisole moiety on the amides **3a** or **4a**. This kind of fluoro compound could be very interesting with a lot of pharmacological targets. Furthermore there were few examples of *ortho* lithiation of difluoro-alkoxyaryl compounds described in literature[13] because of the difficult regioselectivity control. First of all 4-bromo-3,5-difluoroanisole (5 equiv) reacted with *i*-PrMgCl (5.5 equiv) to generate in situ the aryl Grignard using Knochel's procedure.[14a] After 1 h at −84 °C, the indazole **3a** was added, but the quenching procedure and the usual work-up gave the starting material and the debrominated product 3,5-difluoroanisole. In view of this result 3,5-difluoroanisole was chosen to introduce our desired moiety but after 1 h at −84 °C when the amide **3a** and 3,5-difluoroanisole (5 equiv) were added to a cooled stirred solution of the Schlosser's 'super base'[14b] (*n*-BuLi, 5 equiv, *t*-BuOK, 5 equiv), only starting materials were recovered. With this in mind the base was changed and the coupled compound **6a** and the deprotected coupled product **6b** were obtained respectively in 7 and 25% yields using the protected Weinreb amide **4a**, *n*-BuLi (1.5 equiv) and 3,5-difluoroanisole (1.5 equiv). Nevertheless these conditions provided a lot of by-products: a compound resulting from self-condensation of the 3,5-difluoroanisole **7** in 13% yield, indazole **3a** in 5% yield and starting material **4a** in 22% yield (Scheme 3).



Scheme 3. Reagents: (i) 3,5-difluoroanisole (1.5 equiv), *n*-BuLi (1.5 equiv), THF, −84 °C to rt.

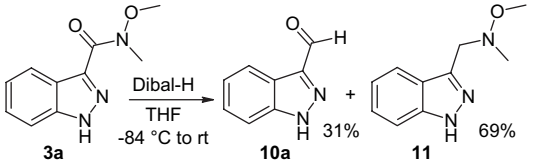
Finally after this encouraging result the protecting group was changed to decrease the rate of formation of the by-products. The [2-(trimethyl-silanyl)-ethoxymethyl] group (SEM) was supposed to be more stable in the presence of lithium species.[15] Thus protection in a biphasic mixture CH_2Cl_2/KOH (50% solution in water) in the presence of SEM-Cl (1.1 equiv) and a catalytic amount of TBABr[4g,16] provided Weinreb amide **8** in a very good yield (Scheme 4).



Scheme 4. Reagents: (i) SEM-Cl (1.1 equiv), CH_2Cl_2/KOH aq 50%, TBABr (0.01 equiv), rt, 91%; (ii) 3,5-difluoroanisole (1.2 equiv), *n*-BuLi (1.2 equiv), THF, −84 °C to rt, 72%.

The lithium reagent was generated in situ with 3,5-difluoroanisole (2 equiv) and *n*-butyllithium (2 equiv). Indazole **8** was added to give mainly, after the quenching procedure, the aromatic trifluoro-compound **7**, whose structure was confirmed according to the 1D and 2D NMR experiments. In order to decrease the rate of formation of this by-product, only 1.2 equiv of 3,5-difluoroanisole and *n*-butyllithium were used, according to the procedure used to obtain 2,6-difluoro-4-methoxyaniline.[17] These conditions provided a mixture of (N-1 and N-2)-SEM-indazole in 72% yield with a **9a/9b** ratio of 3:1, determined by ^{1}H NMR. Indeed the chemical shift of the NCH_2O group is always more unshielded in the case of (N-2)-SEM than (N-1)-SEM compound. Starting material **8** was also obtained in 25% yield but it could be easily separated by simple column chromatography (Scheme 4).

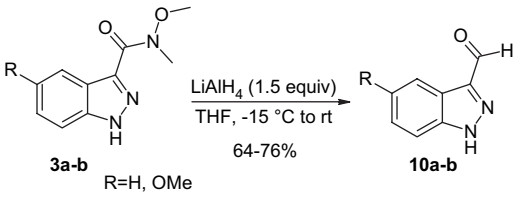
Moreover we wanted to know if aldehydes could be obtained with Dibal-H as described in literature.[1a,18] To this end, the reduction of the amide **3a** was realized in THF at −84 °C with 3 equiv of Dibal-H. The reaction was monitored by TLC and after 2 h the starting material was not completely consumed. Two additional equivalents of Dibal-H were then added to achieve full conversion and after purification aldehyde **10a** was obtained in 31% yield along with the *N*-methoxy-*N*-methylamine **11** in 69% yield (Scheme 5). This result was surprising because the reduction of Weinreb amides into the corresponding amines was usually performed with 9-BBN.[19]



Scheme 5.

Compound **11** also possessed a particularity in ^{1}H NMR because the CH_2 appeared as a broad singlet at δ 4.28 ppm. Crystallization of this amine allowed us to record X-ray data and to confirm its structure.[20]

However, by performing the reaction with $LiAlH_4$ (1.5 equiv) in THF at −15 °C, we could obtain the aldehydes **10a** and **10b** in 76 and 64% yields, respectively, without any detectable amount of by-products (Scheme 6).[21] Finally a new synthesis[22] of 3-formylindazoles was developed in two steps starting from carboxylic acids.



Scheme 6.

In conclusion, with the aim of developing flexible strategies for the design of new indazole libraries, we have studied a new and efficient methodology for the synthesis of 1*H*-indazole-3-Weinreb amides by the use of EDC and the corresponding carboxylic acids. We have developed a strategy to prepare in good yields 3-formylindazoles from carboxylic acids. Comparing with the rare previous syntheses in the 3-acylindazole series, the present one excels by its simplicity and becomes a versatile pathway to access scaffolds to get a broader diversity via a vast range of further reactions. Moreover, a lot of various ketones have been synthesized by direct conversion of *N*-methoxy-*N*-methylamides with organometallic compounds. These original heterocycles can provide valuable building blocks in medicinal chemistry for a wide range of applications, particularly in development of serotonine receptor ligands (5HT).

3. Experimental section

3.1. General

All commercially available reagents were used as received without further purification. Reaction mixtures were stirred magnetically and monitored by TLC using 0.2 mm Macherey–Nagel Polygram SIL G/UV_{254} precoated plates. Column chromatography was performed using CarloErba-SDS 60A 70–200 μm silica gel. Melting points (uncorrected) were determined on a Köfler melting point apparatus. IR spectra were taken with a Perkin–Elmer spectrum X FT-IR spectrometer. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded on a JEOL Lambda 400 Spectrometer. ^{19}F NMR (376 MHz) spectra were recorded on a Brucker Avance DRX 400 instrument using $CFCl_3$ as internal reference. Chemical shifts (δ) are expressed in parts per million downfield from tetramethylsilane as an internal standard and the coupling constants are in hertz. Mass spectra were recorded on a JEOL JMS GCMate with ionizing potential of 70 eV and with pfk as internal standard for high-resolution. Elemental analyses were performed at the 'Institut de Recherche en Chimie Organique Fine' (Rouen, France).

3.2. 5-Methoxy-1*H*-indazole-3-carboxylic acid 2b

5-Methoxyisatine **1** (4.43 g, 25 mmol) was added in a mixture of NaOH (1.03 g, 25.8 mmol, 1.03 equiv) and water (16 mL) heated at 50 °C. The solution was cooled to 0 °C and a cooled solution of sodium nitrite (1.73 g in 8 mL of water, 25 mmol, 1 equiv) was added followed by a cooled solution of H_2SO_4 (95%) (2.6 mL in 40 mL of water, 48.8 mmol, 1.95 equiv). The rate of addition was rapid such that the temperature never rose above 4 °C. After the end of the addition, the cooled solution was stirred for 1 h. Then a cooled solution of HCl (37%) with $SnCl_2 \cdot 2H_2O$ (13.5 g in 20 mL of HCl, 60 mmol, 2.4 equiv) was added and the mixture was stirred for 16 h and then filtrated. The resulting solid was washed with water to give 5-methoxy-1*H*-indazole-3-carboxylic acid **2b** as a yellow solid (4.71 g, 98%); dec 250 °C. IR (KBr): 3140, 2925, 1700, 1489, 1240, 1170, 1057, 802 cm^{-1}. ^{1}H NMR (DMSO-d_6) δ: 3.80 (s, 3H), 7.06 (dd, J=8.9 Hz and J=2.2 Hz, 1H), 7.40 (d, J=2.2 Hz, 1H), 7.54 (d, J=8.8 Hz, 1H), 13.68 (br s, 1H). MS (EI): m/z (%)=192 (M^+, 100), 177 (35), 133 (23), 105 (14). HRMS/ESI calcd for $C_9H_8N_2O_3$ $[M]^+$ 192.0535; found 192.0535.

3.3. General procedure for the synthesis of the Weinreb amides 3

To a solution of the chosen carboxylic acid **2** in THF (350–400 mL) was added at room temperature the *N*,*O*-dimethylhydroxylamine hydrochloride (1.1 equiv). The temperature of the mixture was decreased to 0 °C and distilled pyridine (2.2 equiv) was added. The solution was stirred for 1.5 h at 0 °C and then at room temperature for 1 h. Distilled pyridine (2 equiv) and EDC (2 equiv) were successively added and the reaction mixture was stirred overnight, then concentrated in vacuo. Water (400 mL) was added and the resulting solid was filtered and washed with water to obtain the desired Weinreb amide **3a** or **3b**.

3.3.1. *N*-Methoxy-*N*-methyl-1*H*-indazole-3-carboxamide (3a).[5d] Starting from 1*H*-indazole-3-carboxylic acid **2a** (6 g, 37 mmol) and following the general procedure, *N*-methoxy-*N*-methyl-1*H*-indazole-3-carboxamide **3a** was obtained as a light yellow solid (6.39 g, 84%); mp 106–108 °C. TLC R_f=0.4 (EtOAc/cyclohexane, 2:1). IR (KBr): 3176, 1607, 1494, 1334, 1251, 1098, 981, 911, 779, 756 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 3.57 (s, 3H), 3.84 (s, 3H), 7.28 (t, J=8.3 Hz, 1H), 7.42 (t, J=8.3 Hz, 1H), 7.54 (d, J=8.3 Hz, 1H), 8.22 (d, J=8.3 Hz, 1H), 10.90 (br s, 1H). ^{13}C NMR ($CDCl_3$) δ: 33.9, 61.6, 110.0, 122.4, 122.6, 123.4, 127.1, 138.4, 140.6, 163.4. MS (EI): m/z (%)=205 (M^+, 30), 175 (14), 146 (91), 145 (100), 118 (20), 117 (25), 90 (63). Anal. Calcd for $C_{10}H_{11}N_3O_2$: C, 58.53; H, 5.40; N, 20.48. Found: C, 58.76; H, 5.59; N, 20.67.

3.3.2. *N*,5-Dimethoxy-*N*-methyl-1*H*-indazole-3-carboxamide (3b). Starting from 5-methoxy-1*H*-indazole-3-carboxylic acid **2b** (3.5 g, 18.2 mmol) and following the general procedure, *N*,5-dimethoxy-*N*-methyl-1*H*-indazole-3-carboxamide **3b** was obtained as a brown solid (2.93 g, 68%); dec 180 °C. TLC R_f=0.15 (EtOAc/cyclohexane, 1:1). IR (KBr): 3468, 3139, 1617, 1581, 1462, 1366, 1298, 1281, 1217, 1123, 1046, 993, 945, 844, 814, 725, 697 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 3.57 (s, 3H), 3.86 (s, 3H), 3.87 (s, 3H), 7.09 (dd, J=9.0 Hz and J=2.4 Hz, 1H), 7.44 (d, J=9.0 Hz, 1H), 7.62 (d, J=2.4 Hz, 1H), 10.69 (br s, 1H). MS (EI): m/z (%)=235 (M^+, 16), 176 (12), 175 (100),

147 (8), 120 (15). Anal. Calcd for $C_{11}H_{13}N_3O_3$: C, 56.16; H, 5.57; N, 17.86. Found: C, 56.45; H, 5.42; N, 17.12.

3.4. General procedure for the synthesis of the protected Weinreb amides 4

A catalytic amount of DMAP, TEA (1.1 equiv) and $(Boc)_2O$ (2 equiv) were successively added at 0 °C to a cooled solution of the chosen indazole **3** in CH_2Cl_2. After the end of the addition, the mixture was stirred at 0 °C for 1 h and then for 2 h at room temperature. The organic layer was washed successively with an aqueous HCl (0.5 N) solution, water and brine, dried over $MgSO_4$, filtered and evaporated in vacuo. The crude material was purified by flash column chromatography on silica gel (EtOAc/cyclohexane, 1:2) to give, after trituration with petroleum ether, the desired protected Weinreb amide **4a** or **4b**.

3.4.1. *tert*-Butyl 3-{[methoxy(methyl)amino]carbonyl}-1*H*-indazole-1-carboxylate (4a). Starting from *N*-methoxy-*N*-methyl-1*H*-indazole-3-carboxamide **3a** (600 mg, 2.9 mmol) and following the general procedure, *tert*-butyl 3-{[methoxy(methyl)amino]carbonyl}-1*H*-indazole-1-carboxylate **4a** was obtained as a white solid (875 mg, 98%); mp 75–77 °C. TLC R_f=0.7 (EtOAc/cyclohexane, 1:1). IR (KBr): 3448, 3184, 3064, 2925, 1626, 1449, 1225, 1085, 884, 745, 697, 638 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 1.60 (s, 9H), 3.39 (br s, 3H), 3.80 (s, 3H), 7.24 (t, J=7.8 Hz, 1H), 7.41 (t, J=8.0 Hz, 1H), 8.00–8.06 (m, 2H). ^{13}C NMR ($CDCl_3$) δ: 27.7, 33.1 (br s), 61.6 (br s), 84.9, 113.9, 122.0, 124.1, 124.9, 128.7, 139.7, 142.1, 148.5, 170.5. MS (EI): m/z (%)=305 (M^+, 7), 245 (6), 205 (5), 146 (11), 145 (100). Anal. Calcd for $C_{15}H_{19}N_3O_4$: C, 59.01; H, 6.27; N, 13.76. Found: C, 58.87; H, 6.41; N, 13.49.

3.4.2. *tert*-Butyl 5-methoxy-3-{[methoxy(methyl)amino]-carbonyl}-1*H*-indazole-1-carboxylate (4b). Starting from *N*,5-methoxy-*N*-methyl-1*H*-indazole-3-carboxamide **3b** (600 mg, 2.6 mmol) and following the general procedure, *tert*-butyl 5-methoxy-3-{[methoxy(methyl)amino]carbonyl}-1*H*-indazole-1-carboxylate **4b** was obtained as a yellow oil (494 mg, 58%). TLC R_f=0.5 (EtOAc/cyclohexane, 2:3). IR (KBr): 3622, 3512, 3467, 3104, 2979, 2930, 2852, 1763, 1742, 1652, 1619, 1504, 1456, 1426, 1395, 1371, 1344, 1315, 1281, 1254, 1159, 1099, 1067, 1040, 1010, 976, 913, 853, 819, 762 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 1.72 (s, 9H), 3.53 (br s, 3H), 3.88 (s, 3H), 3.94 (s, 3H), 7.17 (dd, J=9.2 Hz and J=2.4 Hz, 1H), 7.54 (br s, 1H), 8.02 (d, J=9.0 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ: 28.1, 30.2, 55.7, 61.2 (br s), 85.3, 101.8, 115.1, 120.7, 126.4, 135.4, 141.5, 148.8, 157.0, 164.5. MS (EI): m/z (%)=335 (M^+, 23), 235 (42), 176 (14), 175 (100). HRMS/ESI calcd for $C_{16}H_{21}N_3O_5$ $[M]^+$ 335.1481; found 335.1476.

3.5. General procedure for the addition of PhMgBr to 3 or 4

To magnesium turnings (5 equiv) was added slowly bromobenzene (5 equiv) in anhydrous Et_2O (5–16 mL) under argon for 10 min by keeping a mild reflux to start the reaction. The mixture was heated under reflux conditions for 1 h and then cooled to 0 °C. The chosen indazole **3** or **4** in anhydrous Et_2O (10–16 mL) was added slowly and the solution was heated under reflux conditions for 10 min and then kept for 1 h at room temperature and quenched with saturated aqueous NH_4Cl solution. The organic layer was washed with brine, dried over $MgSO_4$, filtered and evaporated in vacuo. The crude material was purified by column chromatography on silica gel (EtOAc/cyclohexane, 1:3) to give the desired indazole **5a** or **5b**.

3.5.1. 1*H*-Indazol-3-yl(phenyl)methanone (5a).[5c] Starting from *N*-methoxy-*N*-methyl-1*H*-indazole-3-carboxamide **3a** (410 mg, 2 mmol) and following the general procedure, 1*H*-indazol-3-yl(phenyl)methanone **5a** was obtained as a white solid (410 mg, 92%); mp 190–192 °C. TLC R_f=0.4 (EtOAc/cyclohexane, 1:3). IR (KBr): 3186, 1626, 1451, 1358, 1226, 1174, 1086, 929, 884, 745, 698 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 7.22–7.64 (m, 6H), 8.31 (d, J=7.1 Hz, 2H), 8.49 (d, J=8.3 Hz, 1H), 10.45 (br s, 1H). ^{13}C NMR ($CDCl_3$) δ: 109.8, 123.0, 123.4, 123.8, 127.7, 127.8, 128.0, 128.2, 130.4, 132.6, 137.9, 140.8, 189.2. MS (EI): m/z (%)=222 (M^+, 100), 221 (28), 194 (48), 193 (13), 145 (38), 105 (71), 90 (14), 77 (75). Anal. Calcd for $C_{14}H_{10}N_2O$: C, 75.66; H, 4.54; N, 12.60. Found: C, 75.32; H, 4.34; N, 11.81.

3.5.2. (5-Methoxy-1*H*-indazol-3-yl)(phenyl)methanone (5b). Starting from *tert*-butyl 5-methoxy-3-{[methoxy-(methyl)amino]carbonyl}-1*H*-indazole-1-carboxylate **4b** (360 mg, 1 mmol) and following the general procedure, (5-methoxy-1*H*-indazol-3-yl)(phenyl)methanone **5b** was obtained as a yellow solid (120 mg, 46%); mp 64 °C. TLC R_f=0.25 (EtOAc/cyclohexane, 1:3). IR (KBr): 3162, 2921, 1618, 1452, 1408, 1366, 1327, 1264, 1206, 1179, 1077, 1023, 806, 716, 689 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 3.94 (s, 3H), 7.15 (dd, J=9.0 Hz and J=2.4 Hz, 1H), 7.29–7.63 (m, 4H), 7.86 (d, J=2.4 Hz, 2H), 8.30 (d, J=7.6 Hz, 1H), 10.50 (br s, 1H). MS (EI): m/z (%)=252 (M^+, 79), 175 (11), 105 (100), 78 (71). Anal. Calcd for $C_{15}H_{12}N_2O_2$: C, 71.42; H, 4.79; N, 11.10. Found: C, 71.52; H, 4.54; N, 11.00.

3.6. General procedure for the addition of the Grignard reagents or lithiated reagents to 3

To a stirred solution under argon of the chosen indazole **3** in freshly distilled THF (18 mL) at −84 °C was added the Grignard reagent (5–6 equiv) or the lithiated reagent (5–7 equiv). The reaction mixture was allowed to react at this temperature over 2 h, then allowed to warm to room temperature and left to react for an additional hour. The solution was quenched with saturated aqueous NH_4Cl solution, then extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, filtered and evaporated in vacuo. The crude material was purified by column chromatography on silica gel to give the desired indazole **5c**, **5d**, **5e**, **5f**, **5g**, **5i**, **5j** or **5k**.

3.6.1. 1*H*-Indazol-3-yl(2-methoxyphenyl)methanone (5c). Starting from *N*-methoxy-*N*-methyl-1*H*-indazole-3-carboxamide **3a** (575 mg, 2.8 mmol) and following the general procedure, 1*H*-indazol-3-yl(2-methoxyphenyl)-methanone **5c** was obtained, after purification by column chromatography using a gradual eluent (EtOAc/cyclohexane, 1:3–1:1), as a white solid (400 mg, 57%); dec 132 °C. TLC R_f=0.4 (EtOAc/cyclohexane, 2:3). ^1H NMR

($CDCl_3$) δ: 3.78 (s, 3H), 7.06–7.10 (m, 2H), 7.39 (t, J=7.1 Hz, 1H), 7.45–7.58 (m, 4H), 8.42 (d, J=8.3 Hz, 1H), 10.70 (br s, 1H). ^{13}C NMR ($CDCl_3$) δ: 56.3, 110.7, 112.2, 120.7, 123.1, 123.2, 124.3, 128.0, 129.7, 130.4, 132.5, 141.1, 144.2, 158.1, 190.8. MS (EI): m/z (%)=252 (M^+, 100), 235 (32), 234 (24), 223 (19), 221 (22), 145 (33), 135 (58), 132 (61), 131 (41), 121 (35), 92 (21), 90 (15). HRMS/EI calcd for $C_{15}H_{12}N_2O_2$ $[M]^+$ 268.0899; found 268.0907.

3.6.2. 1-(1*H*-Indazol-3-yl)-2-methylpropan-1-one (5d). Starting from *N*-methoxy-*N*-methyl-1*H*-indazole-3-carboxamide **3a** (505 mg, 2.5 mmol) and following the general procedure, 1-(1*H*-indazol-3-yl)-2-methylpropan-1-one **5d** was obtained, after purification by column chromatography (EtOAc/cyclohexane, 1:3), as a white solid (375 mg, 81%); mp 130–132 °C. TLC R_f=0.65 (EtOAc/cyclohexane, 2:3). IR (KBr): 3293, 2967, 1652, 1447, 1373, 1325, 1250, 1136, 1100, 965, 907, 857, 735 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 1.31 (d, J=6.8 Hz, 6H), 3.95 (sept, J=6.8 Hz, 1H), 7.34 (t, J=7.3 Hz, 1H), 7.45 (t, J=8.6 Hz, 1H), 7.55 (d, J=8.3 Hz, 1H), 8.41 (d, J=8.0 Hz, 1H), 10.80 (br s, 1H). ^{13}C NMR ($CDCl_3$) δ: 19.0, 36.5, 109.9, 122.2, 122.9, 123.7, 127.4, 141.2, 142.8, 201.9. MS (EI): m/z (%)=188 (M^+, 100), 145 (100), 118 (21), 117 (25), 91 (13), 90 (55). Anal. Calcd for $C_{11}H_{12}N_2O$: C, 70.19; H, 6.43; N, 14.88. Found: C, 70.55; H, 6.66; N, 14.50.

3.6.3. 1-(5-Methoxy-1*H*-indazol-3-yl)-2-methylpropan-1-one (5e). Starting from *N*,5-dimethoxy-*N*-methyl-1*H*-indazole-3-carboxamide **3b** (475 mg, 2 mmol) and following the general procedure, 1-(5-methoxy-1*H*-indazol-3-yl)-2-methylpropan-1-one **5e** was obtained, after purification by column chromatography (CH_2Cl_2/MeOH, 98:2), as a yellow solid (130 mg, 30%); mp 175 °C. TLC R_f=0.6 (CH_2Cl_2/MeOH, 98:2). IR (KBr): 3170, 2970, 1650, 1469, 1450, 1342, 1325, 1256, 1220, 1123, 1098, 1028, 965, 945, 835, 792, 773 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 1.30 (d, J=6.8 Hz, 6H), 3.80–3.95 (m, 4H), 7.10 (dd, J=9.0 Hz and J=2.4 Hz, 1H), 7.43 (d, J=9.0 Hz, 1H), 7.78 (d, J=2.4 Hz, 1H), 10.48 (br s, 1H). ^{13}C NMR ($CDCl_3$) δ: 19.0, 36.3, 55.7, 101.4, 110.9, 120.1, 123.2, 136.9, 142.3, 157.0, 202.0. MS (EI): m/z (%)=218 (M^+, 32), 175 (100), 147 (6), 120 (9). HRMS/EI calcd for $C_{12}H_{14}N_2O_2$ $[M]^+$ 218.1055; found 218.1058.

3.6.4. 1-(1*H*-Indazol-3-yl)ethanone (5f).[5c] Starting from *N*-methoxy-*N*-methyl-1*H*-indazole-3-carboxamide **3a** (575 mg, 2.8 mmol) and following the general procedure, 1-(1*H*-indazol-3-yl)ethanone **5f** was obtained, after purification by column chromatography (EtOAc/cyclohexane, 1:1), as a white solid (370 mg, 82%); mp 184–186 °C. TLC R_f=0.5 (EtOAc/cyclohexane, 2:3). IR (KBr): 3194, 1655, 1584, 1450, 1342, 1251, 1210, 1156, 1045, 1002, 953, 906, 778, 753, 610 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 2.76 (s, 3H), 7.34 (t, J=7.7 Hz, 1H), 7.46 (t, J=8.3 Hz, 1H), 7.55 (d, J=8.3 Hz, 1H), 8.40 (d, J=8.3 Hz, 1H), 10.54 (br s, 1H). ^{13}C NMR ($CDCl_3$) δ: 26.8, 109.8, 121.6, 122.8, 123.8, 127.5, 141.1, 144.2, 195.2. MS (EI): m/z (%)=160 (M^+, 54), 145 (100), 90 (55). Anal. Calcd for $C_9H_8N_2O$: C, 67.49; H, 5.03; N, 17.49. Found: C, 67.29; H, 4.98; N, 17.20.

3.6.5. 1-(1*H*-Indazol-3-yl)pentan-1-one (5g). Starting from *N*-methoxy-*N*-methyl-1*H*-indazole-3-carboxamide **3a** (575 mg, 2.8 mmol) and following the general procedure, 1-(1*H*-indazol-3-yl)pentan-1-one **5g** was obtained, after purification by column chromatography (EtOAc/cyclohexane, 1:2), as a white solid (210 mg, 37%); mp 134 °C. TLC R_f=0.7 (EtOAc/cyclohexane, 2:3). IR (KBr): 3223, 2954, 2361, 1655, 1621, 1586, 1501, 1458, 1354, 1245, 1134, 1047, 960, 904, 778, 739 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 0.97 (t, J=7.3 Hz, 3H), 1.45 (st, J=7.6 Hz, 2H), 1.80 (qt, J=7.6 Hz, 2H), 3.20 (t, J=7.8 Hz, 2H), 7.34 (dt, J=8.0 Hz and J=1.0 Hz, 1H), 7.45 (dt, J=8.3 Hz and J=1.2 Hz, 1H), 7.55 (d, J=8.5 Hz, 1H), 8.41 (d, J=7.8 Hz, 1H), 10.50 (br s, 1H). ^{13}C NMR ($CDCl_3$) δ: 14.6, 23.2, 27.2, 39.4, 110.4, 122.4, 123.5, 124.3, 128.1, 141.1, 144.0, 198.6. MS (EI): m/z (%)=202 (M^+, 55), 173 (11), 161 (13), 160 (100), 146 (18), 145 (100), 132 (28), 118 (20), 90 (29). Anal. Calcd for $C_{12}H_{14}N_2O$: C, 71.26; H, 6.98; N, 13.85. Found: C, 71.34; H, 6.71; N, 13.52.

3.6.6. 1-(1*H*-Indazol-3-yl)but-2-yn-1-one (5i). Starting from *N*-methoxy-*N*-methyl-1*H*-indazole-3-carboxamide **3a** (575 mg, 2.8 mmol) and following the general procedure, 1-(1*H*-indazol-3-yl)but-2-yn-1-one **5i** was obtained, after purification by column chromatography using a gradual eluent (EtOAc/cyclohexane, 1:3–1:2), as a pink solid (42 mg, 8%); dec 159–161 °C. TLC R_f=0.3 (EtOAc/cyclohexane, 2:3). IR (KBr): 3246, 2212, 1610, 1584, 1449, 1358, 1257, 1218, 1159, 1065, 1003, 917, 868, 740 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 2.19 (s, 3H), 7.38 (t, J=8.1 Hz, 1H), 7.49 (t, J=8.0 Hz, 1H), 7.58 (d, J=8.3 Hz, 1H), 8.38 (d, J=8.0 Hz, 1H), 10.68 (br s, 1H). MS (EI): m/z (%)=184 (M^+, 100), 156 (60), 155 (41), 145 (11), 127 (11), 118 (13), 90 (14). Anal. Calcd for $C_{11}H_8N_2O$: C, 71.73; H, 4.38; N, 15.21. Found: C, 71.70; H, 4.24; N, 14.84.

3.6.7. 1-(1*H*-Indazol-3-yl)-3-[methoxy(methyl)amino]-propan-1-one (5j). Starting from *N*-methoxy-*N*-methyl-1*H*-indazole-3-carboxamide **3a** (575 mg, 2.8 mmol) and following the general procedure, 1-(1*H*-indazol-3-yl)-3-[methoxy(methyl)amino]propan-1-one **5j** was obtained, after purification by column chromatography using a gradual eluent (EtOAc/cyclohexane, 1:2–1:1), as a yellow solid (242 mg, 37%); mp 97 °C. TLC R_f=0.3 (EtOAc/cyclohexane, 2:3). IR (KBr): 3227, 2937, 1644, 1585, 1457, 1404, 1348, 1247, 1134, 1106, 1040, 1006, 963, 905, 775, 753 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 2.19 (s, 3H), 3.21 (t, J=6.8 Hz, 2H), 3.46–3.53 (m, 5H), 7.32 (t, J=8.1 Hz, 1H), 7.49 (t, J=8.1 Hz, 1H), 7.55 (d, J=8.5 Hz, 1H), 8.38 (d, J=7.8 Hz, 1H), 11.19 (br s, 1H). ^{13}C NMR ($CDCl_3$) δ: 37.0, 45.3, 55.8, 60.1, 110.1, 122.0, 122.9, 123.8, 127.5, 141.3, 143.9, 196.5. MS (EI): m/z (%)=233 (M^+, 1), 202 (55), 173 (11), 161 (15), 160 (31), 146 (13), 145 (100), 90 (23). Anal. Calcd for $C_{12}H_{15}N_3O_2$: C, 61.79; H, 6.48; N, 18.01. Found: C, 61.85; H, 6.67; N, 17.59.

3.6.8. 1-(1*H*-Indazol-3-yl)prop-2-yn-1-one (5k). Starting from *N*-methoxy-*N*-methyl-1*H*-indazole-3-carboxamide **3a** (575 mg, 2.8 mmol) and following the general procedure, 1-(1*H*-indazol-3-yl)prop-2-yn-1-one **5k** was obtained, after purification by column chromatography (EtOAc/cyclohexane, 1:2), as a yellow solid (110 mg, 23%); dec 158 °C. TLC R_f=0.4 (EtOAc/cyclohexane, 2:3). IR (KBr): 3312, 3212, 2095, 1635, 1453, 1423, 1368, 1252, 1204, 1141, 1109, 1006, 981, 731 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 3.47 (s, 1H), 7.40 (t, J=7.8 Hz, 1H), 7.51 (t, J=7.8 Hz, 1H), 7.60

(d, J=8.5 Hz, 1H), 8.37 (d, J=8.0 Hz, 1H), 10.75 (br s, 1H). ^{13}C NMR ($CDCl_3$) δ: 79.6, 80.8, 110.2, 121.7, 122.4, 124.6, 128.1, 141.2, 144.5, 172.0. MS (EI): m/z (%)=170 (M^+, 100), 142 (68), 118 (19), 115 (33), 114 (14), 91 (12). Anal. Calcd for $C_{10}H_6N_2O$: C, 70.58; H, 3.55; N, 16.46. Found: C, 70.35; H, 3.85; N, 16.10.

3.7. 1-(1*H*-Indazol-3-yl)-3-phenylprop-2-yn-1-one (5h)

To a stirred solution under argon of phenylacetylene (1.85 mL, 16.8 mmol, 6 equiv) in freshly distilled THF (20 mL) at −84 °C was added *n*-butyllithium (6.8 mL, 2.5 M in hexane, 17.08 mmol, 6.1 equiv). After 1 h at −84 °C, a solution of *N*-methoxy-*N*-methyl-1*H*-indazole-3-carboxamide **3a** (575 mg, 2.8 mmol) in distilled THF (12 mL) was added dropwise. The reaction mixture was allowed to react at this temperature over 30 min, then allowed to warm to room temperature and left to react for an additional hour. The solution was quenched with saturated aqueous NH_4Cl solution, then extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, filtered and evaporated in vacuo. The crude material was purified by column chromatography on silica gel (EtOAc/cyclohexane, 1:2) to give 1-(1*H*-indazol-3-yl)-3-phenylprop-2-yn-1-one **5h** as a yellow solid (430 mg, 62%); dec 190 °C. TLC R_f=0.5 (EtOAc/cyclohexane, 2:3). IR (KBr): 3152, 2194, 1636, 1489, 1449, 1406, 1370, 1350, 1272, 1245, 1152, 1136, 1107, 978, 794, 763, 752, 690 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 7.37–7.51 (m, 5H), 7.60 (d, J=8.6 Hz, 1H), 7.71 (d, J=6.8 Hz, 2H), 8.43 (d, J=7.6 Hz, 1H), 11.06 (br s, 1H). ^{13}C NMR ($CDCl_3$) δ: 88.1, 92.7, 110.9, 120.5, 122.2, 122.5, 124.5, 128.1, 128.8, 130.9, 133.4, 141.7, 144.8, 172.9. MS (EI): m/z (%)=246 (M^+, 100), 219 (15), 218 (81), 189 (19), 129 (83), 109 (17), 101 (14). Anal. Calcd for $C_{16}H_{10}N_2O$: C, 78.04; H, 4.09; N, 11.38. Found: C, 77.52; H, 4.17; N, 10.82.

3.8. (2,6-Difluoro-4-methoxyphenyl)(1*H*-indazol-3-yl)-methanone (6a), *tert*-butyl 3-(2,6-difluoro-4-methoxybenzoyl)-1*H*-indazole-1-carboxylate (6b) and 2,3′,6-trifluoro-4,5′-dimethoxybiphenyl (7)

To a stirred solution under argon of 3,5-difluoroanisole (520 μL, 4.4 mmol, 1.5 equiv) in freshly distilled THF (40 mL) at −84 °C was added *n*-butyllithium (1.8 mL, 2.5 M in hexane, 4.4 mmol, 1.5 equiv). After 1 h at −84 °C, a solution of *tert*-butyl 3-{[methoxy(methyl)amino]carbonyl}-1*H*-indazole-1-carboxylate **4a** (900 mg, 3 mmol) in distilled THF (15 mL) was added dropwise. The reaction mixture was allowed to react at this temperature over 2 h, then allowed to warm to room temperature and left to react for an additional hour. The solution was quenched with saturated aqueous NH_4Cl solution, then concentrated in vacuo and taken up in EtOAc. The organic layer was washed with an aqueous solution of HCl (0.5 M), then brine, dried over $MgSO_4$, filtered and evaporated in vacuo. The crude material was purified by column chromatography on silica gel (EtOAc/cyclohexane, 1:3) to give *tert*-butyl 3-(2,6-difluoro-4-methoxybenzoyl)-1*H*-indazole-1-carboxylate **6a** (80 mg, 7%) as a yellow oil, (2,6-difluoro-4-methoxyphenyl)(1*H*-indazol-3-yl)methanone **6b** (210 mg, 25%) as a white solid, 2,3′,6-trifluoro-4,5′-dimethoxybiphenyl **7** (100 mg, 13%) as a white solid, *N*-methoxy-*N*-methyl-1*H*-indazole-3-carboxamide **3a** (30 mg, 5%) and starting material **4a** (200 mg, 22%).

Compound **6a**: TLC R_f=0.5 (EtOAc/cyclohexane, 1:3). ^{1}H NMR ($CDCl_3$) δ: 1.71 (s, 9H), 3.82 (s, 3H), 6.50–6.55 (m, 2H), 7.46 (t, J=8.1 Hz, 1H), 7.58 (t, J=8.6 Hz, 1H), 8.13 (d, J=8.5 Hz, 1H), 8.41 (d, J=8.0 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ: 28.0, 56.0, 86.1, 98.3 (m), 109.9 (t, J_{C-F}= 19.9 Hz), 114.4, 122.7, 124.0, 125.4, 129.3, 140.8, 146.5, 148.4, 161.7 (dd, J_{C-F}=252.0 Hz and J_{C-F}=10.7 Hz), 163.2 (t, J_{C-F}=14.0 Hz), 184.0. HRMS/EI calcd for $C_{20}H_{18}F_2N_2O_4$ $[M]^+$ 388.1234; found 388.1242.

Compound **6b**: mp 210 °C. TLC R_f=0.25 (EtOAc/cyclohexane, 1:3). ^{1}H NMR ($CDCl_3$) δ: 3.65 (s, 3H), 6.36–6.45 (m, 2H), 7.30 (t, J=8.0 Hz, 1H), 7.38–7.43 (m, 2H), 8.30 (d, J=8.0 Hz, 1H), 11.20 (br s, 1H). ^{13}C NMR ($CDCl_3$) δ: 55.8, 98.1 (m), 110.0, 110.4 (t, J_{C-F}=21.5 Hz), 121.8, 122.2, 124.2, 127.7, 140.9, 144.1, 148.4, 160.9 (dd, J_{C-F}= 246.7 Hz and J_{C-F}=10.7 Hz), 162.5 (t, J_{C-F}=13.3 Hz), 183.5. HRMS/EI calcd for $C_{15}H_{10}F_2N_2O_2$ $[M]^+$ 288.0710; found 288.0704.

Compound **7**: mp 64–66 °C. TLC R_f=0.65 (EtOAc/cyclohexane, 1:3). IR (KBr): 3094, 2957, 2853, 1619, 1581, 1512, 1474, 1451, 1422, 1332, 1290, 1248, 1199, 1144, 1079, 1061, 1022, 833, 730, 692 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 3.80 (s, 3H), 3.81 (s, 3H), 6.51–6.57 (m, 2H), 6.63 (dt, J=10.8 Hz and J=2.2 Hz, 1H), 6.78 (dddt, J=10.6 Hz, J=2.4 Hz, J=1.3 Hz and J=1.3 Hz, 1H), 6.78 (m, 1H). ^{13}C NMR ($CDCl_3$) δ: 55.4, 55.7, 98.2 (m), 101.0 (d, J_{C-F}= 24.8 Hz), 109.6 (dt, J_{C-F}=22.3 Hz and J_{C-F}=2.5 Hz), 109.8 (td, J_{C-F}=19.0 Hz and J_{C-F}=2.5 Hz), 112.0 (m), 131.5 (d, J_{C-F}=10.7 Hz), 160.38 (t, J_{C-F}=14.9 Hz), 160.48 (dd, J_{C-F}=247.8 Hz and J_{C-F}=9.9 Hz), 160.54 (d, J_{C-F}= 12.3 Hz), 163.2 (d, J_{C-F}=242.9 Hz). ^{19}F NMR ($CDCl_3$) δ: −112.7 (m, 1F), −113.5 (dt, J=9.9 Hz and J=1.3 Hz, 2F). MS (EI): m/z (%)=268 (M^+, 100), 253 (11), 225 (22). HRMS/EI calcd for $C_{14}H_{11}F_3O_2$ $[M]^+$ 268.0711; found 268.0711. Anal. Calcd for $C_{14}H_{11}F_3O_2$: C, 62.69; H, 4.13. Found: C, 62.34; H, 4.22.

3.9. 1-[2-(Trimethyl-silanyl)-ethoxymethyl]-*N*-methoxy-*N*-methyl-1*H*-indazole-3-carboxamide (8)

To a cooled solution of *N*-methoxy-*N*-methyl-1*H*-indazole-3-carboxamide **3a** (3 g, 14.6 mmol), TBABr (47 mg, 0.15 mmol, 0.01 equiv), KOH (50% solution in water, 15 mL) in CH_2Cl_2 (20 mL) was added at 0 °C dropwise SEM-Cl (2.73 mL, 16.1 mmol, 1.1 equiv). After the end of the addition, the mixture was stirred rapidly at 0 °C for 1 h and then for 2 h at room temperature. CH_2Cl_2 (50 mL) and water (70 mL) were added, and the organic layer was washed with brine, dried over $MgSO_4$, filtered and evaporated in vacuo. The crude material was purified by flash column chromatography on silica gel (EtOAc/cyclohexane, 1:6) to give 1-[2-(trimethyl-silanyl)-ethoxymethyl]-*N*-methoxy-*N*-methyl-1*H*-indazole-3-carboxamide **8** as a light yellow oil (4.47 g, 91%). TLC R_f=0.7 (EtOAc/cyclohexane, 1:1). IR (KBr): 3446, 2953, 1652, 1619, 1487, 1436, 1305, 1249, 1143, 1084, 1026, 973, 860, 786, 751, 694 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: −0.08 (s, 9H), 0.88 (t, J=8.5 Hz, 2H), 3.51 (s, 3H), 3.57 (t, J=8.5 Hz, 2H), 3.87 (s, 3H), 5.73 (s,

2H), 7.26 (t, J=8.0 Hz, 1H), 7.37 (t, J=8.3 Hz, 1H), 7.55 (d, J=8.4 Hz, 1H), 8.21 (d, J=8.0 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ: −1.4, 17.7, 35.0, 61.7, 66.7, 78.3, 109.7, 122.6, 124.9, 127.2, 137.7, 140.1, 163.4. MS (EI): m/z (%)=335 (M^+, 3), 275 (26), 218 (19), 217 (34), 101 (10), 74 (100). HRMS/ESI calcd for $C_{16}H_{25}N_3O_3Si$ $[M]^+$ 335.1665; found 335.1679.

3.10. (2,6-Difluoro-4-methoxyphenyl){1-[2-(trimethylsilanyl)-ethoxymethyl]-1*H*-indazol-3-yl}methanone (9a) and (2,6-difluoro-4-methoxyphenyl){2-[2-(trimethyl-silanyl)-ethoxymethyl]-2*H*-indazol-3-yl}methanone (9b)

To a stirred solution under argon of 3,5-difluoroanisole (700 μL, 6 mmol, 1.2 equiv) in freshly distilled THF (40 mL) at −84 °C was added *n*-butyllithium (2.4 mL, 2.5 M in hexane, 6 mmol, 1.2 equiv). After 1 h at −84 °C, a solution of 1-[2-(trimethyl-silanyl)-ethoxymethyl]-*N*-methoxy-*N*-methyl-1*H*-indazole-3-carboxamide **8** (1.68 g, 5 mmol) in distilled THF (15 mL) was added dropwise. The reaction mixture was allowed to react at this temperature over 2 h, then allowed to warm to room temperature and left to react for an additional hour. The solution was quenched with saturated aqueous NH_4Cl solution, then concentrated in vacuo and taken up in EtOAc. The organic layer was washed with an aqueous solution of HCl (0.5 M), then brine, dried over $MgSO_4$, filtered and evaporated in vacuo. The crude material was purified by column chromatography on silica gel (EtOAc/cyclohexane, 1:4) to give a mixture of (2,6-difluoro-4-methoxyphenyl){1-[2-(trimethyl-silanyl)-ethoxymethyl]-1*H*-indazol-3-yl}methanone **9a** and (2,6-difluoro-4-methoxyphenyl){2-[2-(trimethyl-silanyl)-ethoxymethyl]-2*H*-indazol-3-yl}methanone **9b** as a light yellow oil (1.52 g, 72%) and starting material **8** (426 mg, 25%). TLC R_f=0.9 (EtOAc/cyclohexane, 2:3). IR (KBr): 2953, 1633, 1581, 1471, 1443, 1413, 1347, 1304, 1249, 1201, 1149, 1086, 1042, 882, 836, 786, 753 cm^{-1}. MS (EI): m/z (%)=418 (M^+, 3), 346 (16), 345 (71), 302 (58), 301 (29), 171 (54), 157 (12), 131 (19), 103 (12), 81 (18), 74 (100). HRMS/ESI calcd for $C_{21}H_{24}F_2N_2O_3Si$ $[M]^+$ 418.1524; found 418.1513.

Compound **9a**: ^{1}H NMR ($CDCl_3$) δ: −0.07 (s, 9H), 0.87 (t, J=8.3 Hz, 2H), 3.54 (t, J=8.3 Hz, 2H), 3.84 (s, 3H), 5.76 (s, 2H), 6.51–6.53 (m, 2H), 7.40 (t, J=8.1 Hz, 1H), 7.50 (t, J=8.5 Hz, 1H), 7.64 (d, J=8.3 Hz, 1H), 8.42 (d, J=8.0 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ: −1.2, 18.0, 56.4, 67.2, 78.9, 98.6 (m), 110.6, 111.2 (t, J_{C-F}=20.7 Hz), 123.1, 124.1, 124.8, 127.9, 141.3, 143.5, 161.8 (dd, J_{C-F}=251.0 Hz and J_{C-F}=10.6 Hz), 163.0 (t, J_{C-F}=13.9 Hz), 184.0.

Compound **9b**: ^{1}H NMR ($CDCl_3$) δ: −0.06 (s, 9H), 0.94 (t, J=8.3 Hz, 2H), 3.66 (t, J=8.3 Hz, 2H), 3.89 (s, 3H), 6.24 (s, 2H), 6.57–6.59 (m, 2H), 6.92 (d, J=8.6 Hz, 1H), 7.16 (t, J=8.2 Hz, 1H), 7.33 (t, J=8.3 Hz, 1H), 7.86 (d, J=8.8 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ: −1.1, 18.2, 56.6, 67.6, 82.0, 99.1 (m), 111.2 (t, J_{C-F}=18.2 Hz), 119.7, 119.8, 124.5, 126.7, 127.1, 132.2, 148.2, 161.5 (dd, J_{C-F}=251.5 Hz and J_{C-F}=10.1 Hz), 163.7 (t, J_{C-F}=13.6 Hz), 176.9.

3.11. General procedure for the synthesis of 3-formylindazoles 10

To a cooled solution of the chosen indazole **3** in freshly distilled THF (40 mL) was added at −15 °C $LiAlH_4$ (1.5 equiv). The mixture was stirred at −15 °C for 1 h and then at room temperature for 12 h. The solution was placed at 0 °C and quenched with an aqueous HCl solution (2 N) and extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, filtered and evaporated in vacuo. The crude material was purified by column chromatography on silica gel (EtOAc/cyclohexane, 1:2) to obtain the desired 3-formylindazole **10a** or **10b**.

3.11.1. 1*H*-Indazole-3-carbaldehyde (10a).[22b]

Starting from *N*-methoxy-*N*-methyl-1*H*-indazole-3-carboxamide **3a** (1.63 g, 7.9 mmol) and following the general procedure, 1*H*-indazole-3-carbaldehyde **10a** was obtained as a white solid (880 mg, 76%); mp 140 °C. TLC R_f=0.7 (EtOAc/cyclohexane, 2:1). IR (KBr): 3435, 3188, 2926, 1698, 1670, 1466, 1339, 1257, 1088, 801, 739 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 7.38 (t, J=8.0 Hz, 1H), 7.50 (t, J=8.5 Hz, 1H), 7.58 (d, J=8.3 Hz, 1H), 8.34 (d, J=8.0 Hz, 1H), 10.31 (s, 1H), 10.98 (br s, 1H). ^{13}C NMR ($CDCl_3$) δ: 110.0, 121.0, 122.1, 124.2, 128.0, 141.2, 144.9, 187.4. MS (EI): m/z (%)=146 (M^+, 100), 145 (59), 118 (39), 91 (31), 90 (19), 86 (46), 84 (71). Anal. Calcd for $C_8H_6N_2O$: C, 65.75; H, 4.14; N, 19.17. Found: C, 65.46; H, 4.12; N, 19.09.

3.11.2. 5-Methoxy-1*H*-indazole-3-carbaldehyde (10b).[22d]

Starting from *N*,5-dimethoxy-*N*-methyl-1*H*-indazole-3-carboxamide **3b** (1.6 g, 6.8 mmol) and following the general procedure, 5-methoxy-1*H*-indazole-3-carbaldehyde **10b** was obtained as a brown solid (840 mg, 64%); mp 214–216 °C. TLC R_f=0.5 (EtOAc/cyclohexane, 1:1). IR (KBr): 3204, 1664, 1482, 1452, 1323, 1259, 1217, 1077, 1021, 838, 796, 719 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 3.91 (s, 3H), 7.15 (dd, J=9.0 Hz and J=2.4 Hz, 1H), 7.46 (d, J=9.0 Hz, 1H), 7.67 (d, J=2.2 Hz, 1H), 10.27 (s, 1H), 10.49 (br s, 1H). MS (EI): m/z (%)=176 (M^+, 100), 161 (24), 133 (32), 105 (19). Anal. Calcd for $C_9H_8N_2O_2$: C, 61.36; H, 4.58; N, 15.90. Found: C, 61.76; H, 4.52; N, 15.53.

3.12. 1-(1*H*-Indazol-3-yl)-*N*-methoxy-*N*-methylmethanamine (11)

To a stirred solution under argon of *N*-methoxy-*N*-methyl-1*H*-indazole-3-carboxamide **3a** (575 mg, 2.8 mmol) in freshly distilled THF (16 mL) at −84 °C was added Dibal-H (8.4 mL, 1 M in THF, 8.4 mmol, 3 equiv). The reaction mixture was stirred at −84 °C for 1 h, warmed slowly at room temperature for 1 h, then stirred at room temperature for 1 h. The reaction was monitored by TLC. The solution was placed at 0 °C and Dibal-H (5.6 mL, 5.6 mmol, 2 equiv) was added. The reaction mixture was allowed to react at this temperature over 1 h, then allowed to warm to room temperature and left to react for an additional hour. The solution was quenched with water, filtered on Celite, then extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, filtered and evaporated in vacuo. The crude material was purified by column chromatography on silica gel (EtOAc/cyclohexane, 1:4) to give 1*H*-indazole-3-carbaldehyde **10a** (125 mg, 31%) and 1-(1*H*-indazol-3-yl)-*N*-methoxy-*N*-methylmethanamine **11**, after trituration in petroleum ether, as a white solid (370 mg, 69%); mp 69 °C. TLC R_f=0.4 (EtOAc/cyclohexane, 2:1). IR (KBr): 3224, 2954, 2878, 1620, 1501, 1438, 1354, 1244, 1132, 1122, 1072, 1046, 972, 959, 753 cm^{-1}. ^{1}H NMR ($CDCl_3$)

δ: 2.68 (s, 3H), 3.42 (s, 3H), 4.28 (br s, 2H), 7.14 (t, J=7.8 Hz, 1H), 7.35 (t, J=8.3 Hz, 1H), 7.49 (d, J=8.3 Hz, 1H), 7.89 (d, J=7.8 Hz, 1H), 11.50 (br s, 1H). ^{13}C NMR ($CDCl_3$) δ: 45.0, 56.7, 59.9, 110.1, 120.6, 121.0, 122.5, 126.7, 141.2, 142.6. MS (EI): m/z (%)=191 (M^+, 10), 161 (9), 160 (78), 132 (27), 131 (100). Anal. Calcd for $C_{10}H_{13}N_3O$: C, 62.81; H, 6.85; N, 21.97. Found: C, 62.84; H, 6.46; N, 21.77.

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Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2006.10.063.

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