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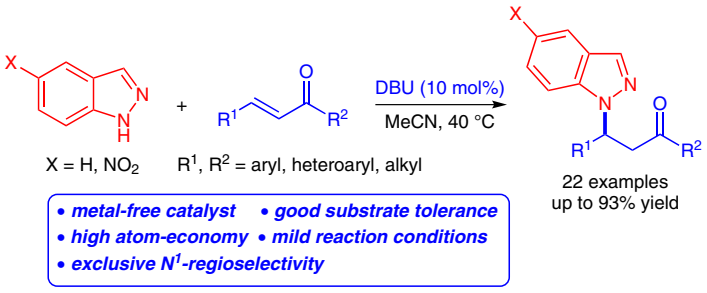
Highly Efficient Synthesis of N^1-Substituted 1*H*-Indazoles by DBU-Catalyzed Aza-Michael Reaction of Indazole with Enones

Jingya Yang[*a]
Yunfen Bao[a]
Hongyan Zhou[b]
Tianyuan Li[a]
Nana Li[a]
Zheng Li[a]

[a] College of Chemistry and Chemical Engineering, Northwest Normal University, Lanzhou 730070, P. R. of China
yangjy@nwnu.edu.cn
[b] College of Science, Gansu Agricultural University, Lanzhou 730070, P. R. of China



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Abstract 1*H*-Indazoles are important heterocycles as they are a substantial part in many drugs. Here, a DBU-catalyzed aza-Michael reaction of indazole with enones is described. A variety of aromatic and aliphatic enones are well tolerated and afford the corresponding N^1-substituted 1*H*-indazoles in high to excellent yields with exclusive N^1-regioselectivity. The use of a metal-free catalyst, good substrate tolerance, mild reaction conditions, and high atom economy make this procedure a direct and facile method for the preparation of N^1-substituted 1*H*-indazoles.

Key words Michael addition, indazoles, enones, catalysis, regioselectivity

The atom-economical aza-Michael reaction has shown great potential for constructing C–N bonds. The products, β-amino carbonyl compounds, represent versatile building blocks for the synthesis of β-amino acids, β-lactams, natural products, and pharmaceuticals.[1] While this reaction has been widely explored,[2] the catalytic addition of aromatic *N*-heterocycles with decreased nucleophilicity still presents a significant challenge in organic synthesis.[3]

Indazole and its derivatives, a typical class of aromatic *N*-heterocycles, have sparked significant concern in synthetic and medicinal chemistry due to their diverse biological activities.[4,5] Furthermore, diverse heterocyclic structures could be accessed from indazole-derived *N*-heterocyclic carbenes.[6] Among indazoles, N^1-substituted 1*H*-indazoles are widely used as anticancer, anti-inflammatory, anti-HIV, and antimicrobial drugs (Figure 1).[4,7]

Generally, the synthesis of N^1-substituted 1*H*-indazoles involves a cyclization procedure from miscellaneous starting materials.[4a,b,8] Beyond that, the aza-Michael reaction of 1*H*-indazoles is undoubtedly a potential and alternative strategy to this target. Unfortunately, general methodologies remain scarce in the literature. In this respect, additions of indazole, 5-chloroindazole, and 5-nitroindazole to acrylamide[9] and of 4-bromoindazole to ethyl acrylate[10] under basic conditions have been demonstrated. Therein, moderate yields were obtained. Moreover, addition of 5-nitroindazole and 6-nitroindazole to Ludartin, a bioactive natural product, at the exocyclic double bond of the α-methylene-γ-lactone motif was handily achieved.[7c] During the preparation of this manuscript, a microwave-assisted aza-Michael addition of indazole to tetraethyl ethylidene-1,1-bisphosphonate was also developed.[11] With respect to enones, however, no systematic work has been described except for an example with cyclohept-2-enone.[12]

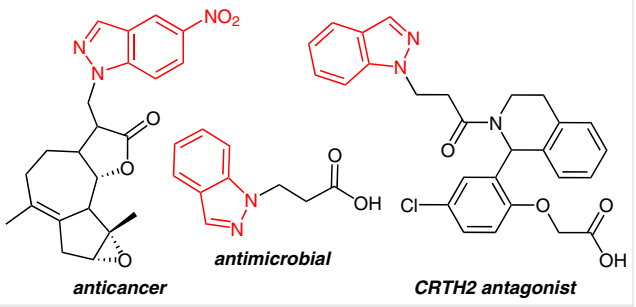
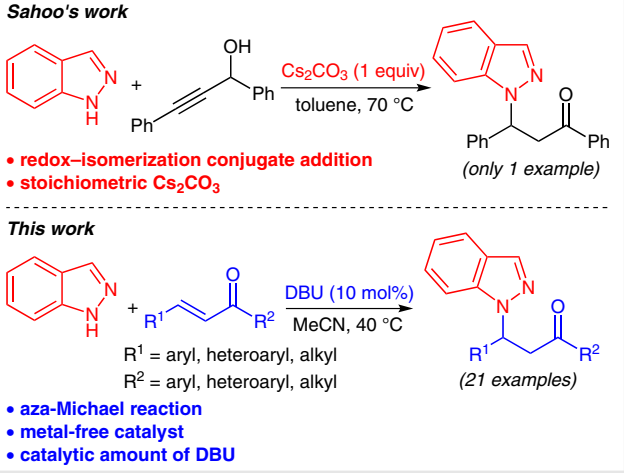


Figure 1 Representative examples of pharmacologically active 1*H*-indazoles

In addition, redox–isomerization of alkynols followed by aza-Michael reaction with indazole can be seen as a variant of the direct aza-Michael reaction of indazole with enones. Han reported the reaction of ethyl 4-hydroxy-4-phenylbut-2-ynoate with four substituted 1*H*-indazoles in CH_2Cl_2 to afford the desired products in 60–76% yield, yet more than 1 equivalent of DBU was needed.[13] When these conditions were employed in the reaction of propargyl alcohols with *N*-heterocycles, however, only 49% yield was

obtained.[14] Recently, the Sahoo group demonstrated a convenient approach to 3-(1*H*-indazol-1-yl)-1,3-diphenylpropan-1-one (**2a**) from 1,3-diphenylprop-2-yn-1-ol and 1*H*-indazole in the presence of 1 equivalent of Cs_2CO_3 in toluene at 70 °C (Scheme 1, top).[14] Although 92% yield was obtained, the high cost of Cs_2CO_3 and the very large amounts of metal-contaminated waste limit the application of such a method. In addition, only one example aimed at N^1-substituted indazoles was investigated. Therefore, further development of a novel protocol with metal-free, direct, and efficient features under mild conditions is still in demand.

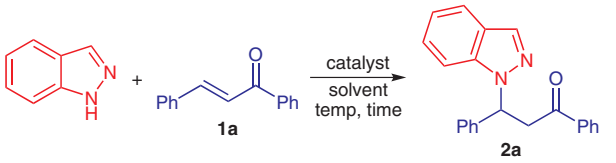
Herein, we disclose a metal-free aza-Michael reaction of indazole with a wide range of enones under mild conditions (Scheme 1, bottom). Only 10 mol% of DBU is required to obtain the target products in good to excellent isolated yields. This investigation opens up the possibility of the direct synthesis of N^1-substituted 1*H*-indazole derivatives.



Scheme 1 Strategies for the synthesis of β-(1*H*-indazol-1-yl) ketones

Initially, chalcone (**1a**) was used as a model substrate to optimize the reaction conditions (Table 1). In the absence of catalyst, none of the desired product **2a** was obtained (Table 1, entry 1). Then, we screened several alkali metal salts, but only Cs_2CO_3 showed effective activity and gave the product in 80% yield after 20 hours (Table 1, entries 2–6). Considering the high cost of Cs_2CO_3, metal waste, and still unsatisfactory results, we turned our attention to commercial organic bases (Table 1, entries 7–9). While DMAP and TBAF did not show catalytic activity, DBU promoted the reaction efficiently to furnish the desired product **2a** in excellent yield after six hours (Table 1, entry 7). DBU appears to be a superior catalyst than Cs_2CO_3 in this reaction. Encouraged by these results, we further optimized the reaction conditions. Then, the effect of solvent on the reaction was investigated (Table 1, entries 10–21). Unfortunately, all of the tested solvents afforded the product **2a** in less-than-desirable yields. In addition, increasing the reaction temperature to 40 °C notably shortened the reaction time to three hours with no influence on the yield (Table 1, entry 22). However, further increasing the reaction temperature resulted in an inferior result (Table 1, entry 23). When the catalyst loading was decreased to 5 mol%, the product was also achieved in unfavorable yield (Table 1, entry 24). Thus, the best conditions for this reaction had been established, 10 mol% of DBU as catalyst in acetonitrile at 40 °C.

Table 1 Optimization of the Reaction Conditions[a]



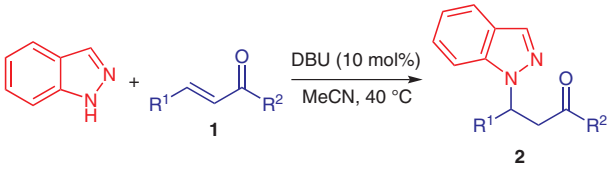
Entry	Catalyst (mol%)	Solvent	Temp (°C)	Time (h)	Isolated yield (%)
1	–	MeCN	r.t.	24	0
2	Na_2CO_3 (10)	MeCN	r.t.	24	0
3	K_2CO_3 (10)	MeCN	r.t.	24	trace
4	Cs_2CO_3 (10)	MeCN	r.t.	20	80
5	KOAc (10)	MeCN	r.t.	24	0
6	LiCl (10)	MeCN	r.t.	24	0
7	DBU (10)	MeCN	r.t.	6	90
8	DMAP (10)	MeCN	r.t.	24	0
9	TBAF (10)	MeCN	r.t.	24	0
10	DBU (10)	PhMe	r.t.	6	trace
11	DBU (10)	hexane	r.t.	6	48
12	DBU (10)	1,4-dioxane	r.t.	6	0
13	DBU (10)	THF	r.t.	6	13
14	DBU (10)	CH_2Cl_2	r.t.	6	50
15	DBU (10)	$CHCl_3$	r.t.	6	70
16	DBU (10)	DCE	r.t.	6	37
17	DBU (10)	DMF	r.t.	6	0
18	DBU (10)	DMSO	r.t.	6	44
19	DBU (10)	MeOH	r.t.	6	trace
20	DBU (10)	EtOH	r.t.	6	0
21	DBU (10)	Et_2O	r.t.	6	55
22	DBU (10)	MeCN	40	3	90
23	DBU (10)	MeCN	60	2	80
24	DBU (5)	MeCN	40	3	80

[a] Reaction conditions: **1a** (0.1 mmol), 1*H*-indazole (0.12 mmol), solvent (1.5 mL).

With the optimized reaction conditions in hand, the substrate scope of enones was examined (Table 2). A variety of chalcone derivatives with different substituents were subjected to the optimal reaction conditions, and afforded the corresponding N^1-substituted 1*H*-indazoles **2a**–**2q** in good to excellent yields (Table 2, entries 1–17). In detail,

when R^1 was 4-nitrophenyl or benzo[*d*][1,3]dioxol-5-yl, the desired compounds **2i** and **2q** were obtained in slightly lower yields than those of other substituted phenyl derivatives (Table 2, entries 9 and 17). Furthermore, the heteroaryl-substituted enones were well tolerated under the optimal conditions (products **2r**, **2s**). To our delight, aliphatic enones were viable and gave the target products **2t**, **2u** in acceptable yields (Table 2, entries 20 and 21). In addition, the structure of product **2s** was confirmed by X-ray crystallographic analysis (Figure 2),[15] which further established the N^1-regioselectivity of this reaction. It should be noted that no N^2-adducts were observed in all cases.

Table 2 DBU-Catalyzed Aza-Michael Reaction of Indazole with Enones[a]



Entry	R^1	R^2	Time (h)	Product	Isolated yield (%)
1	Ph	Ph	4	**2a**	90
2	4-MeC_6H_4	Ph	4	**2b**	89
3	4-MeOC_6H_4	Ph	5	**2c**	80
4	2-MeOC_6H_4	Ph	4	**2d**	88
5	2-ClC_6H_4	Ph	4	**2e**	85
6	4-FC_6H_4	Ph	4	**2f**	83
7	4-ClC_6H_4	Ph	3	**2g**	80
8	4-$F_3C$$C_6H_4$	Ph	5	**2h**	89
9	4-$O_2N$$C_6H_4$	Ph	3	**2i**	66
10	Ph	4-MeC_6H_4	4	**2j**	90
11	Ph	4-ClC_6H_4	3	**2k**	90
12	Ph	4-$O_2N$$C_6H_4$	4	**2l**	81
13	4-MeC_6H_4	4-MeC_6H_4	4	**2m**	93
14	4-MeC_6H_4	4-MeOC_6H_4	5	**2n**	88
15	4-MeC_6H_4	4-ClC_6H_4	4	**2o**	80
16	2,4-$Cl_2C_6H_3$	3-MeOC_6H_4	3	**2p**	90
17	benzo[*d*][1,3]dioxol-5-yl	Ph	4	**2q**	76
18	furan-2-yl	Ph	5	**2r**	70
19	Ph	thiophen-2-yl	4	**2s**	89
20	*n*-butyl	Me	3	**2t**	75
21	*n*-pentyl	Me	3	**2u**	73

[a] Reaction conditions: enone **1** (1.0 mmol), 1*H*-indazole (1.2 mmol), DBU (10 mol%), MeCN (3 mL), 40 °C.

To further explore the substrate scope, the reaction between 5-nitroindazole and chalcone (**1a**) was also examined. Under the standard conditions, chalcone and 5-nitroindazole could be successfully transformed into the corresponding N^1-substituted 5-nitro-1*H*-indazole **3a** in 87% yield (Scheme 2).

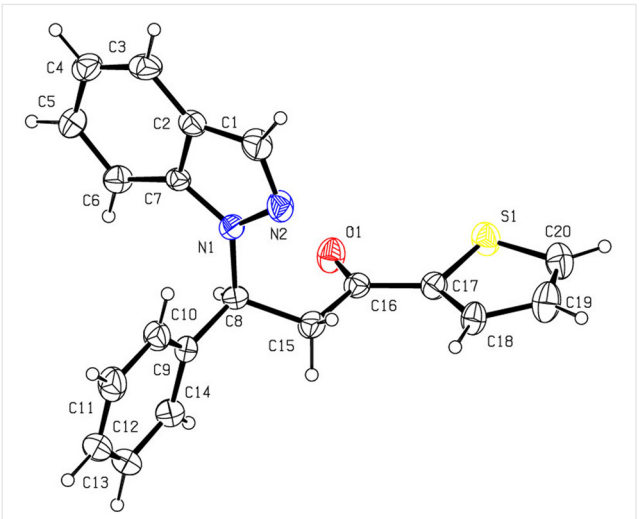
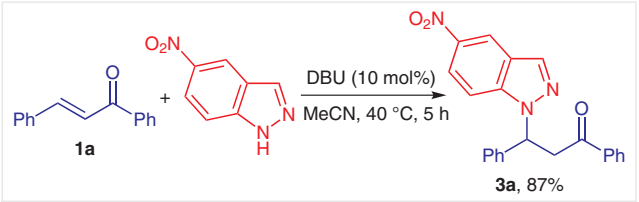


Figure 2 X-ray crystal structure of **2s**



Scheme 2 Aza-Michael addition of 5-nitroindazole to chalcone

In summary, we have developed an efficient and convenient method for the aza-Michael reaction of indazole with enones using 10 mol% of DBU as catalyst. The approach shows good functional group tolerance, in which aryl, heteroaryl, and alkyl enones, as well as 5-nitroindazole, are suitable substrates. Other merits of this strategy include use of a metal-free catalyst, high atom economy, high yield, and exclusive N^1-regioselectivity. The presented reaction provides a direct, complementary, and more attractive pathway than previous methods for the synthesis of N^1-substituted 1*H*-indazoles. The development of asymmetric variants of the current reaction is now under investigation.

^{1}H NMR and ^{13}C NMR spectra were recorded on a Varian Mercury-400 Plus or Agilent Technologies DD2 (600 MHz) spectrometer. IR spectra were recorded on an Alpha Centauri FTIR spectrometer. High-resolution mass spectra (HRMS) were performed on a Thermo Orbitrap Elite instrument with an ESI source. The X-ray single-crystal diffraction was performed on a Bruker APEX II CCD instrument. Melting points were measured on an XT4A apparatus (uncorrected). Reagents and solvents were commercially available, and were used without

further purification. The reaction mixtures were purified by column chromatography over silica gel (PE–EtOAc).

N[1]-Substituted 1*H*-Indazoles 2, 3a; General Procedure

Enone **1** (1.0 mmol), 1*H*-indazole or 5-nitro-1*H*-indazole (1.2 mmol), DBU (15.2 mg, 0.1 mmol), and MeCN (3.0 mL) were sequentially charged into a dry Schlenk tube. The reaction mixture was stirred at 40 °C until reaction completion (monitored by TLC), then cooled to r.t., diluted with EtOAc (3 mL), and washed with brine (3 × 4 mL). The aqueous phase was extracted with EtOAc (4 mL). The organic layer was combined, dried with anhydrous Na_2SO_4, then concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (PE–EtOAc, 20:1, unless otherwise noted) to afford the pure products **2** and **3a**.

3-(1*H*-Indazol-1-yl)-1,3-diphenylpropan-1-one (2a)[14]

White solid; yield: 294 mg (90%); mp 105–107 °C.

IR (KBr): 3057, 2920, 2851, 1686, 1608, 1494, 1449, 1359, 1204, 750, 695 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ = 8.00–7.99 (m, 3 H), 7.68 (d, *J* = 7.8 Hz, 1 H), 7.55–7.51 (m, 2 H), 7.46–7.42 (m, 2 H), 7.35–7.33 (m, 3 H), 7.30–7.27 (m, 2 H), 7.25–7.21 (m, 1 H), 7.13–7.10 (m, 1 H), 6.47 (dd, *J* = 8.4, 4.8 Hz, 1 H), 4.68 (dd, *J* = 17.4, 8.4 Hz, 1 H), 3.76 (dd, *J* = 17.4, 4.8 Hz, 1 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 196.7, 140.9, 139.7, 136.6, 133.3, 133.1, 128.8 (2 C), 128.6 (2 C), 128.2 (2 C), 127.8, 126.6 (2 C), 126.4, 124.3, 120.9, 120.8, 109.6, 57.5, 44.4.

3-(1*H*-Indazol-1-yl)-1-phenyl-3-(*p*-tolyl)propan-1-one (2b)

Pale yellow solid; yield: 303 mg (89%); mp 109–110 °C.

IR (KBr): 3051, 2982, 2942, 2923, 2859, 1678, 1595, 1498, 1448, 1374, 1205, 824, 744, 687 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ = 8.00–7.97 (m, 3 H), 7.67 (d, *J* = 7.8 Hz, 1 H), 7.57–7.51 (m, 2 H), 7.46–7.43 (m, 2 H), 7.35–7.32 (m, 1 H), 7.25 (d, *J* = 9.0 Hz, 2 H), 7.12–7.08 (m, 3 H), 6.43 (dd, *J* = 8.4, 4.8 Hz, 1 H), 4.64 (dd, *J* = 17.4, 8.4 Hz, 1 H), 3.75 (dd, *J* = 17.4, 4.8 Hz, 1 H), 2.28 (s, 3 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 196.8, 139.6, 137.8, 137.5, 136.6, 133.3, 133.0, 129.4 (2 C), 128.6 (2 C), 128.2 (2 C), 126.6 (2 C), 126.3, 124.3, 120.9, 120.7, 109.6, 57.3, 44.3, 21.0.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{23}H_{21}N_2O$: 341.1648; found: 341.1649.

3-(1*H*-Indazol-1-yl)-3-(4-methoxyphenyl)-1-phenylpropan-1-one (2c)

Yellow solid; yield: 285 mg (80%); mp 121–123 °C.

IR (KBr): 3061, 2996, 2908, 2834, 1686, 1610, 1512, 1458, 1367, 1303, 1246, 1021, 829, 758, 689 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ = 8.01–7.97 (m, 3 H), 7.67 (d, *J* = 7.8 Hz, 1 H), 7.56–7.51 (m, 2 H), 7.45–7.42 (m, 2 H), 7.35–7.32 (m, 1 H), 7.30 (d, *J* = 8.4 Hz, 2 H), 7.12–7.09 (m, 1 H), 6.81 (d, *J* = 8.4 Hz, 2 H), 6.41 (dd, *J* = 8.4, 5.4 Hz, 1 H), 4.60 (dd, *J* = 17.4, 8.4 Hz, 1 H), 3.76 (dd, *J* = 17.4, 5.4 Hz, 1 H), 3.74 (s, 3 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 196.8, 159.1, 139.5, 136.7, 133.3, 133.0, 132.9, 128.6 (2 C), 128.2 (2 C), 127.9 (2 C), 126.3, 124.3, 120.9, 120.8, 114.1 (2 C), 109.6, 57.0, 55.2, 44.4.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{23}H_{21}N_2O_2$: 357.1598; found: 357.1610.

3-(1*H*-Indazol-1-yl)-3-(2-methoxyphenyl)-1-phenylpropan-1-one (2d)

White solid; yield: 314 mg (88%); mp 148–150 °C.

IR (KBr): 3064, 2941, 2844, 1682, 1597, 1495, 1458, 1368, 1247, 1022, 749, 684 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ = 8.00–7.97 (m, 3 H), 7.67 (d, *J* = 8.4 Hz, 1 H), 7.57–7.52 (m, 2 H), 7.45–7.41 (m, 2 H), 7.34–7.31 (m, 1 H), 7.23–7.20 (m, 1 H), 7.11–7.08 (m, 1 H), 7.04–7.02 (m, 1 H), 6.93–6.89 (m, 2 H), 6.84–6.81 (m, 1 H), 4.65 (dd, *J* = 17.4, 10.2 Hz, 1 H), 3.91 (s, 3 H), 3.63 (dd, *J* = 17.4, 3.6 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 196.8, 155.7, 139.7, 136.7, 133.0, 132.8, 129.2, 128.7, 128.4 (2 C), 128.1 (2 C), 127.2, 126.0, 124.0, 120.8, 120.6, 120.5, 110.3, 109.8, 55.4, 50.9, 42.7.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{23}H_{21}N_2O_2$: 357.1598; found: 357.1610.

3-(2-Chlorophenyl)-3-(1*H*-indazol-1-yl)-1-phenylpropan-1-one (2e)

Pale yellow solid; yield: 307 mg (85%); mp 109–110 °C.

IR (KBr): 3063, 2926, 2854, 1679, 1595, 1465, 1402, 1361, 1262, 1212, 1018, 833, 756, 619 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ = 8.00–7.99 (m, 3 H), 7.68 (d, *J* = 7.8 Hz, 1 H), 7.57–7.53 (m, 2 H), 7.46–7.43 (m, 2 H), 7.40 (d, *J* = 7.8 Hz, 1 H), 7.37–7.34 (m, 1 H), 7.20–7.17 (m, 2 H), 7.15–7.11 (m, 2 H), 6.94 (dd, *J* = 9.6, 3.6 Hz, 1 H), 4.72 (dd, *J* = 17.4, 9.6 Hz, 1 H), 3.61 (dd, *J* = 17.4, 3.6 Hz, 1 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 196.1, 139.8, 138.6, 136.5, 133.30, 133.27, 131.9, 129.6, 129.0, 128.6 (2 C), 128.3, 128.2 (2 C), 127.5, 126.5, 124.3, 121.0, 120.9, 109.7, 54.0, 42.9.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{22}H_{18}ClN_2O$: 361.1102; found: 361.1113.

3-(4-Fluorophenyl)-3-(1*H*-indazol-1-yl)-1-phenylpropan-1-one (2f)

Eluent: PE–EtOAc, 15:1; white solid; yield: 286 mg (83%); mp 115–117 °C.

IR (KBr): 3055, 2924, 2868, 1683, 1602, 1508, 1448, 1405, 1223, 1164, 832, 746, 689 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ = 8.00–7.98 (m, 3 H), 7.68 (d, *J* = 8.4 Hz, 1 H), 7.57–7.54 (m, 1 H), 7.51 (d, *J* = 8.4 Hz, 1 H), 7.45 (m, 2 H), 7.37–7.33 (m, 3 H), 7.13 (m, 1 H), 6.98–6.95 (m, 2 H), 6.44 (dd, *J* = 8.4, 5.4 Hz, 1 H), 4.60 (dd, *J* = 17.4, 8.4 Hz, 1 H), 3.78 (dd, *J* = 17.4, 5.4 Hz, 1 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 196.5, 163.0, 161.4, 139.6, 136.6 (d, *J* = 3.2 Hz), 136.5, 133.4 (d, *J* = 15.6 Hz), 128.6 (2 C), 128.4 (d, *J* = 8.1 Hz, 2 C), 128.2 (2 C), 126.5, 124.3, 120.9 (d, *J* = 12.3 Hz, 2 C), 115.7, 115.5, 109.4, 56.8, 44.4.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{22}H_{18}FN_2O$: 345.1398; found: 345.1398.

3-(4-Chlorophenyl)-3-(1*H*-indazol-1-yl)-1-phenylpropan-1-one (2g)

White solid; yield: 289 mg (80%); mp 100–102 °C.

IR (KBr): 3054, 2919, 2856, 1682, 1589, 1491, 1447, 1406, 1364, 1205, 828, 743, 690 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.00–7.98 (m, 3 H), 7.69 (d, *J* = 7.8 Hz, 1 H), 7.57–7.54 (m, 1 H), 7.49 (d, *J* = 8.4 Hz, 1 H), 7.47–7.43 (m, 2 H), 7.37–7.34 (m, 1 H), 7.30 (d, *J* = 8.4 Hz, 2 H), 7.25 (d, *J* = 8.4 Hz, 2 H), 7.14–7.11 (m, 1 H), 6.43 (dd, *J* = 7.8, 6.0 Hz, 1 H), 4.60 (dd, *J* = 17.4, 7.8 Hz, 1 H), 3.77 (dd, *J* = 17.4, 6.0 Hz, 1 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 195.6, 140.7, 139.8, 139.7, 134.9, 133.1, 129.7 (2 C), 128.9 (2 C), 128.8 (2 C), 127.9, 126.6 (2 C), 126.4, 124.3, 121.0, 120.9, 109.5, 57.6, 44.3.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{22}H_{18}ClN_2O$: 361.1102; found: 361.1113.

3-(1*H*-Indazol-1-yl)-1-phenyl-3-(4-(trifluoromethyl)phenyl)propan-1-one (2h)

White solid; yield: 351 mg (89%); mp 134–136 °C.

IR (KBr): 3062, 2914, 2865, 1682, 1452, 1321, 1164, 1114, 835, 766, 738, 690, 610 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.02–7.99 (m, 3 H), 7.70 (d, *J* = 7.8 Hz, 1 H), 7.58–7.53 (m, 3 H), 7.50–7.44 (m, 5 H), 7.38–7.35 (m, 1 H), 7.16–7.12 (m, 1 H), 6.52 (dd, *J* = 7.8, 6.0 Hz, 1 H), 4.64 (dd, *J* = 17.4, 7.8 Hz, 1 H), 3.81 (dd, *J* = 17.4, 6.0 Hz, 1 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 196.4, 139.6, 139.4, 136.5, 133.7, 133.4 (d, *J* = 6.2 Hz), 128.9 (2 C), 128.7 (2 C), 128.2 (d, *J* = 10.4 Hz, 2 C), 126.6, 124.4, 121.1 (d, *J* = 7.4 Hz, 2 C), 109.4, 56.9, 44.3.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{23}H_{18}F_3N_2O$: 395.1366; found: 395.1369.

3-(1*H*-Indazol-1-yl)-3-(4-nitrophenyl)-1-phenylpropan-1-one (2i)

Yellow solid; yield: 245 mg (66%); mp 149–151 °C.

IR (KBr): 3063, 2920, 2851, 1681, 1601, 1520, 1347, 1219, 855, 746, 694 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.14 (d, *J* = 9.0 Hz, 2 H), 8.04 (s, 1 H), 8.00–7.98 (m, 2 H), 7.71 (d, *J* = 8.4 Hz, 1 H), 7.59–7.56 (m, 1 H), 7.53 (d, *J* = 9.0 Hz, 2 H), 7.49–7.45 (m, 3 H), 7.39–7.36 (m, 1 H), 7.17–7.14 (m, 1 H), 6.56 (dd, *J* = 7.2, 6.0 Hz, 1 H), 4.62 (dd, *J* = 18.0, 7.2 Hz, 1 H), 3.86 (dd, *J* = 18.0, 6.0 Hz, 1 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 195.9, 147.9, 147.5, 139.7, 136.2, 133.9, 133.7, 128.7 (2 C), 128.2 (2 C), 127.8 (2 C), 126.8, 124.4, 124.0 (2 C), 121.3, 121.2, 109.1, 56.7, 44.1.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{22}H_{18}N_3O_3$: 372.1343; found: 372.1358.

3-(1*H*-Indazol-1-yl)-3-phenyl-1-(*p*-tolyl)propan-1-one (2j)

Pale yellow solid; yield: 307 mg (90%); mp 124–126 °C.

IR (KBr): 3032, 2917, 2849, 1676, 1607, 1494, 1456, 1403, 1360, 1267, 1174, 823, 744, 700 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.99 (s, 1 H), 7.90 (d, *J* = 7.8 Hz, 2 H), 7.68 (d, *J* = 7.8 Hz, 1 H), 7.52 (d, *J* = 8.4 Hz, 1 H), 7.36–7.32 (m, 3 H), 7.30–7.27 (m, 2 H), 7.25–7.21 (m, 3 H), 7.12–7.09 (m, 1 H), 6.46 (dd, *J* = 8.4, 4.8 Hz, 1 H), 4.63 (dd, *J* = 17.4, 8.4 Hz, 1 H), 3.74 (dd, *J* = 17.4, 4.8 Hz, 1 H), 2.40 (s, 3 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 196.8, 139.6, 137.8, 137.5, 136.7, 133.3, 133.0, 129.4 (2 C), 128.6 (2 C), 128.2 (2 C), 126.6 (2 C), 126.3, 124.3, 120.9, 120.7, 109.6, 57.3, 44.3, 21.0.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{23}H_{21}N_2O$: 341.1648; found: 341.1649.

1-(4-Chlorophenyl)-3-(1*H*-indazol-1-yl)-3-phenylpropan-1-one (2k)

White solid; yield: 325 mg (90%); mp 106–108 °C.

IR (KBr): 3057, 2920, 2852, 1684, 1585, 1491, 1400, 1205, 829, 739, 700 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.97 (s, 1 H), 7.93 (d, *J* = 8.4 Hz, 2 H), 7.68 (d, *J* = 7.8 Hz, 1 H), 7.48 (d, *J* = 8.4 Hz, 1 H), 7.41 (d, *J* = 8.4 Hz, 2 H), 7.35–7.32 (m, 3 H), 7.30–7.27 (m, 2 H), 7.25–7.22 (m, 1 H), 7.13–7.09 (m, 1 H), 6.43 (dd, *J* = 9.0, 4.8 Hz, 1 H), 4.65 (dd, *J* = 17.4, 9.0 Hz, 1 H), 3.67 (dd, *J* = 17.4, 4.8 Hz, 1 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 195.6, 140.8, 139.8, 139.7, 134.9, 133.1, 129.7 (2 C), 128.9 (2 C), 128.8 (2 C), 127.9, 126.6 (2 C), 126.4, 124.4, 121.0, 120.9, 109.5, 57.6, 44.3.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{22}H_{18}ClN_2O$: 361.1102; found: 361.1113.

3-(1*H*-Indazol-1-yl)-1-(4-nitrophenyl)-3-phenylpropan-1-one (2l)

Pale yellow solid; yield: 301 mg (81%); mp 158–160 °C.

IR (KBr): 3072, 2915, 2862, 1693, 1604, 1518, 1460, 1408, 1347, 1209, 854, 748, 702 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.25 (d, *J* = 8.4 Hz, 2 H), 8.11 (d, *J* = 9.0 Hz, 2 H), 7.92 (s, 1 H), 7.65 (d, *J* = 8.4 Hz, 1 H), 7.41 (d, *J* = 9.0 Hz, 1 H), 7.31–7.25 (m, 5 H), 7.25–7.22 (m, 1 H), 7.10–7.07 (m, 1 H), 6.38 (dd, *J* = 9.0, 4.2 Hz, 1 H), 4.73 (dd, *J* = 17.4, 9.0 Hz, 1 H), 3.62 (dd, *J* = 17.4, 4.2 Hz, 1 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 195.6, 150.4, 141.1, 140.4, 139.6, 133.1, 129.3 (2 C), 128.9 (2 C), 128.1 (2 C), 126.5, 126.4, 124.4, 123.8 (2 C), 121.0, 120.9, 109.5, 57.7, 44.9.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{22}H_{18}N_3O_3$: 372.1343; found: 372.1358.

3-(1*H*-Indazol-1-yl)-1,3-di(*p*-tolyl)propan-1-one (2m)

Pale yellow solid; yield: 330 mg (93%); mp 101–103 °C.

IR (KBr): 3054, 2919, 2862, 1674, 1605, 1460, 1408, 1362, 1262, 813, 752 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.98 (s, 1 H), 7.90 (d, *J* = 8.4 Hz, 2 H), 7.68–7.64 (m, 1 H), 7.52 (d, *J* = 8.4 Hz, 1 H), 7.35–7.32 (m, 1 H), 7.27–7.23 (m, 4 H), 7.11–7.08 (m, 3 H), 6.43 (dd, *J* = 8.4, 4.8 Hz, 1 H), 4.60 (dd, *J* = 18.0, 8.4 Hz, 1 H), 3.73 (dd, *J* = 18.0, 4.8 Hz, 1 H), 2.39 (s, 3 H), 2.27 (s, 3 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 196.4, 144.1, 139.6, 137.9, 137.5, 134.2, 133.0, 129.4 (2 C), 129.3 (2 C), 128.4 (2 C), 126.6 (2 C), 126.3, 124.3, 120.9, 120.7, 109.6, 57.3, 44.2, 21.6, 21.0.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{24}H_{23}N_2O$: 355.1805; found: 355.1805.

3-(1*H*-Indazol-1-yl)-1-(4-methoxyphenyl)-3-(*p*-tolyl)propan-1-one (2n)

Eluent: PE–EtOAc, 15:1; white solid; yield: 326 mg (88%); mp 126–128 °C.

IR (KBr): 3028, 2968, 2927, 2841, 1672, 1596, 1509, 1456, 1368, 1255, 1167, 1020, 837, 748 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.98–7.95 (m, 3 H), 7.68–7.63 (m, 1 H), 7.52–7.50 (m, 1 H), 7.34–7.30 (m, 1 H), 7.23 (d, *J* = 7.2 Hz, 2 H), 7.10–7.06 (m, 3 H), 6.90–6.88 (m, 2 H), 6.41 (dd, *J* = 8.4, 5.4 Hz, 1 H), 4.56 (dd, *J* = 17.4, 8.4 Hz, 1 H), 3.84 (s, 3 H), 3.70 (dd, *J* = 17.4, 5.4 Hz, 1 H), 2.26 (s, 3 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 195.2, 163.7, 139.6, 138.0, 137.4, 132.9, 130.5 (2 C), 129.8, 129.4 (2 C), 126.6 (2 C), 126.3, 124.3, 120.9, 120.7, 113.7 (2 C), 109.6, 57.4, 55.4, 43.9, 21.1.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{24}H_{23}N_2O_2$: 371.1754; found: 371.1767.

1-(4-Chlorophenyl)-3-(1*H*-indazol-1-yl)-3-(*p*-tolyl)propan-1-one (2o)

Eluent: PE–EtOAc, 15:1; white solid; yield: 300 mg (80%); mp 147–148 °C.

IR (KBr): 3054, 2918, 2862, 1683, 1587, 1463, 1401, 1207, 1089, 830, 742 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.95–7.91 (m, 3 H), 7.66 (d, *J* = 8.4 Hz, 1 H), 7.48 (d, *J* = 9.0 Hz, 1 H), 7.41–7.40 (m, 2 H), 7.33–7.30 (m, 1 H), 7.22 (d, *J* = 8.4 Hz, 2 H), 7.11–7.07 (m, 3 H), 6.38 (dd, *J* = 8.4, 4.8 Hz, 1 H), 4.61 (dd, *J* = 17.4, 8.4 Hz, 1 H), 3.65 (dd, *J* = 17.4, 4.8 Hz, 1 H), 2.27 (s, 3 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 195.7, 139.7, 139.6, 137.7, 137.6, 135.0, 133.0, 129.7 (2 C), 129.4 (2 C), 128.9 (2 C), 126.5 (2 C), 126.3, 124.3, 120.9, 120.8, 109.5, 57.3, 44.3, 21.0.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{23}H_{20}ClN_2O$: 375.1259; found: 375.1271.

3-(2,4-Dichlorophenyl)-3-(1*H*-indazol-1-yl)-1-(3-methoxyphenyl)propan-1-one (2p)

White solid; yield: 383 mg (90%); mp 104–106 °C.

IR (KBr): 3072, 2940, 2840, 1686, 1580, 1468, 1362, 1260, 1020, 785, 742, 686 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.98 (s, 1 H), 7.68 (d, *J* = 7.8 Hz, 1 H), 7.58 (d, *J* = 7.8 Hz, 1 H), 7.52 (d, *J* = 9.0 Hz, 1 H), 7.46–7.44 (m, 1 H), 7.41 (d, *J* = 2.4 Hz, 1 H), 7.38–7.33 (m, 2 H), 7.16–7.08 (m, 4 H), 6.86 (dd, *J* = 9.6, 3.6 Hz, 1 H), 4.63 (dd, *J* = 18.0, 9.6 Hz, 1 H), 3.80 (s, 3 H), 3.58 (dd, *J* = 18.0, 3.6 Hz, 1 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 195.6, 159.8, 139.7, 137.7, 137.1, 134.2, 133.6, 132.7, 129.6, 129.4, 129.2, 127.8, 126.7, 124.3, 121.1, 120.9, 120.8, 120.1, 112.2, 109.4, 55.4, 53.5, 42.9.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{23}H_{19}Cl_2N_2O_2$: 425.0818; found: 425.0837.

3-(Benzo[*d*][1,3]dioxol-5-yl)-3-(1*H*-indazol-1-yl)-1-phenylpropan-1-one (2q)

Yellow solid; yield: 282 mg (76%); mp 159–161 °C.

IR (KBr): 3054, 2920, 2862, 1728, 1689, 1586, 1489, 1402, 1240, 1092, 1032, 809, 769, 746 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.96–7.92 (m, 3 H), 7.67 (d, *J* = 7.8 Hz, 1 H), 7.49 (d, *J* = 8.4 Hz, 1 H), 7.41 (d, *J* = 8.4 Hz, 2 H), 7.36–7.32 (m, 1 H), 7.13–7.09 (m, 1 H), 6.86–6.82 (m, 2 H), 6.71 (d, *J* = 8.4 Hz, 1 H), 6.32 (dd, *J* = 8.4, 4.8 Hz, 1 H), 5.92–5.86 (m, 3 H), 4.57 (dd, *J* = 17.4, 8.4 Hz, 1 H), 3.66 (dd, *J* = 17.4, 4.8 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 195.5, 147.9, 147.2, 139.8, 139.5, 134.9, 134.5, 133.1, 129.6 (2 C), 128.9 (2 C), 126.4, 124.3, 120.9, 120.8, 120.0, 109.4, 108.2, 107.1, 101.1, 57.3, 44.3.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{23}H_{19}N_2O_3$: 371.1390; found: 371.1397.

3-(Furan-2-yl)-3-(1*H*-indazol-1-yl)-1-phenylpropan-1-one (2r)

Yellow solid; yield: 222 mg (70%); mp 129–131 °C.

IR (KBr): 3059, 2907, 1682, 1597, 1446, 1417, 1357, 1301, 1222, 1173, 831, 753, 717, 687 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.98–7.94 (m, 3 H), 7.66–7.60 (m, 2 H), 7.54–7.51 (m, 1 H), 7.42–7.36 (m, 3 H), 7.13–7.09 (m, 2 H), 6.98–6.96 (m, 1 H), 6.86–6.84 (m, 1 H), 6.71 (dd, *J* = 8.4, 4.8 Hz, 1 H), 4.56 (dd, *J* = 18.0, 8.4 Hz, 1 H), 3.88 (dd, *J* = 18.0, 4.8 Hz, 1 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 196.3, 143.7, 139.6, 136.4, 133.8, 133.5, 128.7 (2 C), 128.3 (2 C), 126.7, 126.6, 125.2, 125.1, 124.2, 121.1, 121.0, 109.5, 53.2, 45.0.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{20}H_{17}N_2O_2$: 317.1285; found: 317.1289.

3-(1*H*-Indazol-1-yl)-3-phenyl-1-(thiophen-2-yl)propan-1-one (2s)

White solid; yield: 296 mg (89%); mp 131–133 °C.

IR (KBr): 3082, 2922, 1657, 1613, 1494, 1452, 1410, 1357, 1274, 1214, 850, 744, 698 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.98 (s, 1 H), 7.80 (d, *J* = 4.8 Hz, 1 H), 7.66 (d, *J* = 8.4 Hz, 1 H), 7.59 (d, *J* = 4.8 Hz, 1 H), 7.47 (d, *J* = 8.4 Hz, 1 H), 7.32–7.19 (m, 6 H), 7.10–7.07 (m, 2 H), 6.41 (dd, *J* = 8.4, 4.8 Hz, 1 H), 4.54 (dd, *J* = 16.8, 8.4 Hz, 1 H), 3.71 (dd, *J* = 16.8, 4.8 Hz, 1 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 189.4, 143.8, 140.5, 139.6, 134.0, 133.2, 132.4, 128.7 (2 C), 128.1, 127.8, 126.6 (2 C), 126.3, 124.2, 120.9, 120.8, 109.5, 57.4, 44.9.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{20}H_{17}N_2OS$: 333.1056; found: 333.1057.

4-(1*H*-Indazol-1-yl)octan-2-one (2t)

Yellow liquid; yield: 183 mg (75%).

IR (neat): 3059, 2957, 2930, 2862, 1716, 1615, 1497, 1462, 1423, 1363, 1166, 1012 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.00 (s, 1 H), 7.68 (d, *J* = 7.8 Hz, 1 H), 7.52 (d, *J* = 7.2 Hz, 1 H), 7.39–7.35 (m, 1 H), 7.13–7.10 (m, 1 H), 5.07–5.02 (m, 1 H), 3.35 (dd, *J* = 17.4, 7.8 Hz, 1 H), 2.94 (dd, *J* = 17.4, 5.4 Hz, 1 H), 2.09–2.03 (m, 1 H), 2.02 (s, 3 H), 1.84–1.78 (m, 1 H), 1.29–1.18 (m, 2 H), 1.14–1.07 (m, 1 H), 0.95–0.87 (m, 1 H), 0.77 (t, *J* = 7.4 Hz, 3 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 206.3, 140.1, 133.4, 126.2, 123.4, 120.8, 120.5, 109.3, 53.9, 48.4, 35.1, 30.5, 28.2, 22.2, 13.8.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{15}H_{21}N_2O$: 245.1648; found: 245.1657.

4-(1*H*-Indazol-1-yl)nonan-2-one (2u)

Yellow liquid; yield: 189 mg (73%).

IR (neat): 3059, 2952, 2929, 2859, 1716, 1615, 1462, 1423, 1364, 1165, 1014 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.00 (s, 1 H), 7.68 (d, *J* = 7.8 Hz, 1 H), 7.52 (d, *J* = 8.4 Hz, 1 H), 7.38–7.36 (m, 1 H), 7.13–7.10 (m, 1 H), 5.08–5.02 (m, 1 H), 3.35 (dd, *J* = 17.4, 8.4 Hz, 1 H), 2.94 (dd, *J* = 17.4, 5.4 Hz, 1 H), 2.08–2.03 (m, 1 H), 2.02 (s, 3 H), 1.83–1.76 (m, 1 H), 1.23–1.07 (m, 5 H), 0.98–0.89 (m, 1 H), 0.77 (t, *J* = 6.9 Hz, 3 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 206.3, 140.0, 133.4, 126.2, 123.4, 120.8, 120.5, 109.3, 53.9, 48.4, 35.3, 31.3, 30.6, 25.7, 22.3, 13.9.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{16}H_{23}N_2O$: 259.1805; found: 259.1814.

3-(5-Nitro-1*H*-indazol-1-yl)-1,3-diphenylpropan-1-one (3a)

Yellow solid; yield: 323 mg (87%); mp 70–72 °C.

IR (KBr): 3064, 2980, 2924, 2854, 1864, 1733, 1519, 1450, 1339, 1071, 812, 785, 750, 691 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ = 8.67 (s, 1 H), 8.23 (d, *J* = 9.6 Hz, 1 H), 8.17 (s, 1 H), 7.98 (d, *J* = 7.2 Hz, 2 H), 7.63–7.53 (m, 2 H), 7.48–7.44 (m, 2 H), 7.37–7.27 (m, 5 H), 6.46 (dd, *J* = 9.6, 3.6 Hz, 1 H), 4.74 (dd, *J* = 18.0, 9.6 Hz, 1 H), 3.68 (dd, *J* = 18.0, 3.6 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 196.5, 142.7, 141.6, 140.0, 136.5, 135.9, 133.8, 129.3 (2 C), 128.9 (2 C), 128.6, 128.4 (2 C), 126.8 (2 C), 123.6, 121.7, 119.1, 110.2, 58.5, 44.4.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{22}H_{18}N_3O_3$: 372.1343; found: 372.1358.

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Supporting Information

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