Reductive heterocyclizations *via* indium–iodine-promoted conversion of 2-nitroaryl imines or 2-nitroarenes to 2,3-diaryl-substituted indazoles

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While *N*-(2-nitrobenzylidene)anilines produced mixtures of 2,1-benzisoxazoles and 3-anilino-2-aryl-2*H*-indazoles in the presence of indium and iodine in MeOH, *N*-(2-nitrobenzylidene)anilines were transformed into 3-anilino-2-aryl-2*H*-indazoles as the predominant major product through the change of the solvent from protic MeOH to aprotic THF. In an indium-mediated one-pot reductive reaction, 2-benzaldehydes and anilines in THF were also successfully transformed into the corresponding indazoles.

Introduction

The indazole subunit in organic molecules is an important structure in many drug substances with a wide range of pharmacological effects: *e.g.* antitumor,[1] antimicrobial,[2] antiplatelet,[3] anti-HIV,[4] and anti-iflammatory.[5] For the construction of the 2*H*-indazole skeleton, the reduction of *N*-(2-nitrobenzylidene)amines using triethylphosphite, and the thermal decomposition of *N*-(2-azidobenzylidene)amines are widely used;[6a,6b] other approaches for the construction of the 2*H*-indazole skeleton such as transition-metal catalyzed reactions were also employed.[6c] Recent examples of syntheses of 2*H*-indazoles include the following: copper-mediated cyclizations of 1-(2-ethynylphenyl)-3,3-dialkyltriazenes,[7] DDQ oxidation of pyrazoles made from the Baylis–Hillman adducts of 2-cyclohexen-1-one,[8] and cyclizations of *o*-nitrobenzylamines under ethanolic conditions.[9] There are few reports, however, of general and efficient syntheses of *N*-substituted indazoles.

In our previous study of heterocyclic compound formation *via* the reductive cyclization reaction of nitroarenes,[10] it was found that the nitro group can be reduced through chemical or electrochemical methods, and it can trigger heterocyclization towards nitrogen-containing heterocycles, such as 2,1-benzisoxazoles, benzotriazoles, benzimidazoles, and quinolines when it has a proper functional group such as carbonyl or imino group at the *ortho* position. Moreover, reductive heterocyclizations using indium were also successfully used in transformations forming heterocyclic compounds such as 2,1-benzisoxazoles,[10i] benzimidazoles,[10l] and quinolines.[10m] These indium-mediated reductive heterocyclizations are noteworthy as indium has been receiving increasing interest due to its applications in organic transformations.[11] In particular, among the applications of indium in organic chemistry, indium-mediated reactions in aqueous media have been focused on for synthetic applications because of environmental issues and the ease of these reactions, which obviate the need for inflammable anhydrous organic solvents and inert atmospheres.[11b]

Thus, of special interest to us is the possibility of utilizing the indium-promoted reaction for the efficient synthesis of 2,3-disubstituted indazoles as an extension of the study on the reductive cyclization reaction of 2-nitroarenes, as only a limited number of applications of indium, other than carbon–carbon bond formation, are found in the literature.[12] Thus, the one-pot synthetic approach to new 2,3-disubstituted indazoles through the direct conversion of 2-nitro-substituted iminobenzenes using indium and iodine, which can be useful in biological, agricultural, and industrial applications, is reported herein.[13] As far as we know, there are few applicable general methods for the synthesis of 2,3-disubstituted indazole derivatives, and all the indazoles that were synthesized in this study were new compounds accordingly.

Results and discussion

As indium and related reagents turned out to have reasonable reductive properties, heterocyclizations of substituted 2-nitrobenzaldehydes, 2′-nitroacetophenone, and 2-nitrobenzophenones were examined in a preliminary study.[14] As described in this earlier communication, the reductive cyclization reactions of 2-nitroaryl aldehydes and ketones to 2,1-benzisoxazoles appear generally applicable in most cases, and all of the substrates were consumed within 1.5–6 hours to give the corresponding 2,1-benzisoxazoles in 80–95% yields. However, the reductive cyclization of *N*-(2-nitrobenzylidene)aniline in the presence of indium–iodine in MeOH produced a mixture of 2,1-benzisoxazole (56%) and 3-anilino-2-phenyl-2*H*-indazole (27%) (Table 1, entry 1).

The formation of 3-anilino-2-phenyl-2*H*-indazole was somewhat unexpected, and the reactions of halo- or methoxy- substituted *N*-(2-nitrobenzylidene)anilines exhibited similar results, producing mixtures of 2,1-benzisoxazoles and 3-anilino-2-phenyl-2*H*-indazoles (entries 2–4). It is presumed that the formation of 3-anilino-2-phenyl-2*H*-indazoles might have occurred due to the nucleophilic participation of *in situ*-formed anilines, which are supposed to be leaving groups when 2,1-benzisoxazoles are formed. As indazole derivatives have also attracted much attention due to their pharmaceutical activities, and as the 2,3-disubstituted indazole derivatives in this study are new compounds that could not be easily synthesized using any of the known conventional methods, it is thought that a reinvestigatiton at the point of the

[a]*Department of Chemistry, Kwangwoon University, Seoul, 139-701, Korea. E-mail: bhkim@kw.ac.kr; Fax: +82 29 424 635; Tel: +82 29 405 247*
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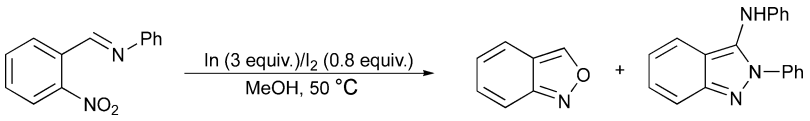
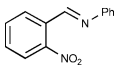
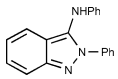
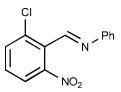
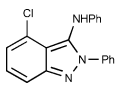
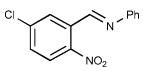
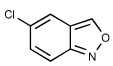
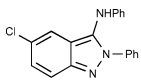
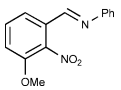
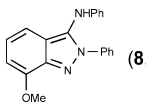
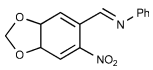
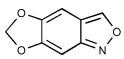
Table 1 Reductive cyclization of the 2-nitroiminobenzenes (1.0 mmol) in the presence of indium (3.0 equiv.) and iodine (0.8 equiv.) in MeOH (3 ml) at 50 °C.[14]



Entry	Substrate	Time/h	Product (% yield[a])		
1		4	 (**1**, 56%)	+	 (**2**, 27%)
2		6	 (**3**, 56%)	+	 (**4**, 25%)
3		6	 (**5**, 70%)	+	 (**6**, 15%)
4		6	 (**7**, 68%)	+	 (**8**, 13%[b])
5		6	 (**9**, 76%)		

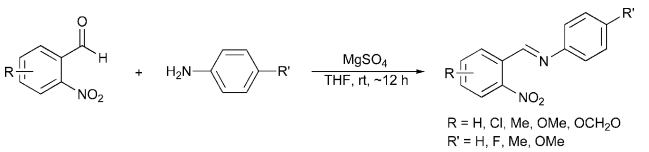
[a] Isolated yield. [b] Trace amount of *N*-[(2-amino-3-methoxyphenyl)methylene]benzamine was observed.

reductive cyclization reactions of *N*-(2-nitrobenzylidene)aniline derivatives to the indazoles as the major product instead of 2,1-benzisoxazoles would be valuable. Thus, it was decided that the reaction would be controlled, focusing on the 3-anilino-2-phenyl-2*H*-indazole formation to develop a new and valuable synthetic methodology for the one-pot reductive indazole synthesis from nitroarenes. Thus, various reaction conditions were carefully reinvestigated to find the indazole-formation-favored reaction conditions.

1) Indium-mediated reductive reaction of *N*-(2-nitrobenzylidene)anilines in the presence of aniline additive whose structure is the same as that of the anilino-subunit of the *N*-(2-nitrobenzylidene)anilines

As was assumed, the indazoles might have come from the contribution of *in situ*-formed anilines. First, how the aniline concentration influences the reaction was checked by adding the corresponding aniline to the reaction mixture. Thus, heterocyclizations of *N*-[(2-nitrophenyl)methylene]benzene in the presence of an excess amount of aniline that was a leaving group of the reaction were examined. A reaction of *N*-(2-nitrobenzylidene)aniline in the presence of indium (3 equiv.), iodine (0.8 equiv.), and aniline (20 equiv.) in MeOH showed an improved indazole–2,1-benzisoxazole ratio (Table 2, entry 2) compared to the same reaction without aniline additive. However, 2,1-benzisoxazole was still one of the major products. In the mean time, as shown in Table 2, by changing the solvent from protic MeOH to aprotic solvent, the formation of 2,1-benzisoxazole was drastically reduced (Table 2, entries 4–15). Among the aprotic solvents that were tried, THF showed the best results in terms of indazole formation. The reaction of *N*-[(2-nitrophenyl)methylene]benzene (1.0 mmol), indium (3 equiv.), iodine (0.8 equiv.) and aniline (20 equiv.) in THF at 50 °C produced the desired (2-phenyl-2*H*-indazol-3-yl)phenylamine (**2**) in a 75% isolated yield (entry 8), accompanied by only a small GC-detectable amount of 2,1-benzisoxazole as a by-product, which was the most desired result of this study.

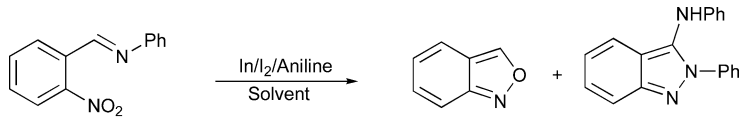
To test the usefulness of the newly developed reaction conditions for the synthesis of indazole derivatives, various *N*-(2-nitrobenzylidene)anilines (*i.e.* 2-nitroiminobenzene derivatives) were examined using the optimized reaction conditions. For the starting substrate, 2-nitroiminobenzenes were prepared using diversely substituted 2-nitrobenzaldehydes and 4-substituted anilines as shown in eqn (1).



(1)

In most cases, 2-nitroiminobenzenes were successfully cyclized, giving the desired indazoles within 4 hours in moderate to good yields, as shown in Table 3, independent of the positions and characters of the substituent, R, which were H, Cl, Me, OMe, and OCH_2O. For the anilino site, the structure of R′ somehow influenced the direction of the heterocyclization of 2-nitroiminobenzenes. The heterocyclizations of *N*-(2-nitrobenzylidene)anilines to give the desired indazoles worked well when R′ was H, an electronegative fluoro atom, or a

Table 2 Indium-mediated reductive heterocyclizations of the *N*-(2-nitrobenzylidene)aniline (1.0 mmol) under various reaction conditions



1 **2**

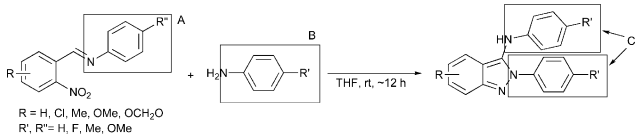
Entry	In–I_2–aniline (equiv.)	Solvent	*T*/°C	Time/h	Product (% yield[a] **1** : **2**)
1	3 : 0.8 : 0	MeOH (3 ml)	50 °C	4	56 : 27
2	3 : 0.8 : 20	MeOH (3 ml)	50 °C	4	27 : 30
3	3 : 0.8 : 20	THF–H_2O (3 ml, 1 ml)	50 °C	5	trace : 22[b]
4	3 : 0.8 : 20	CH_3CN (3 ml)	50 °C	5	trace : 25[b]
5	3 : 0.8 : 20	$CHCl_3$ (3 ml)	50 °C	8	trace : 38[b]
6	3 : 0.8 : 20	CH_2Cl_2 (3 ml)	50 °C	8	trace : 50[b]
7	3 : 0.8 : 10	THF (5 ml)	50 °C	6	trace : 71
8	3 : 0.8 : 20	THF (5 ml)	50 °C	4	trace : 75 (82[b])
9	3 : 0.8 : 30	THF (5 ml)	50 °C	4	trace : 70
10	3 : 0.8 : 20	THF (3 ml)	rt	12	trace : 38
11	3 : 0.8 : 20	THF (3 ml)	50 °C	6	trace : 60
12	3 : 1.5 : 20	THF (3 ml)	50 °C	6	trace : 30
13	2 : 0.8 : 20	THF (3 ml)	50 °C	10	trace : 30
14	4 : 0.8 : 20	THF (3 ml)	50 °C	6	trace : 38
15	3 : 0.8 : 20	THF (5 ml)	reflux	3	trace : 68

[a] Isolated yield. [b] GC yield with an internal standard.

hyperconjugative electron-donating methyl group. However, when R′ was the relatively strong electron-donating methoxy group, the reaction produced an indazole and 2,1-benzisoxazole mixture, as shown in Table 4. At the moment, it is not clear why electron-rich aryl substituents of iminobenzenes favor the formation of 2,1-benzisoxazoles.

2) Indium-mediated reductive reaction of *N*-(2-nitrobenzylidene)anilines in the presence of aniline additive whose structure is different from the anilino subunit of the *N*-(2-nitrobenzylidene)anilines

The following question arose after the results of the indium-mediated reductive reaction of *N*-(2-nitrobenzylidene)anilines in the presence of aniline additive whose structure is the same as those of anilino subunit of *N*-(2-nitrobenzylidene)anilines (*i.e.* the A = B system in eqn (2)), were obtained: should the structure of the added aniline (B) be the same as that of the imino part (A) of the substrate? Since the substituents at the 2- and 3-positions of the indazole product seem to have come from the excessively added anilines, the original structure of A may not be left over as the 2,3-substituents of the product. Thus, even if the aniline (B) whose structure is different from that of A were added, the resulting product may produce the 2,3-aryl-substituted indazole product with a C = B structure (eqn (2)).



(2)

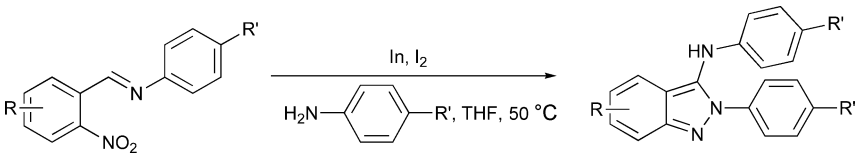
To verify the effect of the added aniline, several control experiments were conducted (Table 5), where varied amounts of *p*-toluidine were added to the reaction of *N*-(2-nitrobenzylidene)aniline. As expected, the amount of *p*-tolyl-substituted product (**13**) was increased gradually with the addition of more *p*-toluidine to the reaction mixture, and the reactions of *N*-[(2-nitrophenyl)methylene]benzene in the presence of indium (3 equiv.), iodine (0.8 equiv.), and more than 10 equiv. of *p*-toluidine produced *p*-tolyl-substituted indazole (**13**) as the major product. The mixed substituted products **34** and **35** (the exact structure of each compound, whether **34** or **35**, was not determined) were observed when less than 10 equiv. of *p*-toluidine were used. It is evident that externally added *p*-toluidine controls the structure of the 2,3-substituents of indazole. Without doubt, the structure of C in eqn (2) came from structure B of the added aniline.

Thus the reactions of various *N*-(2-nitrobenzylidine)anilines (R = H, Cl, OMe, OCH_2O; R′ = H) in the presence of an excess of various 4-R′-substituted anilines were examined, and the B = C structure in eqn (2) was expected to be seen. The results are shown in Table 6. The reactions gave the indazole product with the B = C structure, as expected. In most cases, the yield of each reaction was slightly lower than the yields of the reactions described in Table 4, while the yield of the reactions when 4-methoxyaniline was used improved compared to the reactions described in Table 4. Without doubt, the reactions of *N*-(2-nitrobenzylidine)anilines in the presence of an excess of 4-R′-substituted anilines could be as useful as the reactions shown in Table 3 for the syntheses of diverse 2,3-disubstituted indazoles.

3) Indium-mediated reductive reaction directly starting from 2-nitrobenzaldehydes and anilines toward indazoles

As mentioned earlier, the starting substrates, 2-nitroiminobenzenes, were prepared from the reactions of 2-nitrobenzaldehydes with anilines in the presence of $MgSO_4$ in THF at room temperature. In addition, the cyclization reactions of 2-nitroiminobenzenes to give indazoles were also done in THF. As long as both the 2-nitroiminobenzene preparation reaction and the

Table 3 Indium-mediated reactions of 2-nitroiminobenzenes (0.2 M) in the presence of indium (3 equiv.), iodine (0.8 equiv.), and anilines (20 equiv.) whose structure is the same as that of the anilino subunit of the *N*-(2-nitrobenzylidene)anilines in THF at 50 °C[a]



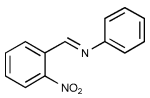
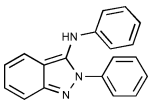
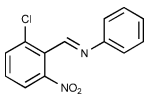
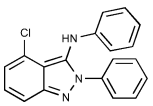
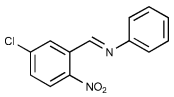
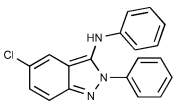
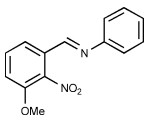
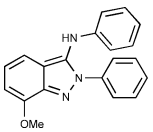
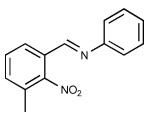
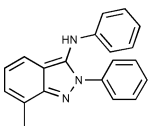
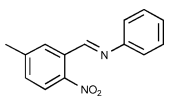
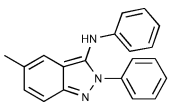
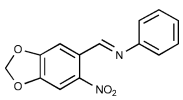
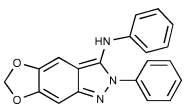
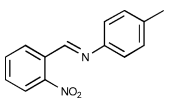
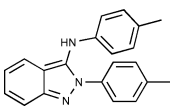
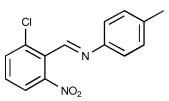
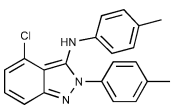
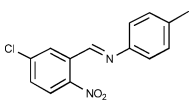
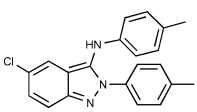
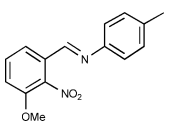
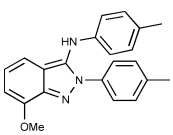
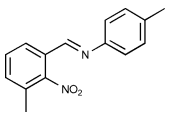
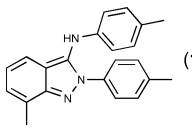
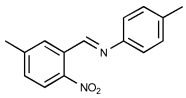
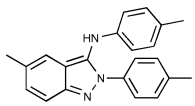
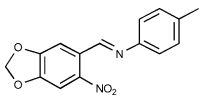
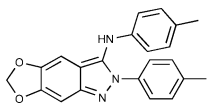
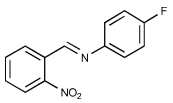
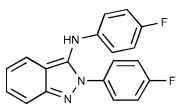
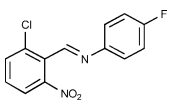
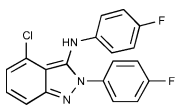
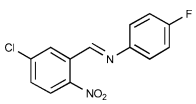
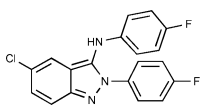
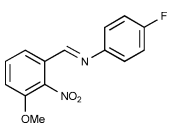
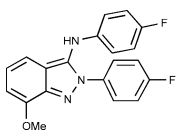
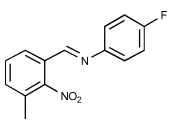
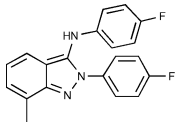
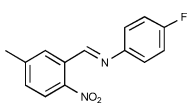
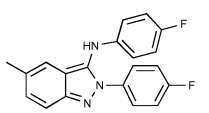
Entry	Substrate	Time/h	Product (% yield[b])
1		4	 (**2**, 75%)
2		4	 (**4**, 50%[c])
3		4	 (**6**, 56%)
4		4	 (**8**, 51%)
5		4	 (**10**, 70%)
6		4	 (**11**, 50%)
7		4	 (**12**, 33%)
8		4	 (**13**, 57%)
9		4	 (**14**, 65%)
10		3	 (**15**, 55%)
11		4	 (**16**, 57%)

Table 3 *Cont.*

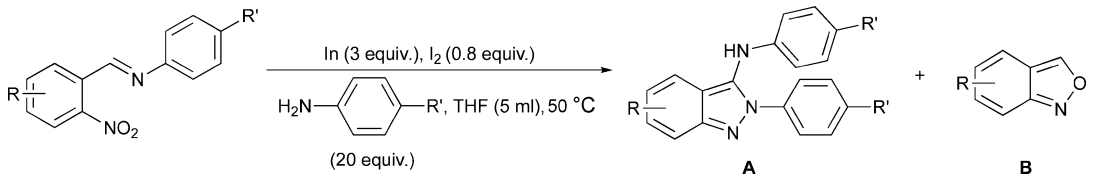
Entry	Substrate	Time/h	Product (% yield[b])
12		4	 (**17**, 69%)
13		4	 (**18**, 65%)
14		4	 (**19**, 20%)
15		4	 (**20**, 65%)
16		4	 (**21**, 61%)
17		4	 (**22**, 59%)
18		3	 (**23**, 63%)
19		3	 (**24**, 74%)
20		4	 (**25**, 54%)

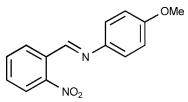
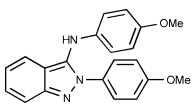
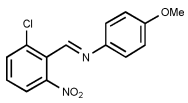
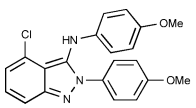
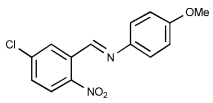
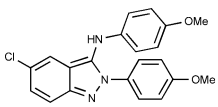
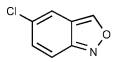
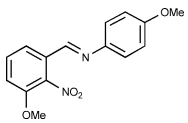
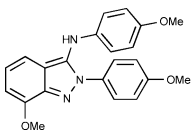
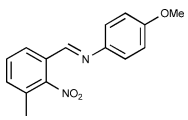
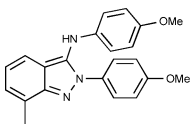
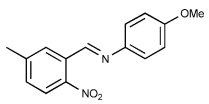
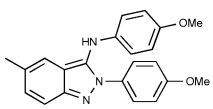
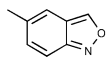
[a] Most reactions produced trace to several % of 2,1-benzisoxazoles as a by-product. [b] Isolated yield. [c] 22% of 2,1-benzisoxazole was observed.

following cyclizations of 2-nitroiminobenzenes to give indazoles are done in the same solvent using similar reaction conditions, a one-pot reaction would be possible instead of a two-step synthesis. Thus, the one-pot synthesis starting from 2-nitrobenzaldehydes was examined. First, 2-nitrobenzaldehyde in the presence of 20 equiv. of aniline and Na_2SO_4 (4 equiv.) in THF was stirred for 12 hours to obtain the corresponding 2-nitroiminobenzene *in situ*, then it was mixed with indium (3 equiv.) and iodine (0.8 equiv.) in THF for the reductive cyclization to indazole. The procedure worked well, as expected, with a 52% yield, which was slightly lower than that of the two-step synthesis. It is believed that the reduced yield was caused primarily by the loss of the product when the solution was transferred by cannula, since the reaction scale is quite small for cannular transferring. It would also be useful, however, to consider that the overall yield of the previous two-step synthesis is 69% [(*i*) imine preparation, 92%; and (*ii*) reductive cyclization, 75%, in entry 1, Table 3]. Thus, various substituted benzaldehydes were examined under these one-pot reaction conditions for the synthesis of 2,3-disubstituted indazoles. The results are summarized in Table 7. Most of the reactions worked well with reasonable yields. Moreover, some of the reactions showed better yields compared to the previous two-step synthesis (entries 2, 6, 9, 11, 13, and 14 in Table 7).

As described in three sections (1), (2), and (3), all the reaction conditions were successful for indazole synthesis. Moreover, based on the results, we could propose that reductive cyclizations may

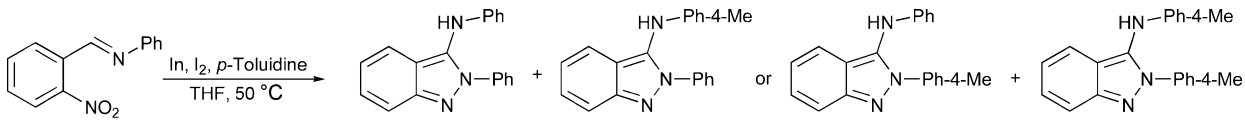
Table 4 Indium-mediated reactions of 2-nitroiminobenzenes (R′ = OMe) (0.2 M) in the presence of indium (3 equiv.), iodine (0.8 equiv.), and aniline (20 equiv.) in THF at 50 °C



Entry	Substrate	Time/h	Product (% yield[a]) A		Product (% yield[a]) B	
1		2		(**26**, 37%)		(**1**, 24%)
2		2		(**27**, 35%)		(**3**, 20%)
3		3		(**28**, 24%)		(**5**, 50%)
4		2		(**29**, 20%)		trace
5		2		(**30**, 25%)		(**32**, 45%)
6		2		(**31**, 10%)		(**33**, 48%)

[a] Isolated yield.

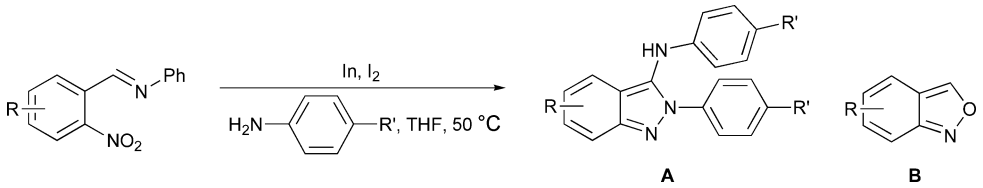
Table 5 Indium-mediated reductive reaction of the *N*-(2-nitrobenzylidene)aniline (1 mmol, 0.2 M) in the presence of indium (3 equiv.), iodine (0.8 equiv.), and *p*-toluidine (20 equiv.) in THF at 50 °C



Entry	*p*-Toluidine/equiv.	Time/h	Product (% yield[a]) **2**	**34**/**35** (or **35**/**34**)	**13**
1	0.5	5	12	7/6	5
2	1	5	8	12/14	12
3	2	4	3	10/15	35
4	3	4	1	5/8	38
5	5	4	—	2/2	48
6	10	3	—	1/1	51
7	20	3	—	—	52

[a] GC yield with an internal standard and structure of **34** and **35** was determined by GCMS only. All reactions produced GC-detectable amount of 2,1-benzisoxazoles.

Table 6 Indium-mediated reactions of the 2-nitroiminobenzenes (0.2 M) in the presence of indium (3 equiv.)/iodine (0.8 equiv.) and aniline additive (20 equiv.) whose structure is different from that of the anilino-subunit of the *N*-(2-nitrobenzylidene)anilines in THF at 50 °C



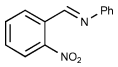
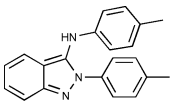
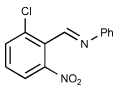
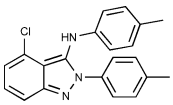
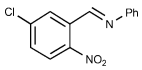
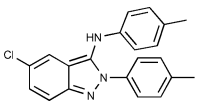
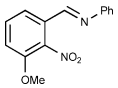
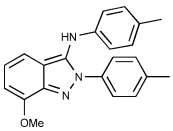
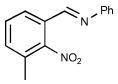
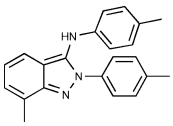
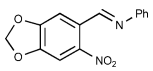
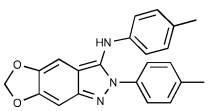
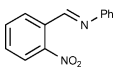
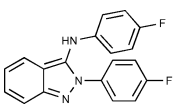
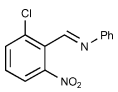
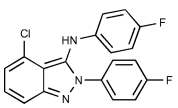
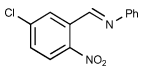
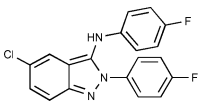
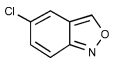
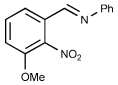
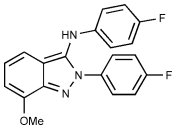
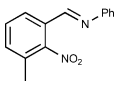
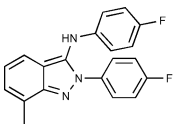
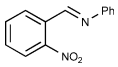
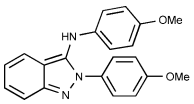
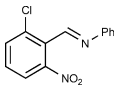
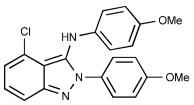
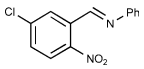
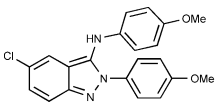
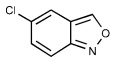
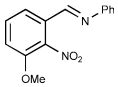
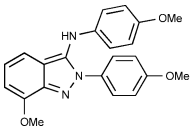
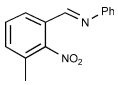
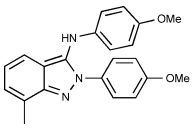
Entry	Substrate	Time/h	R′	Product (% yield[a]) A		Product (% yield[a]) B	
1		3	CH_3		(**13**, 47%)	trace	
2		3	CH_3		(**14**, 39%)		(**3**, 38%)
3		3	CH_3		(**15**, 49%)	trace	
4		3	CH_3		(**16**, 45%)	trace	
5		3	CH_3		(**17**, 53%)	trace	
6		3	CH_3		(**19**, 22%)	trace	
7		3	F		(**20**, 56%)	trace	
8		3	F		(**21**, 40%)	trace	
9		3	F		(**22**, 52%)		(**5**, 26%)
10		3	F		(**23**, 52%)	trace	

Table 6 *Cont.*

Entry	Substrate	Time/h	R′	Product (% yield[a]) A		B	
11		3	F		(**24**, 57%)	trace	
12		2	OCH_3		(**26**, 39%)	trace	
13		2	OCH_3		(**27**, 51%)		(**3**, 12%)
14		2	OCH_3		(**28**, 26%)		(**5**, 36%)
15		2	OCH_3		(**29**, 31%)	trace	
16		2	OCH_3		(**30**, 41%)		(**32**, 10%)

[a] Isolated yield.

start at the same stage, *i.e.* *N*-(2-nitrobenzylidene)aniline, which is the starting substrate in section (1). A plausible path for indazole (major) and 2,1-benzisoxazole (trace or minor in THF, major in MeOH) formation is shown in Scheme 1. Loss of water can be a good driving force for the indazole-formation reaction, which is possibly caused by the push–pull assistance of aniline and aromatization of the product.

Conclusion

New indium-mediated reductive cyclizations towards indazoles were developed in three different ways. One way is the indium-mediated reductive reaction of *N*-(2-nitrobenzylidene)anilines in the presence of aniline additive whose structure is the same as that of the anilino subunit of *N*-(2-nitrobenzylidene)anilines. Another way is the similar reductive reaction of *N*-(2-nitrobenzylidene)-anilines in the presence of aniline additive whose structure is different from that of the anilino subunit of *N*-(2-nitrobenzylidene)anilines. The third method is an indium-mediated reductive reaction starting from 2-nitrobenzaldehydes and anilines to give indazoles, which is an efficient one-pot preparation of indazoles under mild conditions. In conclusion, a simple and efficient method for the preparation of indazoles from 2-nitrobenzaldehydes or *N*-(2-nitrobenzylidene)anilines using indium–iodine in THF under mild conditions is described in this paper.

Experimental

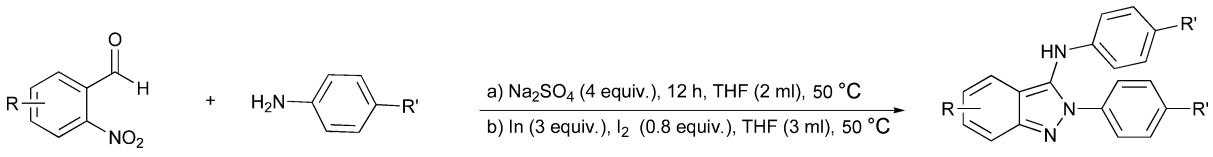
1. General considerations

Most of the chemical reagents were purchased from Aldrich and, in most cases, were used without further purification. Solvents were purchased and dried using the standard method. ^{1}H NMR spectra were recorded on a 400 MHz Jeol instrument, and ^{13}C NMR spectra were recorded on a 100 MHz Jeol instrument. Chemical shifts were reported in ppm relative to the residual solvent as an internal standard. HRMS spectra were recorded on a JEOL JMS-DX 303 mass spectrometer and GC/MS were recorded on an HP6890 mass spectrometer. Infrared (IR) spectra were recorded using MB104 FTIR (ABB Bomem Inc.). Melting points were determined on an electrothermal apparatus and were uncorrected. All the major products were isolated by flash column chromatography on silica gel (230–400 mesh ATSM, purchased from Merck) with eluents of mixed solvents (ethyl acetate and hexane).

2. General procedure for the reductive intermolecular coupling reaction

2-1. Indium-mediated reductive reaction of *N*-(2-nitrobenzylidene)anilines in the presence of aniline. The *N*-(2-nitrobenzylidene)aniline derivative (1.0 mmol) was added to a mixture of indium powder (345 mg, 3.0 mmol) and iodine (203 mg,

Table 7 Indium-mediated reductive reactions starting from the 2-nitrobenzaldehydes and anilines yielding indazoles



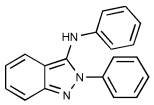
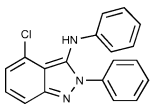
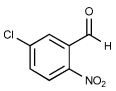
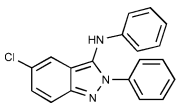
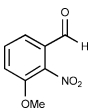
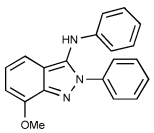
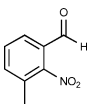
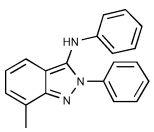
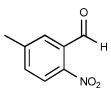
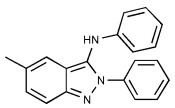
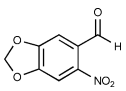
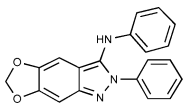
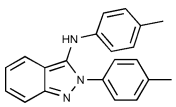
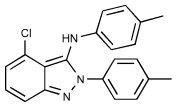
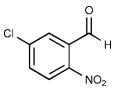
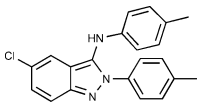
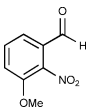
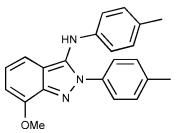
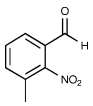
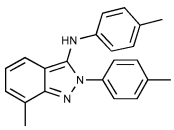
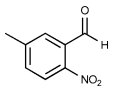
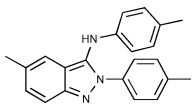
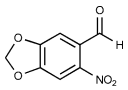
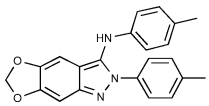
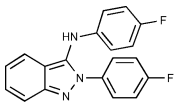
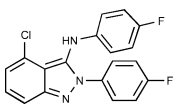
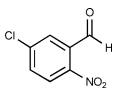
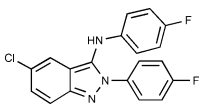
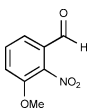
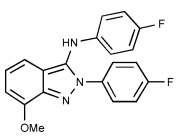
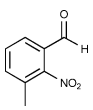
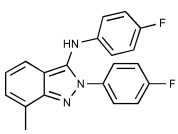
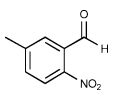
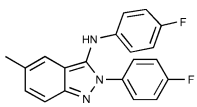
Entry	Substrate	Time/h	R′	Product (% yield[a])
1		4	H	 (**2**, 52%) (69%[b])
2		4	H	 (**4**, 40%) (35%[b])
3		3	H	 (**6**, 42%) (48%[b])
4		3	H	 (**8**, 41%) (46%[b])
5		3	H	 (**10**, 52%) (60%[b])
6		3	H	 (**11**, 44%) (~5%[b])
7		3	H	 (**12**, 14%) (28%[b])
8		4	CH_3	 (**13**, 43%) (48%[b])
9		4	CH_3	 (**14**, 58%) (52%[b])
10		4	CH_3	 (**15**, 32%) (40%[b])
11		4	CH_3	 (**16**, 48%) (44%[b])

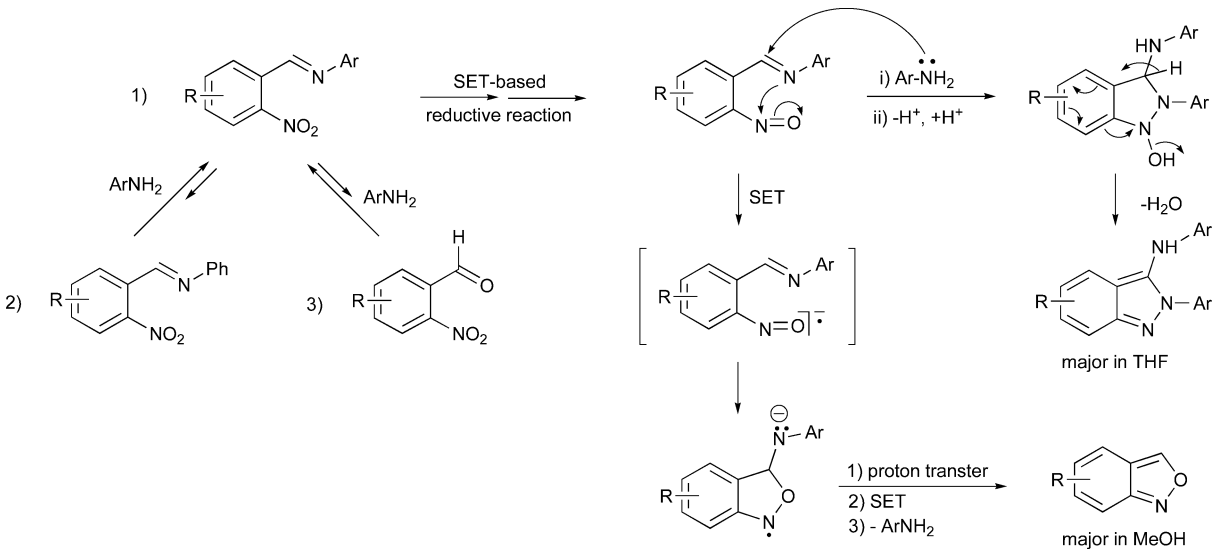
Table 7 *Cont.*

Entry	Substrate	Time/h	R′	Product (% yield[a])
12		4	CH_3	 (**17**, 41%) (51%[b])
13		4	CH_3	 (**18**, 44%) (42%[b])
14		4	CH_3	 (**19**, 21%) (17%[b])
15		4	F	 (**20**, 52%) (57%[b])
16		4	F	 (**21**, 53%) (54%[b])
17		4	F	 (**22**, 42%) (52%[b])
18		4	F	 (**23**, 45%) (46%[b])
19		4	F	 (**24**, 58%) (64%[b])
20		4	F	 (**25**, 31%) (33%[b])

[a] Isolated yield. [b] Combined yield of two-step synthesis (eqn (1) and Table 3).

0.8 mmol) in THF (5 ml). The reaction mixture was stirred at 50 °C under a nitrogen atmosphere. After the reaction was complete, the reaction mixture was diluted with CH_2Cl_2 (30 ml), filtered through Celite, poured into a 10% NH_4Cl solution, and extracted with CH_2Cl_2 (3 × 30 ml). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated. The residue was eluted with ethyl acetate–hexane (v/v = 2/98–20/80) through a silica gel column to give the corresponding indazoles in 22–75% yield. The structures of the indazoles were fully characterized by ^1H NMR, ^{13}C NMR, FTIR, MS, and HRMS. The X-ray crystal structure of one of the indazoles, (4-chloro-2-phenyl-2*H*-indazole-3-yl)phenylamine, was obtained for decisive structure determination.[14]

2-2. Indium-mediated reductive reaction starting from 2-nitrobenzaldehydes and anilines to give indazoles. To a solution of 2-nitrobenzaldehyde in THF (2 ml), aniline (1.9 g, 20 mmol) and Na_2SO_4 (574 mg, 4 mmol) were added, and the mixture was stirred for 12 hours at 50 °C. After the reaction was complete, the mixture was transferred into another round-bottomed flask, using a filter-tipped cannula to remove the Na_2SO_4, and was washed with THF (3 ml). To the transferred solution, indium powder (345 mg, 3 mmol) and iodine (203 mg, 0.8 mmol) were added, and the mixture was stirred at 50 °C under a nitrogen atmosphere. The completed reaction mixture was filtered through Celite, poured into a 1% HCl solution, and extracted with CH_2Cl_2 (3 × 30 ml). The resulting extracts were dried over $MgSO_4$, filtered,



Scheme 1

concentrated, and purified by column chromatography on silica gel, using ethyl acetate–hexane. The corresponding indazoles were obtained in 14–58% yield.

(2-Phenyl-2*H*-indazol-3-yl)phenylamine (2). White solid, TLC (30% ethyl acetate–hexane) R_f 0.51; mp 152.0–153.9 °C (ethyl acetate–hexane); ν_{max}(KBr)/cm^{-1} 3222, 3182, 3121, 1927, 1776 and 1601; ^{1}H NMR (300 MHz, $CDCl_3$; Me_4Si) δ = 7.70–7.60 (3H, m, Ph), 7.47–7.35 (4H, m, Ph), 7.32–7.19 (3H, m, Ph), 7.00–6.88 (2H, m, Ph), 6.80 (2H, m, Ph) and 5.77 (1H, s, NH) ppm; ^{13}C NMR (75 MHz; $CDCl_3$; Me_4Si) δ = 148.4, 143.8, 138.6, 123.3, 129.4, 129.2, 128.4, 127.0, 124.8, 121.1, 120.5, 120.2, 118.0, 115.8 and 115.0 ppm; *m*/*z* (EI) 285.1264 (M$^+$ $C_{19}H_{15}N_3$ requires 285.1266), 269 (6) and 167 (6).

(4-Chloro-2-phenyl-2*H*-indazol-3-yl)phenylamine (4). White solid; TLC (30% ethyl acetate–hexane) R_f 0.46; mp 178.4–180.1 °C (ethyl acetate–hexane); ν_{max}(KBr)/cm^{-1} 3225, 3036, 1601, 1256, 749 and 690; ^{1}H NMR (300 MHz, $CDCl_3$; Me_4Si) δ = 7.67–7.58 (3H, m, Ph), 7.40–7.29 (3H, m, Ph), 7.21–7.11 (3H, m, Ph), 7.00 (1H, d, *J* 7.1 Hz, Ph), 6.82 (1H, dd, *J* 7.3 and 7.5 Hz, Ph), 6.57 (2H, d, *J* 7.7 Hz, Ph) and 5.92 (1H, s, NH) ppm; ^{13}C NMR (75 MHz; $CDCl_3$; Me_4Si) δ = 149.2, 145.5, 138.6, 132.5, 129.2, 129.0, 128.5, 127.1, 125.3, 124.5, 121.8, 120.3, 116.8, 115.1 and 114.7 ppm; *m*/*z* (EI) 319.0874 (M$^+$ $C_{19}H_{14}ClN_3$ requires 319.0876), 283 (11), 207 (9), 178 (7) and 77 (23).

(5-Chloro-2-phenyl-2*H*-indazol-3-yl)phenylamine (6). White solid; TLC (30% ethyl acetate–hexane) R_f 0.43; mp 179–181 °C (ethyl acetate–hexane); ν_{max}(KBr)/cm^{-1} 3232, 3130, 3037, 1937 and 1601; ^{1}H NMR (300 MHz, $CDCl_3$; Me_4Si) δ = 7.64–7.59 (3H, m, Ph), 7.52–7.36 (4H, m, Ph), 7.28–7.21 (3H, m, Ph), 6.94 (1H, dd, *J* 7.3 and 7.1 Hz, Ph), 6.77 (2H, d, *J* 7.7 Hz, Ph) and 5.70 (1H, s, NH) ppm; ^{13}C NMR (75 MHz; $CDCl_3$; Me_4Si) δ = 146.7, 143.5, 138.3, 132.0, 129.6, 129.3, 128.8, 128.4, 126.7, 125.1, 124.7, 120.9, 119.6, 118.8, 116.1, 115.4 and 115.0 ppm; *m*/*z* (EI) 319.0877 (M$^+$ $C_{19}H_{14}ClN_3$ requires 319.0876), 283 (10), 178 (6) and 77 (23).

(7-Methoxy-2-phenyl-2*H*-indazol-3-yl)phenylamine (8). White solid; TLC (30% ethyl acetate–hexane) R_f 0.41; mp 183.7–186.2 °C (ethyl acetate–hexane); ν_{max}(KBr)/cm^{-1} 3200, 3098, 3027, 1703, 1604 and 1503; ^{1}H NMR (300 MHz, $CDCl_3$; Me_4Si) δ = 7.67 (3H, d, *J* 6.8 Hz, Ph), 7.53–7.30 (3H, m, Ph), 7.23 (3H, dd, *J* 8.3 and 7.7 Hz, Ph), 6.93 (3H, d, *J* 7.9 Hz, Ph), 6.80 (1H, d, *J* 7.7 Hz, Ph), 6.58 (1H, d, *J* 7.9 Hz, Ph), 5.70 (1H, s, NH) and 4.04 (3H, s, OCH_3) ppm; ^{13}C NMR (75 MHz; $CDCl_3$; Me_4Si) δ = 150.3, 143.6, 141.9, 138.4, 132.7, 129.4, 129.1, 128.5, 125.1, 121.8, 120.6, 117.3, 115.1, 112.1, 103.3 and 55.4 ppm; *m*/*z* (EI) 315.1376 (M$^+$ $C_{20}H_{17}N_3O$ requires 315.1372), 300 (18), 286 (19), 79 (11) and 77 (22).

(7-Methyl-2-phenyl-2*H*-indazol-3-yl)phenylamine (10). White solid; TLC (30% ethyl acetate–hexane) R_f 0.55; mp 161–162 °C (ethyl acetate–hexane); ν_{max}(KBr)/cm^{-1} 3215, 3114, 2955, 1597, 1532 and 1360; ^{1}H NMR (400 MHz, $CDCl_3$; Me_4Si) δ = 7.62 (2H, d, *J* 7.8 Hz, Ph), 7.42–7.45 (2H, m, Ph), 7.36–7.39 (1H, m, Ph), 7.19–7.23 (3H, m, Ph), 7.05 (1H, d, *J* 6.1 Hz, Ph), 6.87–6.91 (2H, m, Ph), 6.76 (2H, d, *J* 8.0 Hz, Ph), 5.65 (1H, s, NH) and 2.64 (3H, s, CH_3) ppm; ^{13}C NMR (100 MHz; $CDCl_3$; Me_4Si) δ = 148.68, 143.85, 138.68, 132.47, 129.43, 129.28, 128.47, 128.04, 125.88, 125.11, 121.41, 120.44, 117.60, 115.45, 114.90 and 16.78 ppm; *m*/*z* (EI) 299.1432 (M$^+$ $C_{20}H_{17}N_3$ requires 299.1422), 283 (14), 268 (3), 207 (9) and 77 (25).

(5-Methyl-2-phenyl-2*H*-indazol-3-yl)phenylamine (11). White solid; TLC (30% ethyl acetate–hexane) R_f 0.48; mp 184–185 °C (ethyl acetate–hexane); ν_{max}(KBr)/cm^{-1} 3233, 3056, 2910, 1602, 1499 and 1319; ^{1}H NMR (400 MHz, $CDCl_3$; Me_4Si) δ = 7.61–7.65 (3H, m, Ph), 7.44–7.48 (2H, m, Ph), 7.38–7.42 (1H, m, Ph), 7.22–7.26 (2H, m, Ph), 7.15–7.17 (2H, m, Ph), 6.92 (1H, t, *J* 7.6 Hz, Ph), 6.78 (2H, d, *J* 7.6 Hz, Ph), 5.60 (1H, s, NH) and 2.36 (3H, s, CH_3) ppm; ^{13}C NMR (100 MHz; $CDCl_3$; Me_4Si) δ = 147.51, 144.24, 138.79, 131.11, 130.85, 130.05, 129.52, 129.22, 128.35, 124.77, 120.31, 117.92, 117.84, 116.51, 114.64 and 21.72 ppm; *m*/*z* (EI) 299.1418 (M$^+$ $C_{20}H_{17}N_3$ requires 299.1422), 283 (11), 192 (6), 165 (5) and 116 (6).

(2-Phenyl-2*H*-5,7-dioxa-1,2-diaza-*s*-indacen-3-yl)-phenylamine (12). White solid; TLC (30% ethyl acetate–hexane) R_f 0.44; mp

205–206.5 °C (ethyl acetate–hexane); ν_{max}(KBr)/cm^{-1} 3261, 2908, 1507, 1208, 835 and 742; ^{1}H NMR (400 MHz, $CDCl_3$; Me_4Si) δ = 7.58–7.61 (2H, m, Ph), 7.40–7.44 (2H, m, Ph), 7.33–7.37 (1H, m, Ph), 7.20–7.26 (2H, m, Ph), 6.96 (1H, s, Ph), 6.88 (1H, t, *J* 7.4 Hz, Ph), 6.73 (2H, dd, *J* 8.2 and 0.8 Hz, Ph), 6.57 (1H, s, Ph), 5.91 (2H, s, CH_2) and 5.52 (1H, s, NH) ppm; ^{13}C NMR (100 MHz; $CDCl_3$; Me_4Si) δ = 149.87, 146.11, 145.22, 144.20, 138.84, 131.52, 129.56, 129.20, 127.97, 124.38, 120.28, 114.56, 112.12, 100.97, 94.61 and 94.44 ppm; *m*/*z* (EI) 329.1163 (M^+ $C_{20}H_{15}N_3O_3$ requires 329.1164), 313 (3), 270 (4) and 77 (17).

[2-(4-Methylphenyl)-2*H*-indazol-3-yl]-4-methylphenylamine (13). White solid; TLC (30% ethyl acetate–hexane) R_f 0.53; mp 162–163 °C (ethyl acetate–hexane); ν_{max}(KBr)/cm^{-1} 3404, 3057, 2984, 1611, 1516 and 1264; ^{1}H NMR (400 MHz, $CDCl_3$; Me_4Si) δ = 7.69 (1H, d, *J* 8.0 Hz, Ph), 7.52 (2H, d, *J* 8.0 Hz, Ph), 7.36 (1H, d, *J* 8.0 Hz, Ph), 7.26–7.31 (3H, m, Ph), 7.05 (2H, d, *J* 8.0 Hz, Ph), 6.96 (1H, t, *J* 8.0 Hz, Ph), 6.75 (2H, d, *J* 8.0 Hz, Ph), 5.61 (1H, s, NH), 2.40 (3H, s, CH_3) and 2.30 (3H, s, CH_3) ppm; ^{13}C NMR (100 MHz; $CDCl_3$; Me_4Si) δ = 148.34, 141.21, 138.54, 136.09, 132.86, 130.09, 129.95, 129.85, 126.84, 124.68, 120.66, 120.32, 117.86, 115.39, 115.15, 21.13 and 20.52 ppm; *m*/*z* (EI) 313.1576 (M^+ $C_{21}H_{19}N_3$ requires 313.1579), 297 (16), 192 (8), 165 (5) and 106(5).

[4-Chloro-2-(4-methylphenyl)-2*H*-indazol-3-yl]-4-methylphenylamine (14). Pale yellowish white solid; TLC (30% ethyl acetate–hexane) R_f 0.56; mp 223–224.5 °C (ethyl acetate–hexane); ν_{max}(KBr)/cm^{-1} 3407, 3057, 2985, 1617, 1264 and 735; ^{1}H NMR (400 MHz, $CDCl_3$; Me_4Si) δ = 7.60 (1H, d, *J* 8.6 Hz, Ph), 7.55 (2H, d, *J* 8.30 Hz, Ph), 7.17–7.21 (3H, m, Ph), 6.99 (1H, d, *J* 7.08 Hz, Ph), 6.95 (2H, d, *J* 8.30 Hz, Ph), 6.49 (2H, d, *J* 8.30 Hz, Ph), 5.75 (1H, s, NH), 2.35 (3H, s, CH_3) and 2.23 (3H, s, CH_3) ppm; ^{13}C NMR (100 MHz; $CDCl_3$; Me_4Si) δ = 149.13, 143.24, 138.60, 136.28, 132.87, 129.80, 129.72, 129.68, 127.01, 125.38, 124.33, 121.60, 116.81, 115.01, 114.87, 21.13 and 20.50 ppm; *m*/*z* (EI) 347.1176 (M^+ $C_{21}H_{18}ClN_3$ requires 347.1189), 331 (5), 297 (7), 165 (6) and 91 (11).

[5-Chloro-2-(4-methylphenyl)-2*H*-indazol-3-yl]-4-methylphenylamine (15). Pale yellowish white solid; TLC (30% ethyl acetate–hexane) R_f 0.50; mp 157.5–159 °C (ethyl acetate–hexane); ν_{max}(KBr)/cm^{-1} 3399, 3053, 2987, 1612, 1519 and 1263; ^{1}H NMR (400 MHz, $CDCl_3$; Me_4Si) δ = 7.57 (1H, d, *J* 9.1 Hz, Ph), 7.45 (2H, d, *J* 8.2 Hz, Ph), 7.31 (1H, s, Ph), 7.18–7.25 (3H, m, Ph), 7.05 (2H, d, *J* 8.2 Hz, Ph), 6.70 (2H, d, *J* 8.2 Hz, Ph), 5.74 (1H, s, NH), 2.37 (3H, s, CH_3) and 2.30 (3H, s, CH_3) ppm; ^{13}C NMR (100 MHz; $CDCl_3$; Me_4Si) δ = 146.67, 140.89, 138.88, 135.84, 132.64, 130.48, 130.12, 129.94, 128.26, 126.19, 124.58, 119.45, 118.91, 115.53, 115.41, 21.14 and 20.55 ppm; *m*/*z* (EI) 347.1191 (M^+ $C_{21}H_{18}ClN_3$ requires 347.1189), 331 (6), 165 (5), 136 (5) and 91 (14).

[7-Methoxy-2-(4-methylphenyl)-2*H*-indazol-3-yl]-4-methylphenylamine (16). White solid; TLC (30% ethyl acetate–hexane) R_f 0.38; mp 211.5–214 °C (ethyl acetate–hexane); ν_{max}(KBr)/cm^{-1} 3296, 3027, 2948, 1610, 1511 and 1242; ^{1}H NMR (400 MHz, $CDCl_3$; Me_4Si) δ = 7.41 (2H, d, *J* 8.1 Hz, Ph), 7.06 (2H, d, *J* 8.1 Hz, Ph), 6.96 (2H, d, *J* 8.1 Hz, Ph), 6.77–6.86 (2H, m, Ph), 6.64 (2H, d, *J* 8.1 Hz, Ph), 6.47 (1H, d, *J* 7.0 Hz, Ph), 5.87 (1H, s, NH), 3.92 (3H, s, OCH_3), 2.27 (3H, s, CH_3) and 2.24 (3H, s, CH_3) ppm; ^{13}C NMR (100 MHz; $CDCl_3$; Me_4Si) δ = 150.10, 141.60, 141.28, 137.96, 135.91, 132.96, 129.64, 129.42, 129.30, 124.49, 120.97, 116.78, 114.99, 112.16, 102.81, 55.05, 20.89 and 20.33 ppm; *m*/*z* (EI) 343.1692 (M^+ $C_{22}H_{21}N_3O$ requires 343.1685), 328 (14), 314 (16), 208 (6), 193 (6) and 106 (5).

[7-Methyl-2-(4-methylphenyl)-2*H*-indazol-3-yl]-4-methylphenylamine (17). White solid; TLC (30% ethyl acetate–hexane) R_f 0.61; mp 192.5–194 °C (ethyl acetate–hexane); ν_{max}(KBr)/cm^{-1} 3232, 3034, 2919, 1610, 1544 and 748; ^{1}H NMR (400 MHz, $CDCl_3$; Me_4Si) δ = 7.50–7.53 (2H, m, Ph), 7.25–7.27 (2H, m, Ph), 7.19 (1H, d, *J* 8.4 Hz, Ph), 7.02–7.06 (3H, m, Ph), 6.87 (1H, dd, *J* 8.4 and 1.7 Hz, Ph), 6.71–6.74 (2H, m, Ph), 5.54 (1H, s, NH), 2.64 (3H, s, CH_3), 2.40 (3H, s, CH_3) and 2.28 (3H, s, CH_3) ppm; ^{13}C NMR (100 MHz; $CDCl_3$; Me_4Si) δ = 148.61, 141.36, 138.51, 136.23, 133.10, 129.97, 129.91, 129.85, 127.89, 125.75, 125.00, 120.99, 117.74, 115.35, 114.90, 21.12, 20.52 and 16.79 ppm; *m*/*z* (EI) 327.1737 (M^+ $C_{22}H_{21}N_3$ requires 327.1735), 311 (9), 205 (5) and 91 (10).

[5-Methyl-2-(4-methylphenyl)-2*H*-indazol-3-yl]-4-methylphenylamine (18). White solid; TLC (30% ethyl acetate–hexane) R_f 0.57; mp 162–163 °C (ethyl acetate–hexane); ν_{max}(KBr)/cm^{-1} 3262, 3029, 2918, 1615, 1514 and 798; ^{1}H NMR (400 MHz, $CDCl_3$; Me_4Si) δ = 7.58 (1H, d, *J* 8.8 Hz, Ph), 7.47 (2H, d, *J* 8.3 Hz, Ph), 7.21 (2H, d, *J* 8.3 Hz, Ph), 7.11–7.14 (2H, m, Ph), 7.01 (2H, d, *J* 8.3 Hz, Ph), 6.68 (2H, d, *J* 8.3 Hz, Ph), 5.87 (1H, s, NH), 2.37 (3H, s, CH_3), 2.34 (3H, s, CH_3) and 2.29 (3H, s, CH_3) ppm; ^{13}C NMR (100 MHz; $CDCl_3$; Me_4Si) δ = 147.32, 141.74, 138.33, 136.21, 131.57, 130.36, 129.97, 129.84, 129.76, 129.62, 124.55, 118.05, 117.66, 115.98, 114.80, 21.69, 21.12 and 20.52 ppm; *m*/*z* (EI) 327.1728 (M^+ $C_{22}H_{21}N_3$ requires 327.1735), 311 (10), 206 (5) and 91 (10).

[2-(4-Methylphenyl)-2*H*-5,7-dioxa-1,2-diaza-s-indacen-3-yl]-4-methylphenylamine (19). White solid; TLC (30% ethyl acetate–hexane) R_f 0.43; mp 215–216 °C (ethyl acetate–hexane); ν_{max}(KBr)/cm^{-1} 3385, 3029, 2894, 1741, 1512, 1197 and 833; ^{1}H NMR (400 MHz, $CDCl_3$; Me_4Si) δ = 7.46 (2H, d, *J* 8.1 Hz, Ph), 7.22 (2H, d, *J* 8.1 Hz, Ph), 7.03 (2H, d, *J* 8.1 Hz, Ph), 6.96 (1H, s, Ph), 6.66 (2H, d, *J* 8.1 Hz, Ph), 6.55 (1H, s, Ph), 5.93 (2H, s, CH_2), 5.41 (1H, s, NH), 2.38 (3H, s, CH_3) and 2.28 (3H, s, CH_3) ppm; ^{13}C NMR (100 MHz; $CDCl_3$; Me_4Si) δ = 149.71, 145.93, 144.89, 141.71, 137.96, 136.34, 132.09, 130.02, 129.76, 129.69, 124.26, 114.87, 114.47, 100.88, 94.81, 94.36, 21.09 and 20.50 ppm; *m*/*z* (EI) 357.1494 (M^+ $C_{22}H_{19}N_3O_2$ requires 357.1477), 341 (5), 118 (5) and 91 (14).

[2-(4-Fluorophenyl)-2*H*-indazol-3-yl]-4-fluorophenylamine (20). White solid; TLC (30% ethyl acetate–hexane) R_f 0.44; mp 162–163.5 °C (ethyl acetate–hexane); ν_{max}(KBr)/cm^{-1} 3417, 3232, 3044, 2991, 1624 and 1517; ^{1}H NMR (400 MHz, $CDCl_3$; Me_4Si) δ = 7.68 (1H, d, *J* 8.9 Hz, Ph), 7.58–7.62 (2H, m, Ph), 7.29–7.33 (2H, m, Ph), 7.11–7.16 (2H, m, Ph), 6.99 (1H, t, *J* 8.0 Hz, Ph), 6.91–6.95 (2H, m, Ph), 6.71–6.74 (2H, m, Ph) and 5.69 (1H, s, NH) ppm; ^{13}C NMR (100 MHz; $CDCl_3$; Me_4Si) δ = 163.52, 161.04, 158.78, 156.40, 148.46, 139.82, 139.79, 134.70, 134.67, 132.71, 127.41, 126.70, 126.61, 121.41, 119.87, 118.01, 116.43, 116.39, 116.35, 116.29, 116.16, 116.06 and 115.49 ppm; *m*/*z* (EI) 321.1068 (M^+ $C_{19}H_{13}F_2N_3$ requires 321.1078), 305 (10), 197 (6) and 95 (13).

[4-Chloro-2-(4-fluorophenyl)-2*H*-indazol-3-yl]-4-fluorophenylamine (21). White solid; TLC (30% ethyl acetate–hexane) R_f 0.63; mp 145–147 °C (ethyl acetate–hexane); ν_{max}(KBr)/cm^{-1} 3386, 3044, 1621, 1507, 1217 and 788; ^{1}H NMR (400 MHz, $CDCl_3$; Me_4Si) δ = 7.61–7.66 (2H, m, Ph), 7.59 (1H, d, *J* 8.8 Hz, Ph), 7.21 (1H, dd, *J* 8.8 and 7.1 Hz, Ph), 7.03–7.10 (2H, m, Ph), 7.01 (1H, d, *J* 7.1 Hz, Ph), 6.81–6.87 (2H, m, Ph), 6.48–6.53 (2H, m, Ph) and 5.93 (1H, s, NH) ppm; ^{13}C NMR (100 MHz; $CDCl_3$; Me_4Si) δ = 163.49, 161.01, 158.74, 156.36, 149.22, 141.23, 141.21, 134.79, 134.75, 132.99, 127.40, 126.34, 126.26, 125.18, 121.91, 116.87, 116.30, 116.22, 116.19, 116.09, 115.96, 115.86 and 114.76 ppm; *m*/*z* (EI) 355.0696 (M^+ $C_{19}H_{12}ClF_2N_3$ requires 355.0688), 319 (13), 210 (8) and 95 (16).

[5-Chloro-2-(4-fluorophenyl)-2*H*-indazol-3-yl]-4-fluorophenylamine (22). White solid; TLC (30% ethyl acetate–hexane) R_f 0.50; mp 157.5–159 °C (ethyl acetate–hexane); ν_{max}(KBr)/cm^{-1} 3399, 3053, 2987, 1612, 1519 and 1263; ^{1}H NMR (400 MHz, $CDCl_3$; Me_4Si) δ = 7.57 (1H, d, *J* 9.1 Hz, Ph), 7.45 (2H, d, *J* 8.2 Hz, Ph), 7.31 (1H, s, Ph), 7.18–7.25 (3H, m, Ph), 7.05 (2H, d, *J* 8.2 Hz, Ph), 6.70 (2H, d, *J* 8.2 Hz, Ph) and 5.74 (1H, s, NH) ppm; ^{13}C NMR (100 MHz; $CDCl_3$; Me_4Si) δ = 146.67, 140.89, 138.88, 135.84, 132.64, 130.48, 130.12, 129.94, 128.26, 126.19, 124.58, 119.45, 118.91, 115.53, 115.41, 21.14 and 20.55 ppm; *m*/*z* (EI) 347.1191 (M^+ $C_{21}H_{18}ClN_3$ requires 347.1189), 331 (6), 165 (5), 136 (5) and 91 (14).

[7-Methoxy-2-(4-fluorophenyl)-2*H*-indazol-3-yl]-4-fluorophenylamine (23). White solid; TLC (30% ethyl acetate–hexane) R_f 0.38; mp 211.5–214 °C (ethyl acetate–hexane); ν_{max}(KBr)/cm^{-1} 3296, 3027, 2948, 1610, 1511 and 1242; ^{1}H NMR (400 MHz, $CDCl_3$; Me_4Si) δ = 7.41 (2H, d, *J* 8.1 Hz, Ph), 7.06 (2H, d, *J* 8.1 Hz, Ph), 6.96 (2H, d, *J* 8.1 Hz, Ph), 6.77–6.86 (2H, m, Ph), 6.64 (2H, d, *J* 8.1 Hz, Ph), 6.47 (1H, d, *J* 7.0 Hz, Ph), 5.87 (1H, s, NH) and 3.92 (3H, s, OCH_3) ppm; ^{13}C NMR (100 MHz; $CDCl_3$; Me_4Si) δ = 150.10, 141.60, 141.28, 137.96, 135.91, 132.96, 129.64, 129.42, 129.30, 124.49, 120.97, 116.78, 114.99, 112.16, 102.81, 55.05, 20.89 and 20.33 ppm; *m*/*z* (EI) 343.1692 (M^+ $C_{22}H_{21}N_3O$ requires 343.1685), 328 (14), 314 (16), 208 (6), 193 (6) and 106 (5).

[7-Methyl-2-(4-fluorophenyl)-2*H*-indazol-3-yl]-4-fluorophenylamine (24). White solid; TLC (30% ethyl acetate–hexane) R_f 0.61; mp 192.5–194 °C (ethyl acetate–hexane); ν_{max}(KBr)/cm^{-1} 3232, 3034, 2919, 1610, 1544 and 748; ^{1}H NMR (400 MHz, $CDCl_3$; Me_4Si) δ = 7.50–7.53 (2H, m, Ph), 7.25–7.27 (2H, m, Ph), 7.19 (1H, d, *J* 8.4 Hz, Ph), 7.02–7.06 (3H, m, Ph), 6.87 (1H, dd, *J* 8.4 and 1.7 Hz, Ph), 6.71–6.74 (2H, m, Ph), 5.54 (1H, s, NH) and 2.64 (3H, s, OCH_3) ppm; ^{13}C NMR (100 MHz; $CDCl_3$; Me_4Si) δ = 148.61, 141.36, 138.51, 136.23, 133.10, 129.97, 129.91, 129.85, 127.89, 125.75, 125.00, 120.99, 117.74, 115.35, 114.90, 21.12, 20.52 and 16.79 ppm; *m*/*z* (EI) 327.1737 (M^+ $C_{22}H_{21}N_3$ requires 327.1735), 311 (9), 205 (5) and 91 (10).

[5-Methyl-2-(4-fluorophenyl)-2*H*-indazol-3-yl]-4-fluorophenylamine (25). White solid; TLC (30% ethyl acetate–hexane) R_f 0.57; mp 162–163 °C (ethyl acetate–hexane); ν_{max}(KBr)/cm^{-1} 3262, 3029, 2918, 1615, 1514 and 798; ^{1}H NMR (400 MHz, $CDCl_3$; Me_4Si) δ = 7.58 (1 H, d, *J* 8.8 Hz, Ph), 7.47 (2H, d, *J* 8.3 Hz, Ph), 7.21 (2H, d, *J* 8.3 Hz, Ph), 7.11–7.14 (2H, m, Ph), 7.01 (2H, d, *J* 8.3 Hz, Ph), 6.68 (2H, d, *J* 8.3 Hz, Ph), 5.87 (1H, s, NH) and 2.37 (3H, s, CH_3) ppm; ^{13}C NMR (100 MHz; $CDCl_3$; Me_4Si) δ = 147.32, 141.74, 138.33, 136.21, 131.57, 130.36, 129.97, 129.84, 129.76, 129.62, 124.55, 118.05, 117.66, 115.98, 114.80, 21.69, 21.12 and 20.52 ppm; *m*/*z* (EI) 327.1728 (M^+ $C_{22}H_{21}N_3$ requires 327.1735), 311 (10), 206 (5) and 91 (10).

[2-(4-Methoxyphenyl)-2*H*-indazol-3-yl]-4-methoxyphenylamine (26). White solid; TLC (30% ethyl acetate–hexane) R_f 0.34; mp 175.5–178 °C (ethyl acetate–hexane); ν_{max}(KBr)/cm^{-1} 3360, 3053, 2969, 2839, 1511 and 1239; ^{1}H NMR (400 MHz, $CDCl_3$; Me_4Si) δ = 7.65 (1H, d, *J* 8.3 Hz, Ph), 7.54–7.58 (2H, m, Ph), 7.26–7.29 (2H, m, Ph), 6.96–7.00 (2H, m, Ph), 6.91 (1H, dd, *J* 8.3 and 1.4 Hz, Ph), 6.80–6.84 (4H, m, Ph), 5.57 (1H, s, NH), 3.85 (3H, s, OCH_3) and 3.78 (3H, s, OCH_3) ppm; ^{13}C NMR (100 MHz; $CDCl_3$; Me_4Si) δ = 159.48, 154.44, 148.27, 136.94, 133.99, 131.54, 126.75, 126.19, 120.35, 120.22, 117.63, 117.57, 114.77, 114.37, 114.25, 55.55 and 55.43 ppm; *m*/*z* (EI) 345.1475 (M^+ $C_{21}H_{19}N_3O_2$ requires 345.1477), 330 (32), 209 (10) and 122 (6).

[4-Chloro-2-(4-methoxyphenyl)-2*H*-indazol-3-yl]-4-methoxyphenylamine (27). Pale yellowish white solid; TLC (30% ethyl acetate–hexane) R_f 0.39; mp 144–146 °C (ethyl acetate–hexane); ν_{max}(KBr)/cm^{-1} 3361, 3057, 2972, 2839, 1507, 1241 and 737; ^{1}H NMR (400 MHz, $CDCl_3$; Me_4Si) δ = 7.50–7.55 (3H, m, Ph), 7.14 (1H, dd, *J* 8.5 and 7.2 Hz, Ph), 6.94 (1 H, d, *J* 7.2 Hz, Ph), 6.80–6.84 (2H, m, Ph), 6.66–6.70 (2H, m, Ph), 6.49–6.53 (2H, m, Ph), 5.92 (1H, s, NH), 3.73 (3H, s, OCH_3) and 3.67 (3H, s, OCH_3) ppm; ^{13}C NMR (100 MHz; $CDCl_3$; Me_4Si) δ = 159.36, 153.89, 148.92, 139.09, 133.47, 131.71, 126.85, 125.68, 125.28, 121.23, 116.55, 116.41, 114.56, 114.52, 114.04, 55.38 and 55.31 ppm; *m*/*z* (EI) 379.1082 (M^+ $C_{21}H_{18}ClN_3O_2$ requires 379.1088), 364 (48), 243 (6) and 122 (5).

[5-Chloro-2-(4-methoxyphenyl)-2*H*-indazol-3-yl]-4-methoxyphenylamine (28). Pale yellowish white solid; TLC (30% ethyl acetate–hexane) R_f 0.43; mp 179–181 °C (ethyl acetate–hexane); ν_{max}(KBr)/cm^{-1} 3227, 3039, 2932, 1616 and 1514; ^{1}H NMR (400 MHz, $CDCl_3$; Me_4Si) δ = 7.54 (1H, dd, *J* 8.6 and 0.6 Hz, Ph), 7.47–7.51 (2H, m, Ph), 7.22 (1H, dd, *J* 1.9 and 0.6 Hz, Ph), 7.17 (1H, dd, *J* 8.6 and 1.9 Hz, Ph), 6.91–6.95 (2H, m, Ph), 6.76–6.83 (4H, m, Ph), 5.71 (1H, s, NH), 3.82 (3H, s, OCH_3) and 3.78 (3H, s, OCH_3) ppm; ^{13}C NMR (100 MHz; $CDCl_3$; Me_4Si) δ = 159.74, 154.75, 146.59, 136.45, 133.74, 131.24, 126.63, 128.17, 126.17, 125.70, 119.23, 118.95, 117.74, 114.95, 114.51, 55.60 and 55.51 ppm; *m*/*z* (EI) 379.1086 (M^+ $C_{21}H_{18}ClN_3O_2$ requires 379.1088), 364 (25), 243 (11) and 122 (10).

[7-Methoxy-2-(4-methoxyphenyl)-2*H*-indazol-3-yl]-4-methoxyphenylamine (29). White solid; TLC (30% ethyl acetate–hexane) R_f 0.13; mp 148–150 °C (ethyl acetate–hexane); ν_{max}(KBr)/cm^{-1} 3215, 3174, 3046, 2951, 2832, 1508 and 1254; ^{1}H NMR (400 MHz, $CDCl_3$; Me_4Si) δ = 7.51–7.55 (2H, m, Ph), 6.89–6.93 (2H, m, Ph), 6.82–6.83 (2H, m, Ph), 6.78 (4H, br s, Ph), 6.52 (1H, dd, *J* 8.0 and 1.7 Hz, Ph), 5.61 (1H, s, NH), 3.99 (3H, s, OCH_3), 3.81 (3H, s, OCH_3) and 3.76 (3H, s, OCH_3) ppm; ^{13}C NMR (100 MHz; $CDCl_3$; Me_4Si) δ = 159.48, 154.40, 150.17, 141.81, 136.95, 134.05, 131.57, 126.46, 120.89, 117.48, 115.84, 114.76, 114.21, 112.29, 103.00, 55.57, 55.46 and 55.27 ppm; *m*/*z* (EI) 375.1579 (M^+ $C_{22}H_{21}N_3O_3$ requires 375.1583), 360 (15), 346 (5), 329 (5), 238 (7) and 122(17).

[7-Methyl-2-(4-methoxyphenyl)-2*H*-indazol-3-yl]-4-methoxyphenylamine (30). White solid; TLC (30% ethyl acetate–hexane)

R_f 0.37; mp 141–143 °C (ethyl acetate–hexane); ν_{max}(KBr)/cm^{-1} 3211, 3007, 2954, 2837, 1507 and 1239; ^{1}H NMR (400 MHz, $CDCl_3$; Me_4Si) δ = 7.55 (1 H, d, *J* 8.8 Hz, Ph), 7.49–7.55 (2H, m, Ph), 7.11 (1H, dd, *J* 8.8 and 1.3 Hz, Ph), 7.05 (1H, br s, Ph), 6.91–6.95 (2H, m, Ph), 6.78–6.82 (2H, m, Ph), 6.72–6.76 (2H, m, Ph), 5.53 (1H, s, NH), 3.82 (3H, s, OCH_3), 3.77 (3H, s, OCH_3) and 2.33 (3H, s, CH_3) ppm; ^{13}C NMR (100 MHz; $CDCl_3$; Me_4Si) δ = 159.47, 154.15, 147.32, 137.59, 132.51, 131.77, 130.04, 129.78, 126.16, 118.07, 117.52, 116.77, 115.23, 114.86, 114.38, 55.61, 55.50 and 21.68 ppm; *m/z* (EI) 359.1634 (M^+ $C_{22}H_{21}N_3O_2$ requires 359.1638), 344 (27), 223 (8) and 122 (5).

[5-Methyl-2-(4-methoxyphenyl)-2*H*-indazol-3-yl]-4-methoxyphenylamine (31). White solid; TLC (30% ethyl acetate–hexane) R_f 0.47; mp 136–139 °C (ethyl acetate–hexane); ν_{max}(KBr)/cm^{-1} 3175, 3033, 2940, 2829, 1508 and 1241; ^{1}H NMR (400 MHz, $CDCl_3$; Me_4Si) δ = 7.47–7.50 (2H, m, Ph), 7.08 (1H, d, *J* 8.0 Hz, Ph), 7.01 (1H, d, *J* 6.8 Hz, Ph), 6.88–6.83 (2H, m, Ph), 6.80 (1H, dd, *J* 8.0 and 1.7 Hz, Ph), 6.76 (3H, br s, Ph), 5.64 (1H, s, NH), 3.78 (3H, s, OCH_3), 3.74 (3H, s, OCH_3) and 2.60 (3H, s, CH_3) ppm; ^{13}C NMR (100 MHz; $CDCl_3$; Me_4Si) δ = 159.52, 154.35, 148.53, 137.06, 134.17, 131.67, 127.58, 126.50, 125.66, 120.54, 117.76, 117.51, 114.73, 114.40, 113.94, 55.55, 55.46 and 16.76 ppm; *m/z* (EI) 359.1634 (M^+ $C_{22}H_{21}N_3O_2$ requires 359.1634), 344 (32), 223 (6), 208 (6) and 122 (5).

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