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Indium triflate catalyzed one-pot multicomponent synthesis of spiro-hexahydropyrimidines explained by multiple covalent bond formation

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ABSTRACT

A mild, efficient, and expeditious method has been developed for the synthesis of spiro-hexahydropyrimidine derivatives via a three-component, one-pot cyclocondensation reaction of aromatic amines, formaldehyde, and cyclic ketones in 4–6 h using $In(OTf)_3$ as Lewis acid catalyst for the first time. The reaction involving creation of six new covalent bonds was efficiently promoted by 10 mol % $In(OTf)_3$ and the catalyst could be recovered easily after the reaction and reused without any loss of its catalytic activity. The advantageous features of this methodology are high atom-economy, operational simplicity, shorter reaction time, and easy handling.

The importance of Lewis acid catalysis in organic synthesis has been well documented in the literature.[1a–e] The majority of the strong and efficient Lewis acids such as $AlCl_3$, $FeCl_3$, $ZnCl_2$, SbF_5, $TiCl_4$, and $SnCl_4$ used in various organic transformations[2a–e] are prone to fast hydrolysis by atmospheric moisture, and therefore they should be treated strictly in dry conditions to prevent the loss of their catalytic activities. Quite often, they are required in stoichiometric amounts, are not reusable, and lead to secondary reactions, making the reaction work-up and product isolation tedious. Because of the increasing awareness of environmental problems in chemical research and industry, the search for a more efficient Lewis acid catalyst still continues.

Indium(III) compounds have evolved as mild and water-tolerant Lewis acids, imparting high regio-, stereo-, and chemoselectivities in various organic transformations.[3a–d] In contrast to classical Lewis acids, which are often required in stoichiometric quantities, Indium(III) compounds readily promote a wide variety of organic reactions in catalytic quantities soluble both in organic solvents and in aqueous media.[4a,b] Particularly, in accordance with the recent surge of interest in moisture-stable metal triflates, $In(OTf)_3$ has emerged as a promising catalyst for various types of organic reactions.[5–14]

The hexahydropyrimidine skeleton is present in a number of alkaloids, eudistomidines H and I,[15] tetraponerines,[16] verbamethrine,[17] and verbamethine.[18] Hexetidine is a formaldehyde-releasing antimicrobial agent employed in mouthwashes and numerous products of veterinary and human drugs.[19] Different N-substituted hexahydropyrimidines are synthones for spermidine-nitroimidazole drugs for the treatment of A549 lung carcinoma.[20] They form structural units in trypanothione reductase inhibiting ligands for the regulation of oxidative stress in parasite cells.[21] *N*-(4-Aminobutyl) hexahydropyrimidine and *N*-(3-aminopropyl) hexahydropyrimidine are shown to compete with spermidine for uptake by L1210 cells.[22] Due to their significant biological activity, hexahydropyrimidines have received a great deal of attention in recent years.

Hexahydropyrimidines are classically prepared by condensation between substituted propane-1,3-diamines and aldehydes or ketones.[23a–f] This method, however, limits the range of substitution at 5-position of the hexahydropyrimidines, being restrained by the availability of appropriately functionalized 1,3-diamines. There are also a few reports in the literature describing the synthesis of substituted hexahydropyrimidine derivatives by using α,β-unsaturated nitriles, by the reaction of substituted alanine and carbamide[24a,b] or by the reaction of 1,3-dicarbonyl compounds or cyclic ketones, aromatic amines, and formaldehyde.[25a,b] Thus each of the known procedure has its own merits; however, further studies are still necessary for the versatile, simple, environmental, and economical multi component methodology.

Inspired by the initial investigation of the metal triflate catalyzed Mannich reaction[26a–d] and the classical method for the synthesis of hexahydropyrimidines, and in continuation of our aim to develop novel and highly efficient synthetic reaction methodologies for the synthesis of spiroheterocycles,[27a–f] we report herein a straightforward one-pot three-component method for the synthesis of substituted spiro-hexahydropyrimidine derivatives by multiple covalent bond formation at room temperature. To the best of our knowledge, this is the first report for the synthesis of spiro-hexahydropyrimidine scaffolds using $In(OTf)_3$ as a reusable Lewis acid catalyst.

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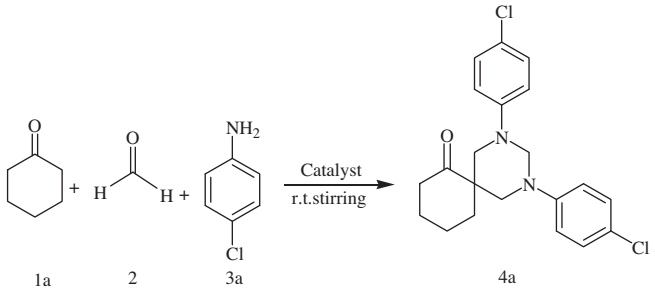
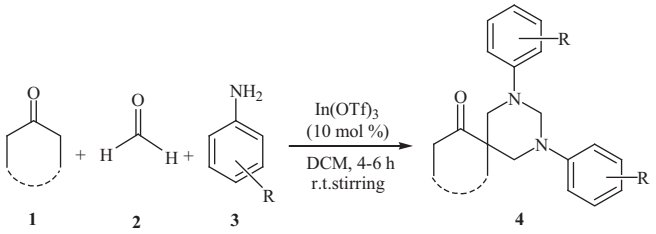


Scheme 1. Synthesis of spiro-hexahydropyrimidine **4a**.



Scheme 2. Synthesis of spiro-hexahydropyrimidines **4a–p**.

To explore an appropriate reaction condition is of crucial importance for the targeted synthesis. Initially, the three-component condensation reaction of cyclohexanone, formaldehyde, and 4-chloroaniline as a simple model substrate was investigated to establish the feasibility of the strategy and to optimize the reaction conditions (Scheme 1). In the beginning, the model reaction was carried out in the absence of catalyst in CH_2Cl_2 at room temperature. The reaction yielded the desired product **4a** in poor yield after running the reaction for 18 h (Table 1, entry 1). To improve the yield, a representative selection of Lewis acids, including $Sc(OTf)_3$, $In(OTf)_3$, $Bi(OTf)_3$, $Cu(OTf)_2$, and Ag(OTf) were tested. Catalysts such as $Sc(OTf)_3$, $Bi(OTf)_3$, $Cu(OTf)_2$, and Ag(OTf), have low efficiency as compared to $In(OTf)_3$. The promising activity of indium triflate as compared to triflate of other metals and halide salts can be explained due to the soft character of indium as compared to other metals,[28a–c] which shows strong affinity for soft Lewis bases such as enol moiety on the basis of the hard and soft acids and bases (HSAB) principle.[29] The catalytic activity of other In(III) complexes such as $InCl_3$, InF_3, and $InBr_3$, was significantly lower than that of $In(OTf)_3$. Possibly, the triflate anion coordinates with cyclohexenol better than other halide ions such as Cl^-, Br^-, and F^- ions and helps in promoting the reaction.

With $In(OTf)_3$ as catalyst, we next investigated the effect of solvents and found that less coordinating solvent CH_2Cl_2 was superior to strong coordinating solvents such as THF, nitromethane, and acetonitrile, perhaps because the interaction between the indium catalyst and the substrate was disturbed by its strong coordinating ability as observed by other workers.[28b,c] Moreover, in proton releasing solvent like ethanol, protonation of secondary amine prior to attack may retard the nucleophilicity of the amine moiety thus resulting in lower yields. Further, the formation of traces of final product in aqueous medium may be attributed to low solubility of the substrate in water.

Performing the reaction with a higher catalyst loading 20 mol % had no significant effect on yield. However, if the amount of the catalyst was reduced to 5 and 1 mol %, the product yield was reduced to 48% and 23% respectively. To our delight, the reaction worked very well in CH_2Cl_2 at room temperature under the catalysis of 10 mol % $In(OTf)_3$ to give spiro-hexahydropyrimidine (**4a**) in 78% yield.

With these encouraging results in hand, we turned to explore the scope of the reaction using different aromatic amines as substrate under the optimized reaction conditions (Scheme 2). It was observed that the aromatic amine with electron donating as well as electron withdrawing groups reacted successfully to furnish the final product in good yields. In addition, we have also explored the reactivity of cyclic ketones (**1a–c**, Fig. 1) for this transformation. From the results, it is clear that cyclohexanone showed better reactivity than 4-methylcyclohexanone and slightly higher yields were obtained, while, 1,4-dioxaspiro[4.5]decan-8-one is found to be less active than cyclohexanone (Table 2).

The proposed mechanism for the formation of spiro-hexahydropyrimidine derivatives is shown in Scheme 3. It is clear from the sequence of steps that the role of indium triflate is to

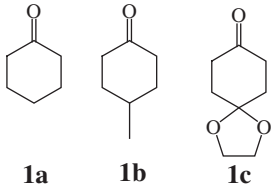


Figure 1.

Table 1
Optimization for the synthesis of **4a**

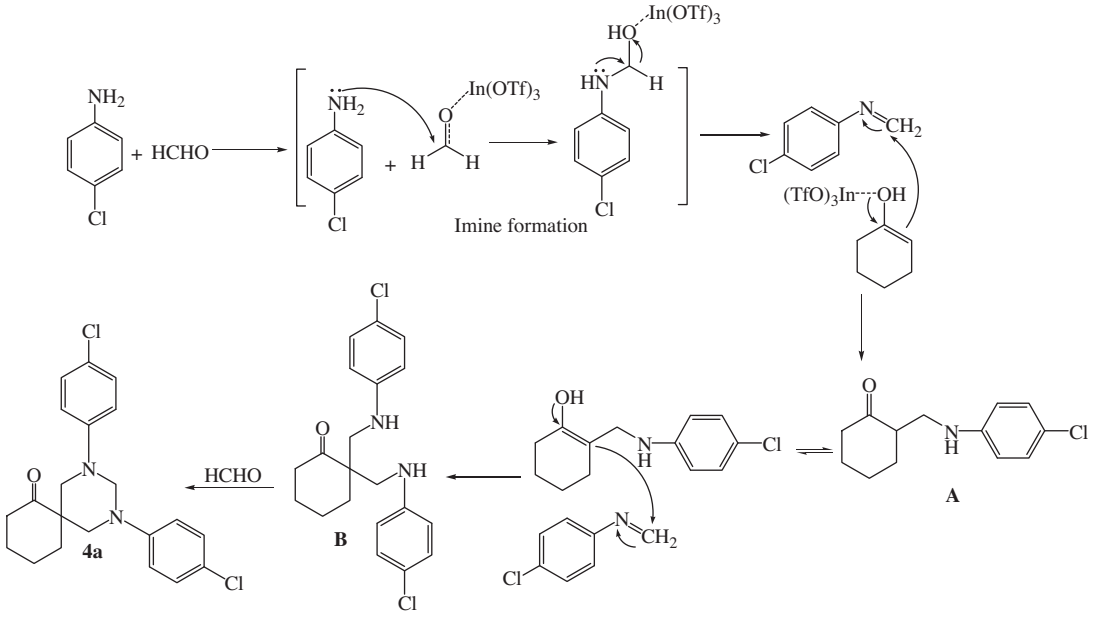
Entry	Solvents	Catalysts	Mol (%)	Time (h)	Yield* (%)
1	Dichloromethane	—	—	18	14
2	Dichloromethane	$In(OTf)_3$	10	4	78
3	Dichloromethane	$Sc(OTf)_3$	10	8	63
4	Dichloromethane	$Bi(OTf)_3$	10	11	56
5	Dichloromethane	$Cu(OTf)_2$	10	7	62
6	Dichloromethane	Ag(OTf)	10	8	42
7	Dichloromethane	$InCl_3$	10	10	48
8	Dichloromethane	$InBr_3$	10	10	53
9	Dichloromethane	InF_3	10	8	58
10	THF	$In(OTf)_3$	10	5	32
11	Ethanol	$In(OTf)_3$	10	7	47
12	Water	$In(OTf)_3$	10	12	Trace
13	Acetonitrile	$In(OTf)_3$	10	10	42
14	Nitromethane	$In(OTf)_3$	10	9	Trace
15	Dichloromethane	$In(OTf)_3$	20	4	78
16	Dichloromethane	$In(OTf)_3$	5	5	48
17	Dichloromethane	$In(OTf)_3$	1	6	23

* Isolated yield.

Table 2
Synthetic results of spiro-hexahydropyrimidine derivatives **4a–p**

Entry	Products	Ketone	R	Time (h)	Yield[a] (%)	Mp (°C)
1	**4a**	**1a**	4-Cl	4	78	160–162
2	**4b**	**1a**	4-CH_3	4	74	124–126
3	**4c**	**1a**	3-Cl,4-F	5	72	248–250
4	**4d**	**1a**	3,4-diCH_3	4	78	96–98
5	**4e**	**1a**	4-OCH_3	5	80	106–108
6	**4f**	**1a**	4-Br	6	66	154–156
7	**4g**	**1a**	4-$N(CH_3)_2$	5	71	106–108
8	**4h**	**1b**	4-Cl	5	73	166–168
9	**4i**	**1b**	4-CH_3	5	72	104–106
10	**4j**	**1b**	3-Cl,4-F	6	61	236–238
11	**4k**	**1c**	4-Cl	6	58	132–134
12	**4l**	**1c**	4-CH_3	6	50	126–128
13	**4m**	**1c**	3-Cl,4-F	5.5	54	206–208
14	**4n**	**1c**	3,4-diCH_3	5	63	120–122
15	**4o**	**1c**	4-OCH_3	5.5	68	118–120
16	**4p**	**1c**	4-Br	6	50	134–136

[a] Isolated yield.



Scheme 3. Plausible mechanism for the reaction of 4-chloroaniline and formaldehyde with cyclohexanone.

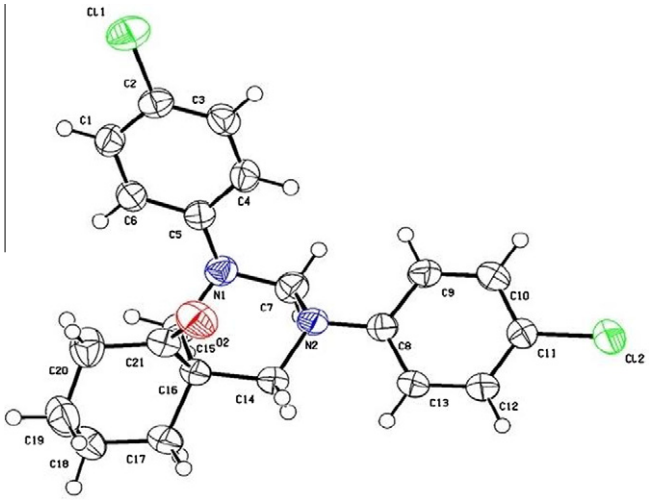


Figure 2. Single crystal X-ray structure of 2,4-bis-(4-chlorophenyl)-2,4-diazaspiro[5.5]undecan-7-one (**4a**).

activate carbonyl group of formaldehyde to generate carbonium ion, facilitating nucleophilic attack by aromatic amine resulting in imine formation. After the imine formation, in situ generated enolate attacks imine to afford β-amino carbonyl derivative A as observed by earlier workers in metal triflate catalyzed Mannich reaction.[26a,26b] Intermediate A reacts further in the same manner to form substituted propane-1,3-diamine B involving double Mannich reaction at the same position. Finally the condensation of the resulting substituted propane-1,3-diamine B with formaldehyde furnishes the desired spiro-hexahydropyrimidines.

The reusability of the catalyst is a significant advantage particularly for commercial applications. Thus, the recovery and reusability of indium triflate were investigated. After completion of the reaction, the reaction mixture was diluted with cold water (5 mL) and extracted with ethylacetate (3 × 10 mL) to obtain the desired product. The catalyst was recovered almost quantitatively after removal of water under reduced pressure. The catalyst was reused in the reaction and it showed the same activity as a fresh catalyst without any loss of its activity. After four recycles, the catalyst still had a high activity and gave the desired product in fairly good yield.

All the products were well characterized by IR, ^{1}H, ^{13}C NMR, mass spectra and elemental analyses.[30] The final structure was confirmed by single crystal X-ray analysis of 2,4-bis-(4-chlorophenyl)-2,4-diazaspiro[5.5]undecan-7-one (**4a**) (Fig. 2).[31]

In conclusion, we have described an efficient three-component reaction for the synthesis of a series of substituted spiro-hexahydropyrimidine derivatives catalyzed by indium triflate from simple and readily available starting materials in one pot operation with good yields. In the present investigation six molecules of reactants are involved and six new covalent bonds are generated, and only water is generated as waste, thus, atom economy of the reaction is high.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.07.79.

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30. General procedure for the synthesis of compounds **4**(**a**–**p**)

To a solution of cyclic ketones (1 mmol), aromatic amines (2 mmol), formaldehyde (3.3 mmol, 36% aqueous solution), and a catalytic amount of $In(OTf)_3$ (10 mol %) in CH_2Cl_2 (5 mL) was stirred at room temperature for the stipulated times. After completion of the reaction, as indicated by TLC, the reaction mixture was diluted with cold water (5 mL) and extracted with EtOAc (3 × 10 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated in vacuum to give pure spiro-hexahydropyrimidine derivatives.

(**4a**) 2,4-Bis-(4-chlorophenyl)-2,4-diazaspiro[5.5]undecan-7-one. White Solid; (Yield: 78%); mp 160–162 °C; IR (KBr): 2948, 2782, 1708, 1592, 1488, 1232, 1216, 828 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.71–1.67 (m, 2H), 1.90–1.86 (m, 4H), 2.37 (t, J = 6.3 Hz, 2H), 3.51 (m, 4H), 4.22 (d, J = 11.4 Hz, 1H), 4.74 (d, J = 11.4 Hz, 1H), 6.98 (d, J = 7.2 Hz, 4H), 7.24 (d, J = 10.2 Hz, 4H), ^{13}C NMR (75 MHz, $CDCl_3$): 20.8, 27.6, 34.7, 39.1, 49.9, 55.2, 67.9, 118.2, 125.2, 129.1, 148.3, 212.5; MS (ESI) m/z: 389 $[M]^+$. Anal. Calcd for $C_{21}H_{22}Cl_2N_2O$: C, 64.79; H, 5.70; N, 7.20. Found: C, 64.88; H, 5.77; N, 7.08.

(**4b**) 2,4-di-*p*-Tolyl-2,4-diazaspiro[5.5]undecan-7-one.[25b] White Solid; (Yield: 74%); mp 124–126 °C; IR (KBr): 2932, 1708, 1546, 1460, 1234, 1210, 816 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.68–1.66 (m, 2H), 1.88–1.86 (m, 4H), 2.29 (s, 6H), 2.39 (t, J = 6.0 Hz, 2H), 3.40 (d, J = 12.3 Hz, 2H), 3.52 (d, J = 12.6 Hz, 2H), 4.10 (d, J = 11.4 Hz, 1H), 4.79 (d, J = 11.1 Hz, 1H), 6.96 (d, J = 8.1 Hz, 4H), 7.10 (d, J = 8.1 Hz, 4H), ^{13}C NMR (75 MHz, $CDCl_3$): 20.4, 20.8, 27.7, 29.6, 34.6, 39.1, 50.0, 55.4, 69.4, 117.4, 129.7, 147.8, 213.3; MS (ESI) m/z: 348 $[M]^+$. Anal. Calcd for $C_{23}H_{28}N_2O$: C, 79.27; H, 8.10; N, 8.04. Found: C, 79.41; H, 8.21; N, 7.95.

(**4c**) 2,4-Bis-(3-chloro-4-fluorophenyl)-2,4-diazaspiro[5.5]undecan-7-one. White Solid; (Yield: 72%); mp 248–250 °C; IR (KBr): 2948, 2782, 1708, 1592, 1488, 1232, 1216, 828 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.72–1.69 (m, 2H), 1.99–1.81 (m, 4H), 2.46 (t, J = 6.9 Hz, 2H), 3.35 (d, J = 12.6 Hz, 2H), 3.59 (d, J = 12.6 Hz, 2H), 4.28 (d, J = 11.4 Hz, 1H), 4.71 (d, J = 11.4 Hz, 1H), 6.87 (d, J = 8.4 Hz, 2H), 6.92 (s, 2H), 7.24 (d, J = 8.7 Hz, 2H), ^{13}C NMR (75 MHz, $CDCl_3$): 20.3, 27.9, 34.8, 39.2, 50.8, 55.5, 69.3, 114.4, 119.9, 129.2, 131.6, 135.5, 148.7, 213.3; MS (ESI) m/z: 425 $[M]^+$. Anal. Calcd for $C_{21}H_{20}Cl_2F_2N_2O$: C, 59.31; H, 4.74; N, 6.59. Found: C, 59.19; H, 4.82; N, 6.69.

(**4d**) 2,4-Bis(3,4-dimethylphenyl)-2,4-diazaspiro[5.5]undecan-7-one.[25b] White Solid; (Yield: 78%); mp 96–98 °C; IR (KBr): 2936, 1706, 1610, 1506, 1448, 1242, 1126, 1018, 912, 810, 732 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.69–1.66 (m, 2H), 1.92–1.84 (m, 4H), 2.21 (s, 6H), 2.24 (s, 6H), 2.41 (t, J = 6.0 Hz, 2H), 3.34 (d, J = 12.6 Hz, 2H), 3.51 (d, J = 12.3 Hz, 2H), 4.02 (d, J = 11.4 Hz, 1H), 4.78 (d, J = 11.4 Hz, 1H), 6.78 (d, J = 8.1 Hz, 2H), 6.86 (s, 2H), 7.02 (d, J = 8.7 Hz, 2H), ^{13}C NMR (75 MHz, $CDCl_3$): 18.5, 20.6, 21.8, 28.3, 34.6, 39.8, 50.9, 55.8, 70.1, 115.5, 119.8, 129.2, 130.6, 138.1, 148.3, 213.8; MS (ESI) m/z: 376 $[M]^+$. Anal. Calcd for $C_{25}H_{32}N_2O$: C, 79.75; H, 8.57; N, 7.44. Found: C, 79.86; H, 8.71; N, 7.32.

(**4e**) 2,4-Bis(4-methoxyphenyl)-2,4-diazaspiro[5.5]undecan-7-one.[25b] White Solid; (Yield: 80%); mp 106–108 °C; IR (KBr): 2939, 1704, 1512, 1458, 1246, 1228, 1036, 830, 762, 538 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.66–1.65 (m, 2H), 1.92–1.80 (m, 4H), 2.36 (t, J = 6.8 Hz, 2H), 3.39 (l, 4H), 3.75 (s, 6H), 4.06 (d, J = 10.8 Hz, 1H), 4.56 (d, J = 11.2 Hz, 1H), 6.84 (d, J = 8.7 Hz, 4H), 7.03 (d, J = 8.7 Hz, 4H), ^{13}C NMR (75 MHz, $CDCl_3$): 20.8, 27.9, 34.8, 39.1, 50.6, 55.2, 56.7, 70.8, 114.2, 120.1, 144.6, 155.1, 213.3; MS (ESI) m/z: 380 $[M]^+$. Anal. Calcd for $C_{23}H_{28}N_2O_3$: C, 72.60; H, 7.42; N, 7.36. Found: C, 72.46; H, 7.54; N, 7.45.

(**4f**) 2,4-bis(4-bromophenyl)-2,4-diazaspiro[5.5]undecan-7-one.[25b] White Solid; (Yield: 66%); mp 154–156 °C; IR (KBr): 2936, 2858, 1700, 1592, 1490, 1236, 1222, 814 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.70–1.67 (m, 2H), 1.88–1.78 (m, 4H), 2.37 (t, J = 6.8 Hz, 2H), 3.54 (l, 4H), 4.21 (d, J = 11.6 Hz, 1H), 4.74 (d, J = 11.6 Hz, 1H), 6.88 (d, J = 9.4 Hz, 4H), 7.36 (d, J = 9.2 Hz, 4H), ^{13}C NMR (75 MHz, $CDCl_3$): 21.0, 27.8, 35.7, 39.6, 50.3, 55.2, 68.4, 113.5, 119.3, 132.8, 148.8, 212.7; MS (ESI) m/z: 478 $[M]^+$. Anal. Calcd for $C_{21}H_{22}Br_2N_2O$: C, 52.74: H, 4.64; N, 5.86. Found: C, 52.89; 4.77; N, 5.99.

(**4g**) 2,4-Bis(4-dimethylaminophenyl)-2,4-diazaspiro[5.5]undecan-7-one.[25b] Yellow Solid, (Yield: 71%); mp 106–108 °C; IR (KBr): 2928, 1702, 1522, 1450, 1216, 946, 818, 736 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.72–1.68 (m, 2H), 1.88–1.80 (m, 2H), 1.96–1.90 (m, 2H), 2.38 (t, J = 6.8 Hz, 2H), 2.88 (s, 12H), 3.38–3.32 (m, 4H), 3.98 (d, J = 10.8 Hz, 1H), 4.56 (d, J = 10.8 Hz, 1H), 6.73 (d, J = 8.6 Hz, 4H), 7.03 (d, J = 8.6 Hz, 4H), ^{13}C NMR (75 MHz, $CDCl_3$): 21.7, 27.9, 35.7, 39.4, 41.8, 50.7, 56.4, 72.5, 114.8, 119.7, 141.9, 146.2, 213.5; MS (ESI) m/z: 406 $[M]^+$. Anal. Calcd for $C_{25}H_{34}N_4O$: C, 73.85; H, 8.43; N, 13.78. Found: C, 73.96; H, 8.51; N, 13.66.

(**4h**) 2,4-Bis-(4-chlorophenyl)-10-methyl-2,4-diazaspiro[5.5]undecan-7-one. White Solid, (Yield: 73%); mp 166–168 °C; IR (KBr): 2960, 2928, 2860, 1704, 1618, 1502, 1462, 1240, 1126, 1014, 910, 814, 736 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 0.85 (d, J = 6.3 Hz, 3H), 1.09 (t, J = 12.6 Hz, 1H), 2.04–1.98 (m, 3H), 2.35–2.28 (m, 2H), 2.51–2.49 (m, 1H), 3.14 (d, J = 12.9 Hz, 1H), 3.39 (d, J = 12.6 Hz, 1H), 3.71 (d, J = 12.6 Hz, 1H), 3.84 (d, J = 12.9 Hz, 1H), 4.25 (d, J = 11.4 Hz, 1H), 4.75 (d, J = 11.7 Hz, 1H), 7.06–6.98 (m, 4H), 7.27–7.23 (m, 4H), ^{13}C NMR (75 MHz, $CDCl_3$): 21.2, 27.4, 35.6, 38.6, 42.9, 49.4, 55.0, 56.1, 68.1, 118.0, 118.6, 125.0, 125.6, 129.1, 129.2, 148.3, 212.6; MS (ESI) m/z: 403 $[M]^+$. Anal. Calcd for $C_{22}H_{24}Cl_2N_2O$: C, 65.51; H, 6.00; N, 6.95. Found: C, 65.42; H, 6.07; N, 6.82.

(**4i**) 10-Methyl-2,4-di-p-tolyl-2,4-diazaspiro[5.5]undecan-7-one.[25b] White Solid, (Yield: 72%); mp 104–106 °C; IR (KBr): 2962, 2926, 1710, 1614, 1520, 1456, 1388, 1224, 1136, 918, 816, 732, 524 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 0.79 (d, J = 5.6 Hz, 3H), 1.03 (t, J = 12.8 Hz, 1H), 1.42–1.25 (m, 1H), 1.99–1.94 (m, 2H), 2.28–2.22 (l, 7H), 2.42–2.38 (m, 1H), 2.60–2.49 (m, 1H), 3.16 (d, J = 12.6 Hz, 1H), 3.21 (d, J = 12.6 Hz, 1H), 3.56 (d, J = 12.6 Hz, 1H), 3.82 (d, J = 12.6 Hz, 1H), 4.10 (d, J = 11.4 Hz, 1H), 4.78 (d, J = 11.4 Hz, 1H), 6.88–6.83 (m, 4H), 7.11 (d, J = 9.2 Hz, 4H), ^{13}C NMR (75 MHz, $CDCl_3$): 20.5, 21.0, 27.3, 35.4, 37.1, 43.1, 49.8, 55.0, 56.9, 70.3, 116.7, 117.6, 129.5, 130.3, 147.9, 212.8; MS (ESI) m/z: 362 $[M]^+$. Anal. Calcd for $C_{24}H_{30}N_2O$: C, 79.52; H, 8.34; N, 7.73. Found: C, 79.63; H, 8.26; N, 7.62.

(**4j**) 2,4-Bis-(3-chloro-4-fluorophenyl)-10-methyl-2,4-diazaspiro[5.5]undecan-7-one. White Solid, (Yield: 61%); mp 236–238 °C; IR (KBr): 2960, 2928, 2860, 1704, 1618, 1502, 1462, 1240, 1126, 1014, 910, 814, 736 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 0.91 (d, J = 6.9 Hz, 3H), 1.03 (t, J = 12.6 Hz, 1H), 1.68–1.61 (m, 1H), 2.04–1.98 (m, 2H), 2.51–2.45 (m, 3H), 3.29 (d, J = 12.3 Hz, 2H), 3.54 (d, J = 12.3 Hz, 1H), 3.83 (d, J = 12.3 Hz, 1H), 4.21 (d, J = 11.1 Hz, 1H), 4.73 (d, J = 11.1 Hz, 1H), 6.81–6.74 (m, 2H), 6.91(s, 2H), 7.19 (d, J = 8.4 Hz, 2H), ^{13}C NMR (75 MHz, $CDCl_3$): 21.9, 27.8, 36.2, 39.7, 42.9, 50.3, 55.1, 56.8, 67.4, 115.3, 118.8, 120.5, 124.1, 130.5, 136.7, 151.3, 212.6; MS (ESI) m/z: 439 $[M]^+$. Anal. Calcd for $C_{22}H_{22}Cl_2F_2N_2O$: C, 60.15; H, 5.05; N, 6.38. Found: C, 60.03; H, 5.14; N, 6.27.

(**4k**) 2,4-Bis(4-chlorophenyl)-10-(1,1-dioxa-2,2-dimethylene)-2,4-diazaspiro [5.5]undecan-7-one. White Solid, (Yield: 58%); mp 132–134 °C; IR (KBr): 2954, 1708, 1512, 1456, 1244, 1042, 918, 826, 726 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.02 (t, J = 6.9 Hz, 2H), 2.11 (s, 2H), 2.58 (t, J = 6.9 Hz, 2H), 3.37 (d, J = 12.6 Hz, 2H), 3.85–3.74 (m, 4H), 3.93–3.88 (m, 2H), 4.08 (d, J = 11.1 Hz, 1H), 4.84 (d, J = 11.4 Hz, 1H), 6.98 (d, J = 9.0 Hz, 4H), 7.23 (d, J = 9.0 Hz, 4H), ^{13}C NMR (75 MHz, $CDCl_3$): 34.9, 36.3, 40.4, 48.7, 56.0, 64.4, 67.7, 106.9, 118.3, 125.2, 129.1, 148.4, 211.2; MS (ESI) m/z: 447 $[M]^+$. Anal. Calcd for $C_{23}H_{24}Cl_2N_2O_3$: C, 61.75; H, 5.41; N, 6.26. Found: C, 61.84; H, 5.47; N, 6.18.

(**4l**) 10-(1,1-Dioxa-2,2-dimethylene)-2,4-di-*p*-tolyl-2,4-diazaspiro[5.5]undecan-7-one.[25b] White Solid, (Yield: 50%); mp 126–128 °C; IR (KBr): 2928, 1710, 1522, 1108, 914, 734, 652 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.02 (t, J = 7.6 Hz, 2H), 2.16 (s, 2H), 2.27 (s, 6H), 2.62 (t, J = 6.6 Hz, 2H), 3.24 (d, J = 12.8 Hz, 2H), 3.79–3.72 (l, 4H), 3.88–3.82 (m, 2H), 3.93 (d, J = 11.1 Hz, 1H), 4.92 (d, J = 10.8 Hz, 1H), 6.98 (d, J = 8.6 Hz, 4H), 7.08 (d, J = 8.6 Hz, 4H), ^{13}C NMR (75 MHz, $CDCl_3$): 20.7, 35.3, 36.4, 40.1, 49.6, 56.4, 64.3, 69.7, 107.2, 117.4,

129.3, 149.7, 212.4; MS (ESI) *m*/*z*: 406 $[M]^+$. Anal. Calcd for $C_{25}H_{30}N_2O_3$: C, 73.86; H, 7.44; N, 6.89. Found: C, 73.75; H, 7.54; N, 6.74.

(**4m**) 2,4-Bis(3-chloro-4-fluorophenyl)-10-(1,1-dioxa-2,2-dimethylene)-2,4-diazaspiro[5.5]undecan-7-one. White Solid, (Yield: 54%); mp 206–208 °C; IR (KBr): 2954, 1708, 1512, 1456, 1244, 1042, 918, 826, 726 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.09 (t, *J* = 7.5 Hz, 2H), 2.23 (s, 2H), 2.64 (t, *J* = 6.9 Hz, 2H), 3.38 (d, *J* = 12.3 Hz, 2H), 3.84–3.72 (m, 4H), 3.92–3.88 (m, 2H), 4.21 (d, *J* = 11.7 Hz, 1H), 4.85 (d, *J* = 11.7 Hz, 1H), 6.91 (s, 2H), 6.99 (d, *J* = 9.0 Hz, 2H), 7.29 (d, *J* = 9.0 Hz, 2H), ^{13}C NMR (75 MHz, $CDCl_3$): 21.1, 34.8, 37.5, 40.3, 48.6, 56.3, 65.3, 68.8, 106.5, 115.3, 119.7, 124.5, 130.2, 137.2, 147.9, 213.4; MS (ESI) *m*/*z*: 483 $[M]^+$. Anal. Calcd for $C_{23}H_{22}Cl_2F_2N_2O_3$: C, 57.15; H, 4.59; N, 5.80. Found: C, 57.26; H, 4.70; N, 5.63.

(**4n**) 2,4-Bis(3,4-dimethylphenyl)-10-(1,1-dioxa-2,2-dimethylene)-2,4-diaza spiro[5.5] undecan-7-one.[25b] White Solid, (Yield: 63%); mp 120–122 °C; IR (KBr): 3416, 2928, 1712, 1608, 1506, 1452, 1246, 1118, 1032, 918, 742 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.07 (t, *J* = 7.6 Hz, 2H), 2.25–2.22 (l, 14H), 2.65 (t, *J* = 7.6 Hz, 2H), 3.19 (d, *J* = 12.8 Hz, 2H), 3.86–3.78 (l, 4H), 3.92–3.84 (l, 3H), 4.91 (d, *J* = 10.8 Hz, 1H), 6.86–6.78 (m, 2H), 6.89 (s, 2H), 7.06 (d, *J* = 8.4 Hz, 2H), ^{13}C NMR (75 MHz, $CDCl_3$): 19.1, 20.4, 35.5, 36.8, 40.3, 48.9, 56.4, 65.1, 68.9, 108.9, 115.7, 118.4, 128.5, 130.9, 137.3, 147.8, 211.2; MS (ESI) *m*/*z*: 434 $[M]^+$. Anal. Calcd for $C_{27}H_{34}N_2O_3$: C, 74.62; H, 7.89; N, 6.45. Found: C, 74.70; H, 7.71; N, 6.34.

(**4o**) 2,4-Bis(4-methoxyphenyl)-10-(1,1-dioxa-2,2-dimethylene)-2,4-diazaspiro[5.5] undecan-7-one.[25b] White Solid, (Yield: 68%); mp 118–120 °C; IR (KBr): 2954, 1702, 1518, 1454, 1248, 1112, 1042, 912, 834, 738 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.01 (t, *J* = 6.9 Hz, 2H), 2.21 (s, 2H), 2.58 (t, *J* = 7.2 Hz, 2H), 3.24 (d, *J* = 12.4 Hz, 2H), 3.63 (d, *J* = 12.8 Hz, 2H), 3.82–3.76 (l, 8H), 3.94–3.84 (l, 3H), 4.72 (d, *J* = 11.4 Hz, 1H), 6.84 (d, *J* = 9.6 Hz, 4H), 7.02 (d, *J* = 9.6 Hz, 4H), ^{13}C NMR (75 MHz, $CDCl_3$): 35.7, 37.1, 40.8, 49.3, 55.8, 57.3, 64.7, 71.9, 109.1, 115.3, 119.8, 144.5, 154.9, 212.6; MS (ESI) *m*/*z*: 438 $[M]^+$. Anal. Calcd for $C_{25}H_{30}N_2O_5$: C, 68.47; H, 6.90; N, 6.39. Found: C, 68.62; H, 6.73; N, 6.48.

(**4p**) 2,4-Bis(4-bromophenyl)-10-(1,1-dioxa-2,2-dimethylene)-2,4-diazaspiro [5.5] undecan-7-one.[25b] White Solid, (Yield: 50%); mp 134–136 °C; IR (KBr): 1712, 1498, 1136, 1122, 914, 732, 642 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.16–2.11 (m, 4H), 2.61 (t, *J* = 7.6 Hz, 2H), 3.43 (d, *J* = 12.4 Hz, 2H), 3.80–3.72 (l, 4H), 3.96–3.82 (m, 2H), 4.11 (d, *J* = 11.8 Hz, 1H), 4.92 (d, *J* = 12.0 Hz, 1H), 6.84 (d, *J* = 9.4 Hz, 4H), 7.28 (d, *J* = 8.6 Hz, 4H), ^{13}C NMR (75 MHz, $CDCl_3$): 35.7, 36.9, 40.4, 48.8, 56.2, 64.8, 66.9, 107.3, 111.6, 118.1, 132.8, 149.7, 212.1; MS (ESI) *m*/*z*: 536 $[M]^+$. Anal. Calcd for $C_{23}H_{24}Br_2N_2O_3$: C, 51.51; H, 4.51; N, 5.22. Found: C, 51.62; H, 4.41; N, 5.15.

31. The crystal structure (**4a**: CCDC 858922) has been deposited at the Cambridge Crystallographic Data Center and is available on request from the Director, CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK (Fax: +44 1223 336033; e-mail: deposit@ccdc.cam.ac.uk, http://www.ccdc.cam.ac.uk/deposit).