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New Synthetic Technologies for the Construction of Heterocycles and Tryptamines

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Abstract: New synthetic methods for the construction of novel heterocycles and tryptamines are described. Thus, *N*-Boc anilines (**I**) are sequentially converted to heterocycles **II** ((3-(2-aminophenyl)pyrrolidin-3-ol) derivatives), **III** (substituted 2-oxo-1,2-dihydrospirobenzo[*d*][1,3]oxazine-4,3′-pyrrolidines), and **VI** (2-(4,5-dihydro-1*H*-pyrrol-3-yl)aniline) derivatives through a route involving *t*-BuLi induced ortho-metalation/$LaCl_3 \cdot 2LiCl$ metal exchange, reaction with *N*-Boc pyrrolidin-3-one (**5**), and subsequent decarboxylative fragmentation. Labile intermediates **VI** are effectively converted to tryptamines **Xa** and **Xb** under controlled protic acid conditions. In addition to providing expedient access to the 2-oxo-1,2-dihydrospirobenzo[*d*][1,3]oxazine-4,3′-pyrrolidines (**III**), the method is applicable to the synthesis of the corresponding 2-oxo-1,2-dihydrospirobenzo[*d*][1,3]oxazine-4,3′-piperidine series of spirocycles (e.g., **42**) and their precursors (3-(2-aminophenyl)piperidin-3-ol derivatives, e.g., **43**) by using *N*-Boc-protected piperidin-3-one (**40**). Applications of the developed synthetic technologies to the synthesis of regioisomeric spirocycles **87** and **90**, tryptamines **88** and **91**, Corey's aspidophytine tryptamine (**97**), and efavirenz (**1**) are also described.

Introduction

Heterocycles are important chemical entities whose deployment in pharmaceutical and agricultural research resulted in myriad applications in medicine and food production over the past few decades. Despite the plethora of synthetic approaches to such intermediates, the advent of new synthetic technologies for their synthesis is, therefore, most welcome, particularly when these technologies lead to new types of heterocyclic compounds and involve efficient and short sequences. Stimulated by the synthetic challenge posed by certain alkaloid natural products, we initiated a program directed toward new strategies for the synthesis of heterocycles and tryptamines.[1] In this article, we describe in detail our investigations along these lines, which culminated in expedient synthetic technologies for the construction of novel spiroheterocycles (i.e., **III**), *N*-Boc-protected cyclic enamines (i.e., **VI**), and tryptamines (**X**, Figure 1). Selected examples[2] of related bioactive compounds possessing the 2-oxo-1,2-dihydrobenzo[*d*][1,3]oxazine framework, found within the spirocycles **III**, include the reverse transcriptase inhibitor efavirenz (**1**), a clinically used anti-HIV-1 drug (Sustiva),[2a] the progesterone antagonist **2** and agonist **3** (currently in clinical trials as a contraceptive),[2b,e] and the antihypertensive agent **4**,[2] the latter containing a spiropiperidine ring (Figure 1). To the best of our knowledge, synthetic methods for the preparation of spiropyrrolidines of type **III** (Scheme 1) are lacking.

Results and Discussion

Our initial goal was to employ *N*-Boc-protected anilines (**I**), a readily available class of synthetic intermediates, for the preparation of *N*-Boc-protected enamines of type **VI** (that we needed for synthetic purposes) through metalation[3] and quenching with *N*-Boc-protected pyrrolidin-3-one (**5**), followed by dehydration[4] (Scheme 1). As it turned out, and as we reported in a preliminary communication,[1] this approach was successful, not directly but rather through a cascade sequence of reactions that proceed through intermediates **II**−**V** as shown in Scheme 1. Compounds **II** and **III** are stable and isolable.

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(1) Nicolaou, K. C.; Krasovskiy, A.; Trépanier, V. É.; Chen, D. Y.-K. *Angew. Chem., Int. Ed.* **2008**, *47*, 4217–4220.
(2) (a) Rizzo, R. C.; Udier-Blagovic, M.; Wang, D.-P.; Watkins, E. K.; Kroeger Smith, M. B.; Smith, R. H., Jr.; Triado-Rives, J.; Jorgensen, W. L. *J. Med. Chem.* **2002**, *45*, 2970–2987. (b) Zhang, P.; Terefenko, E. A.; Fensome, A.; Wrobel, J.; Winneker, R.; Lundeen, S.; Marschke, K. B.; Zhang, Z. *J. Med. Chem.* **2002**, *45*, 4379–4382. (c) Collins, M. A.; Hudak, V.; Bender, R.; Fensome, A.; Zhang, P.; Miller, L.; Winneker, R. C.; Zhang, Z.; Zhu, Y.; Cohen, J.; Unwalla, R. J.; Wrobel, J. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 2185–2189. (d) Fensome, A.; et al. *J. Med. Chem.* **2005**, *48*, 5092–5095. (e) Kern, J. C.; Terefenko, E. A.; Fensome, A.; Unwallla, R.; Wrobel, J.; Zhu, Y.; Cohen, J.; Winneker, R.; Zhang, Z.; Zhang, P. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 189–192. (f) Lagu, B.; Pio, B.; Lebedev, R.; Yang, M.; Pelton, P. D. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 3497–3503.
(3) For the use of the *tert*-butoxycarbonyl moiety (Boc) as ortho-directing group in arene metalations, see: (a) Stanetty, P.; Koller, H.; Mihovilovic, M. *J. Org. Chem.* **1992**, *57*, 6833–6837. (b) Reed, J. N.; Snieckus, V. S. *Tetrahedron Lett.* **1984**, *25*, 5505–5508. (c) Takagishi, K.; Katsoulos, G.; Schlosser, M. *Synlett* **1992**, 360–362.
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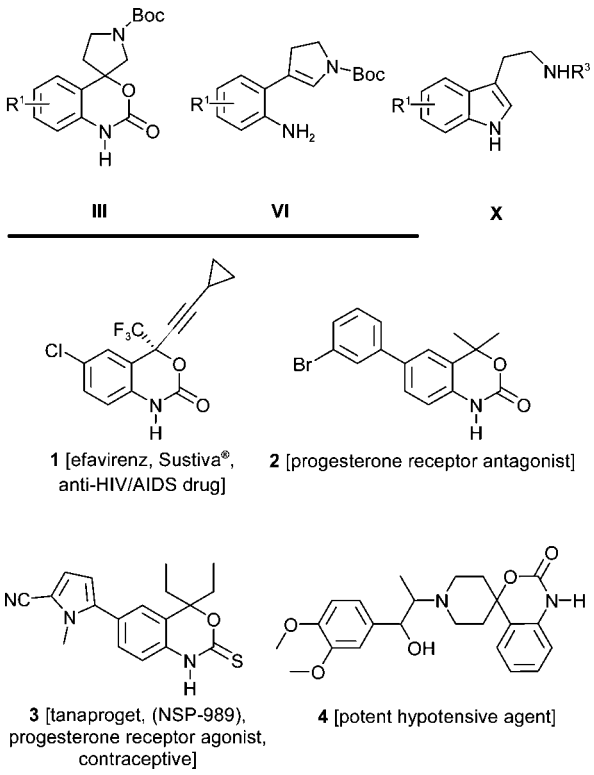
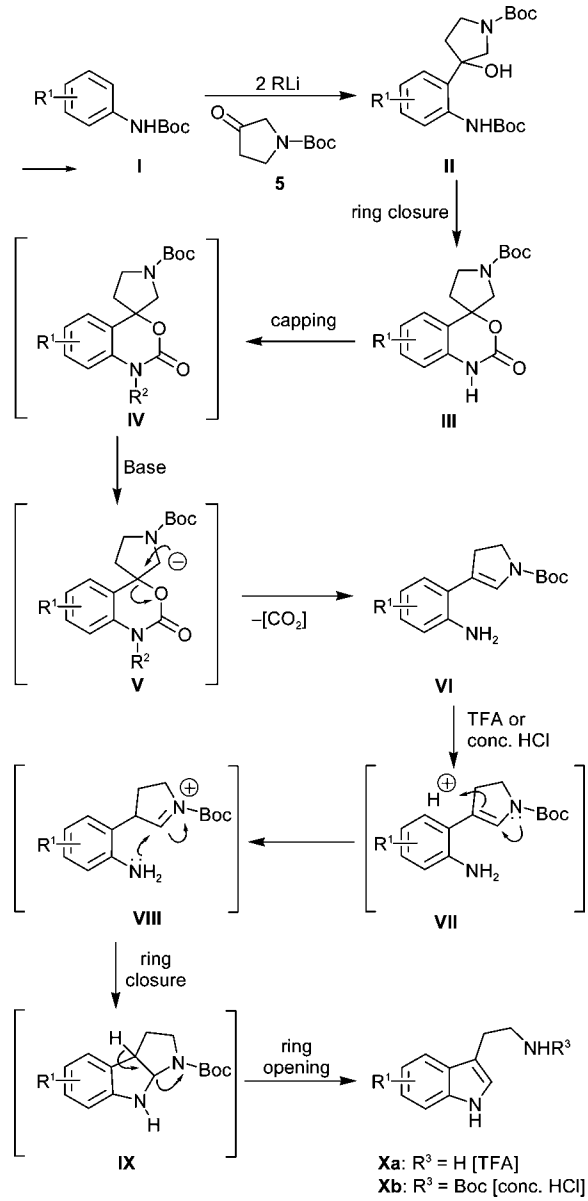


Figure 1. Selected heterocycles synthesized in this work (**III**, **VI**, **X**) and examples of related bioactive molecules containing the 2-oxo-1,2-dihydrobenzo[*d*][1,3]oxazine structural motif (**1**−**4**).

Capping the NH group of compounds **III** with a labile group (e.g., TBS) allowed access to reactive intermediates **IV**, which underwent facile elimination of CO_2 upon treatment with strong base (e.g., LDA) to afford aniline enamines **VI**. The latter, although isolable by careful manipulations, proved rather labile and were reacted immediately under a variety of conditions. In a useful reaction with protic acids, enamines **VI** were converted either to tryptamines (TFA, **Xa**) or to *N*-Boc tryptamines (conc. HCl, **Xb**) as shown in Scheme 1. The latter conversions presumably proceed through transient species **VII**−**IX** as depicted in Scheme 1. As our chemistry developed along these lines, we recognized the relevance of structures **II** and **III** (both stable and isolable) to chemistry and biology due to their rich functionality and potential medicinal properties.

Evolution of the Synthetic Technology for the Synthesis of 2-Oxo-1,2-dihydrospirobenzo[*d*][1,3]oxazine-4,3′-pyrrolidines and 2-Oxo-1,2-dihydrospirobenzo[*d*][1,3]oxa-zine-4,3′-piperidines. Among the many protecting groups for aniline, we chose the *tert*-butoxycarbonyl (Boc) group for the ease of both its installment and removal, as well as its stability under metalation conditions.[3] The desired bis-metalation of *N*-Boc aniline (**6**, Table 1, top) was most efficiently carried out in ether solution at −10 °C with *t*-BuLi as monitored by quenching reaction aliquots (i.e., species **8**) with CD_3OD and NMR spectroscopic analysis (≥98% of deuterium incorporation by ^{1}H NMR after 4 h). Optimization of the reaction of the bis-lithiated *N*-Boc aniline (**8**) with *N*-Boc-protected pyrrolidin-3-one (**5**), however, required extensive experimentation as shown in Table 1. Thus, while PhLi (**7**) reacted smoothly with ketone **5** under a variety of conditions to produce the desired product **9** (entries 1−3), the reaction of the dilithiated *N*-Boc aniline species **8** furnished product **10** in satisfactory yields only in the presence of

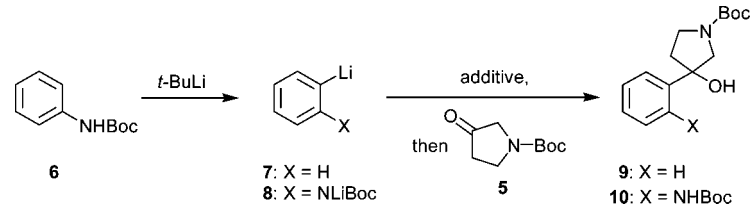
Scheme 1. General Strategy for the Construction of 3-(2-Aminophenyl)pyrrolidin-3-ols (**II**), Spiroheterocycles (**III**), 2,3-Dihydro-1*H*-pyrroles (**VI**), and Tryptamines (**X**)



$LaCl_3 \cdot 2LiCl$[5] (1.1−3.0 equiv) (entries 6−8). Interestingly, in the presence of $CeCl_3$ and according to Imamoto's procedure, the reaction between **8** and **5** gave a low yield (19%, entry 5) of the desired product **10**; in the absence of any additive, the reaction gave an even lower yield (7%, entry 4). In both cases the starting *N*-Boc aniline (**6**) was recovered in high yield. These results can be explained by the acidic nature of ketone **5**, which can react with organometallic species not only as an electrophile but also as a proton donor to effectively quench the reaction, leading to recovery of starting material. The different reactivities of PhLi and dilithiated species **8** demonstrated higher basicity of the latter as opposed to the former and led to, first, our adoption of $CeCl_3$, and, finally, $LaCl_3 \cdot 2LiCl$ as a means to avoid the mutual inactivation of the reacting partners. Using more than 1.1 equiv of $LaCl_3 \cdot 2LiCl$ (entry 6) improved the yield slightly, but the gain was trivialized by workup complications (Table 1,

(5) Krasovskiy, A.; Kopp, F.; Knochel, P. *Angew. Chem., Int. Ed.* **2006**, *45*, 497–500.

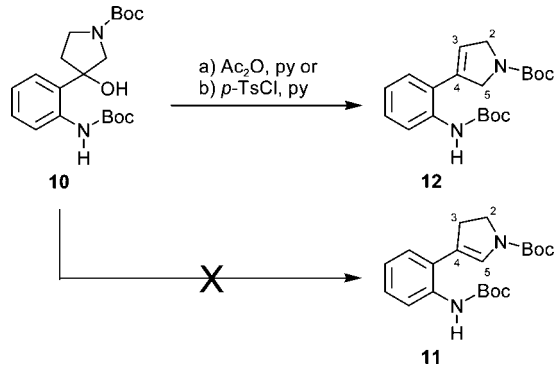
Table 1. Optimization of Addition of Organometallic Reagents to Ketone **5**



Entry	Substrate	Organometallic species	Additive	Product[a]	Yield[b] (%)
1	–	7	None	9	65
2			$CeCl_3$ (1.5 equiv)		82
3			$LaCl_3$•2LiCl (1.1 equiv)		94
4	6	8	None	10	7
5			$CeCl_3$ (1.5 equiv)		19
6[c]			$LaCl_3$•2LiCl (1.1 equiv)		75
7			$LaCl_3$•2LiCl (2.0 equiv)		78
8			$LaCl_3$•2LiCl (3.0 equiv)		79

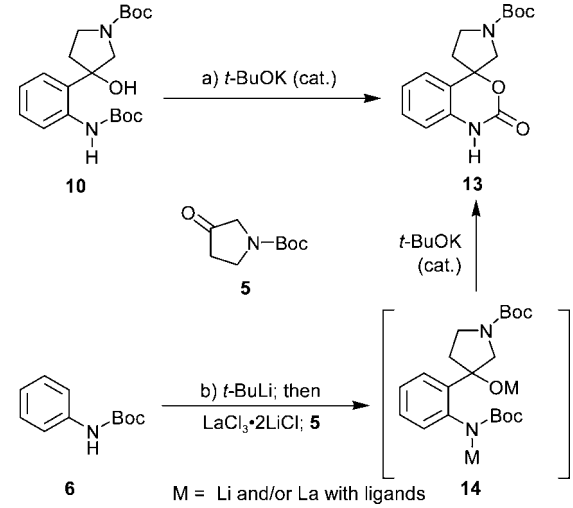
[a] Reactions were carried out on 1.0−5.0 mmol scale. [b] Yield of isolated product. [c] Optimized conditions: **6**, *t*-BuLi (1.7 M in pentane, 2.4 equiv), Et_2O, −10 °C, 4 h; then $LaCl_3$•2LiCl (0.33 M in THF, 1.1 equiv), −70 °C, 5 min, then **5** (1.0 M in THF, 1.2 equiv), −70 → 25 °C, 1 h.

Scheme 2. Attempted Dehydration of **10** and Preparation of 2,5-Dihydro-1*H*-pyrrole (**12**)[a]



[a] Reagents and conditions: (a) Ac_2O (1.2 equiv), pyridine (3.0 equiv), CH_2Cl_2, 40 °C, 12 h, 88%; (b) *p*-TsCl (1.2 equiv), pyridine (1.2 equiv), CH_2Cl_2, 40 °C, 12 h, 84%.

Scheme 3. Synthesis of 2,3-Dihydro-1*H*-pyrrole (**13**)[a]



[a] Reagents and conditions: (a) *t*-BuOK (0.1 equiv), THF, 70 °C, 4 h, 90%; (b) *t*-BuLi (1.7 M in pentane, 2.4 equiv), Et_2O, −10 °C, 4 h; then $LaCl_3$•2LiCl (0.33 M in THF, 1.1 equiv), −70 °C, 5 min; then **5** (1.0 M in THF, 1.2 equiv), −70 → 25 °C, 1 h; then *t*-BuOK (0.1 equiv), THF, 70 °C, 4 h, 72%.

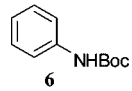
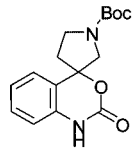
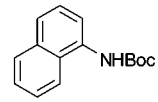
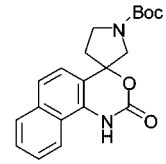
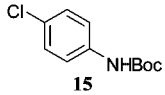
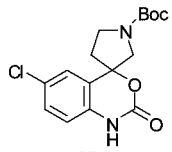
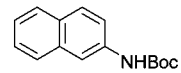
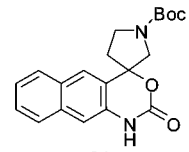
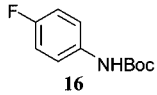
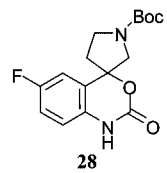
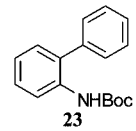
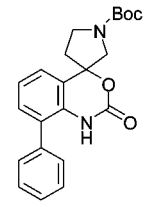
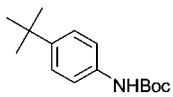
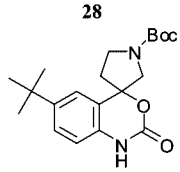
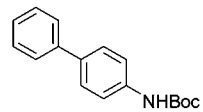
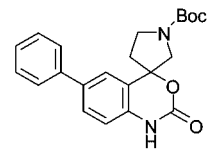
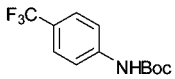
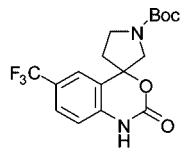
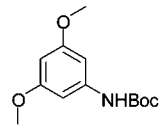
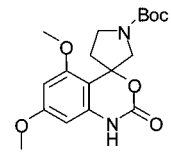
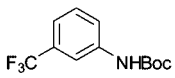
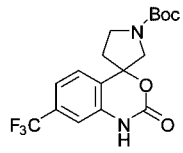
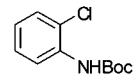
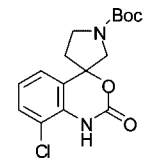
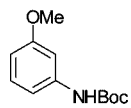
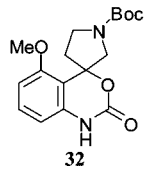
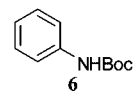
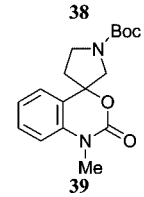
entries 7−8). In all these cases, *N*-Boc aniline (**6**) was recovered with ≥95% mass balance. The transmetalation event (from Li to La) was of crucial importance, with good yields (≥75%) obtained only when it was performed at internal temperatures below −70 °C and only for 5 min. The ability of $LaCl_3$•2LiCl to undergo fast transmetalation may be the key to its success as opposed to $CeCl_3$, a reagent requiring longer transmetalation times.[5]

With a reliable procedure for the preparation of ortho-substituted aniline **10** secured, we then investigated its dehydration to afford 2,3-dihydro-1*H*-pyrrole (**11**, Scheme 2) (structure of type **VI**, Scheme 1). All attempts to dehydrate directly intermediate **10**, however, failed to produce the intended 2,3-dihydro-1*H*-pyrrole (**11**), leading instead to the 2,5-dihydro-1*H*-pyrrole (**12**) in good yield as shown in Scheme 2. Thus, treatment of **10** with Ac_2O or *p*-TsCl in the presence of pyridine at 40 °C gave **12** in 88% and 84% yields, respectively.[6]

Interestingly, however, we found that heating **10** in THF at 70 °C in the presence of 10 mol % of *t*-BuOK afforded spiroheterocycle **13** in 90% yield (Scheme 3). The same spiroheterocycle **13** was obtained directly from *N*-Boc aniline **6** in 72% yield by adding *t*-BuOK and THF to the reaction mixture of entry 6, Table 1, and heating at 70 °C. This procedure amounts to a convenient cascade-based synthesis of spiroheterocycle **13**, its relatives from *N*-Boc aniline, and its substituted siblings. In contrast, previous syntheses of this type of compounds (**III**, Scheme 1) relied on the reaction of 2-aminobenzyl alcohols with phosgene[2,7] or its less toxic surrogates.[8,9]

Table 2 demonstrates the generality and scope of the reaction of *N*-Boc-substituted anilines with *N*-Boc-protected pyrrolidin-

Table 2. Synthesis of Pyrrolidine-Based Spiroheterocycles **13** and **27**−**39**

Entry	*N*-Boc-aniline	Spiroheterocycle[a]	Yield[b] (%)	Entry	*N*-Boc-aniline	Spiroheterocycle[a]	Yield[b] (%)
1	 **6**	 **13**	72	8	 **21**	 **33**	79
2	 **15**	 **27**	81	9	 **22**	 **34**	63
3	 **16**	 **28**	70	10	 **23**	 **35**	61
4	 **17**	 **29**	74	11	 **24**	 **36**	80
5	 **18**	 **30**	72	12	 **25**	 **37**	69
6	 **19**	 **31**	74	13	 **26**	 **38**	22
7	 **20**	 **32**	76	14	 **6**	 **39**	71

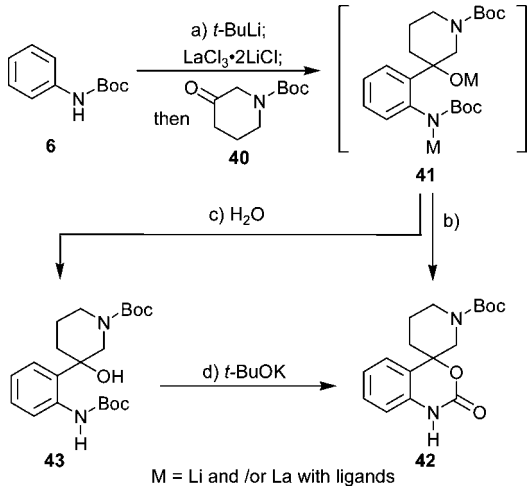
[a] Reactions were carried out on 1.0−5.0 mmol scale in anhydrous ether. [b] Yield of isolated product.

3-one (**5**) to form spiroheterocycles under the prescribed conditions. In addition to *N*-Boc aniline (entry 1), a number of meta- and para-substituted *N*-Boc anilines entered the reaction, furnishing the corresponding *N*-Boc-protected tricycles (entries 2−7) in good yields (70−81%). The process tolerates both the chloride (entry 2) and fluoride (entry 3) residues and the trifluoromethyl group (entries 5 and 6), all relevant to medicinal chemistry.[10,11] Both *N*-Boc 1- and 2-aminonaphthalenes serve smoothly as substrates in this reaction to afford the corresponding spiroheterocycles [entries 8 (79% yield) and 9 (63% yield)]. In addition, *N*-Boc-protected ortho- and para-biphenyls enter the reaction, furnishing regioisomeric spiroheterocycles in good yields [entries 10 (61% yield) and 11 (80% yield)] and demonstrating further expansion of the developed synthetic technology. In the case of ortho-chloroaniline (**26**, entry 13), a

(6) (a) Lee, Y.; Ling, K.-Q.; Li, X.; Silverman, R. B.; Shepard, E. M.; Dooley, D. M.; Sayre, L. M. *J. Am. Chem. Soc.* **2002**, *124*, 12135–12143. (b) Zhang, Y.; Ran, C.; Zhou, G.; Sayre, L. M. *Bioorg. Med. Chem. Lett.* **2007**, *15*, 1868–1877.

(7) (a) Bernardi, L.; Coda, S.; Bonsignori, A.; Pegrassi, L.; Suchowsky, G. K. *Experientia* **1969**, *5*, 787–788. (b) Canonne, P.; Boulanger, R.; Chantegrel, B. *J. Heterocycl. Chem.* **1989**, *26*, 113–117.

Scheme 4. Synthesis of Novel Spiroheterocycle **42** and ortho-Substituted Aniline **43**[a]



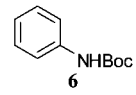
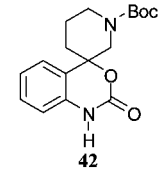
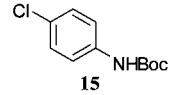
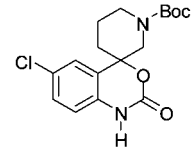
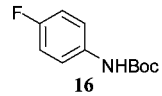
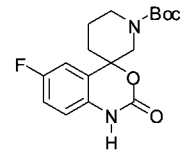
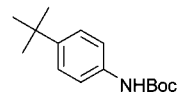
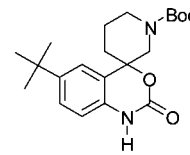
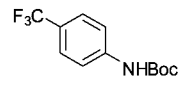
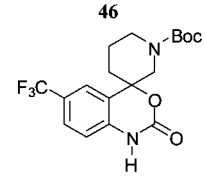
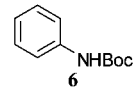
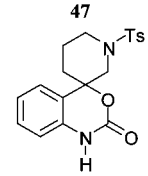
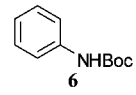
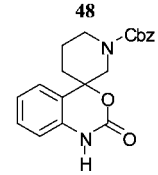
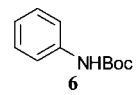
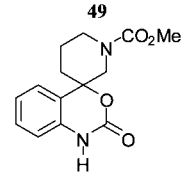
[a] Reagents and conditions: (a) *t*-BuLi (1.7 M in pentane, 2.4 equiv), Et_2O, −10 °C, 4 h; then $LaCl_3$•2LiCl (0.33 M in THF, 1.1 equiv), −70 °C, 5 min; then **40** (1.0 M in THF, 1.2 equiv); (b) −70 → 25 °C, 6 h; then H_2O, 73%; (c) H_2O, −70 → 25 °C, 77%; (d) *t*-BuOK (0.1 equiv), THF, 0 → 25 °C, 0.5 h, 92%.

mixture of spirocycles (**13** and **38**) was obtained in ca. 2.5/1 ratio, presumably due to substantial chlorine−lithium exchange reaction. Pure chloro-substituted spiroheterocycle **38** was chromatographically isolated in 22% yield. Finally, the *N*-Me spirocycle **39** was obtained in 71% yield by in situ methylation (MeI, 0 → 25 °C) of the initially formed spirocyclic anionic species in the reaction of *N*-Boc aniline (**6**) and ketone **5** (entry 14), demonstrating additional flexibility of the method in forming molecular diversity.

Encouraged by our results with the *N*-Boc-protected pyrrolidin-3-one (**5**), we proceeded to explore the same chemistry with its higher homologue, *N*-Boc-protected piperidin-3-one (**40**), in the hope that we would be able to access the corresponding 2-oxo-1,2-dihydrospirobenzo[*d*][1,3]oxazine-4,3′-piperidine series of spiroheterocycles. To this end, *N*-Boc aniline (**6**) was converted to its dilithiated species and transmetalated (*t*-BuLi; then $LaCl_3$•2LiCl, as noted above; see Table 1). To the resulting solution was added *N*-Boc-protected piperidin-3-one (**40**) (−70 °C); the dianionic intermediate (**41**) so-formed was then allowed to warm to room temperature, affording, through spontaneous cyclization, spiroheterocycle **42** in 73% yield as shown in Scheme 4. Quenching dianion **41** at low temperature with water (−70 → 25 °C) allowed the isolation of *N*-Boc hydroxy compound **43**. The latter compound was formed as a mixture of isomers (rotamers), observable by NMR spectroscopy, in 77% yield. Treating this mixture with a base (e.g., *t*-BuOK) at 0 → 25 °C converted it to spirocycle **42** in 92% yield. It is noteworthy that the adducts of *N*-Boc pyrrolidin-3-one (**5**) cyclized in situ upon addition of *t*-BuOK and heating, whereas in the latter case with the *N*-Boc piperidin-3-one (**40**), the reaction proceeded spontaneously (**6** → **41** → **42**) upon warming to 25 °C.

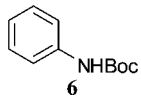
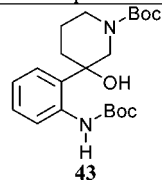
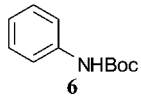
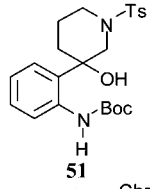
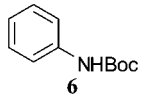
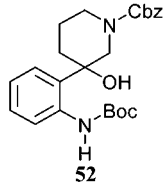
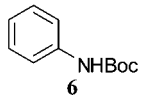
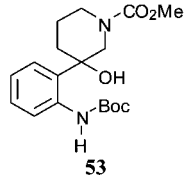
The generality and scope of this reaction was investigated, and the results are shown in Tables 3 and 4. Thus, as shown in Table 3, the one-pot direct preparation of piperidine spiroheterocycles proceeds well with a variety of substituted *N*-Boc anilines (entries 1−5) and *N*-substituted piperidin-3-ones (containing Ts, Cbz, and CO_2Me groups, entries 6−8) in good to excellent yields (62−83%). The tolerance of both electron-donating (entry 4) and electron-withdrawing (entry 5) groups on the aromatic ring, as well as of different protecting groups on the nitrogen of the electrophile (e.g., Ts, Cbz, CO_2Me, entries 6−8), makes this method particularly useful and flexible, especially when further manipulations are intended. Although Table 4 includes only four examples of *N*-Boc hydroxy anilines [3-(2-aminophenyl)piperidin-3-ol derivatives] obtained by quenching the reaction prior to cyclization, all reactions in Table 3 are

Table 3. Synthesis of Piperidine-Based Spiroheterocycles

Entry	*N*-Boc-aniline	Spiroheterocycle[a]	Yield[b] (%)
1	 **6**	 **42**	73
2	 **15**	 **44**	80
3	 **16**	 **45**	77
4	 **17**	 **46**	79
5	 **18**	 **47**	83
6	 **6**	 **48**	81
7	 **6**	 **49**	62
8	 **6**	 **50**	71

[a] Reactions were carried out on 1.0−5.0 mmol scale in anhydrous ether. [b] Yield of isolated product.

Table 4. Synthesis of 2-(3-Hydroxypiperidine-3-yl)phenylcarbamates **43** and **51**−**53**

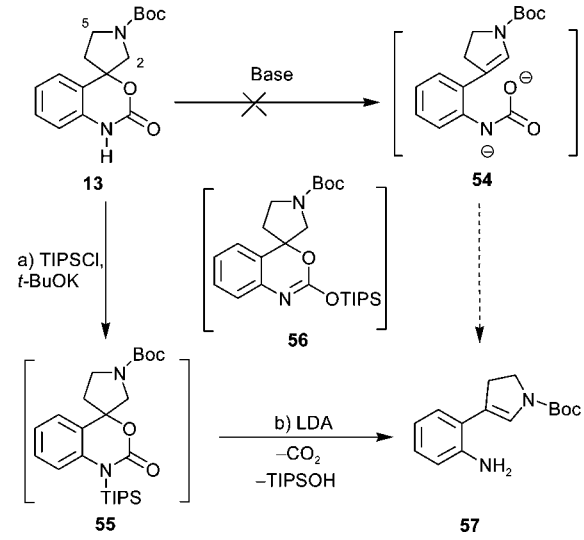
Entry	*N*-Boc-aniline	*N*-Boc hydroxy compound[a]	Yield[b] (%)
1	 **6**	 **43**	77
2	 **6**	 **51**	85
3	 **6**	 **52**	81
4	 **6**	 **53**	83

[a] Reactions were carried out on 1.0−5.0 mmol scale in anhydrous ether. [b] Yield of isolated product.

presumed to lead to the corresponding opened *N*-Boc hydroxy compounds upon appropriate workup.

Having demonstrated the viability of the method for the synthesis of the spiroheterocycles in both the 5- and 6-membered ring series, our next goal became the fragmentation of the pyrrolidine spirocycles of type **III** to the enamine aniline structures of type **VI** (Scheme 1). It was reasoned that, while anion generation at C-5 within the pyrrolidine system of **13** (Scheme 5) would be a dead end, the anion at C-2 may lead to fragmentation, as shown, to afford the desired aniline enamine **57** upon workup, provided the barrier to the incipient gem dianion **54** could be overcome. Experimentation with a variety of bases (e.g., *t*-BuLi, *n*-BuLi, LDA, LTMP), however, did not lead to the desired product, leaving, in most instances, the starting material intact. We then proceeded to investigate the capping of the active NH moiety within substrate **13** with a suitably labile group in order to avoid dianion formation. We found that capping of the carbamate moiety with TBSCl or TIPSCl in the presence of *t*-BuOK was the most appropriate, leading to the corresponding silyl derivatives (e.g., **55**) in essentially quantitative yield (as observed by ^{1}H NMR spectroscopy). These derivatives turned out to be highly labile, even to silica gel. They were, therefore, generated in situ under argon and treated immediately with LDA at −50 °C to afford, after aqueous workup, the desired aniline enamine **57** in 77% overall yield from carbamate **13**. The alternative structure **56** of intermediate **55** could not be excluded on the basis of its spectroscopic data, although literature data of similar compounds, including X-ray crystallographic analysis, support the

Scheme 5. Synthesis of 2,3-Dihydro-1*H*-pyrrole **57**[a]



[a] Reagents and conditions: (a) *t*-BuOK (1.2 equiv), TIPSCl (1.2 equiv), THF, 25 °C, 1 h; (b) LDA (1.0 M in THF, 5.0 equiv), −50 → −30 °C, 2 h, 77% overall for the two steps.

N-silicon-protected structure.[12] For handling convenience, the TIPS derivative was preferred. Enamine **57** also proved rather labile and the less than perfect yield of the fragmentation was attributed to decomposition during isolation.

Crystalline spiroheterocycles **13** (mp = 176−177 °C, EtOAc) and **42** (mp = 124−125 °C, EtOAc) and aniline enamine **57** (mp = 182−183 °C, EtOAc) were subjected to X-ray crystallographic analysis, proving their structural assignments beyond doubt[13] (see ORTEP drawings, Figure 2).

Synthesis of Tryptamines from 2-Oxo-1,2-dihydrospirobenzo[*d*][1,3]oxazine-4,3′-pyrrolidines III. The viability of 2-oxo-1,2-dihydrospirobenzo[*d*][1,3]oxazine-4,3′-pyrrolidines as precursors to tryptamines was then demonstrated. The cascade sequence **III** → **VI** (Scheme 1) was implemented as demonstrated with the unraveling of the rather labile ortho-substituted aniline **57** under acidic conditions (Scheme 6). Thus, treatment of compound **57** with TFA in CH_2Cl_2 at 0 → 25 °C led to tryptamine **58** in 98% yield, whereas use of concentrated HCl in CH_2Cl_2 at 0 → 25 °C furnished the *N*-Boc-protected tryptamine derivative **59** in 98% yield.

(8) Takai, H.; Obase, H.; Teranishi, M.; Karasawa, A.; Kubo, K.; Shuto, K.; Kasya, Y.; Hashikami, M.; Karashima, N.; Shigenobu, K. *Chem. Pharm. Bull.* **1985**, *33*, 1129–1139.
(9) Recently, Japanese workers reported the synthesis of compounds of type **III** based on selenium-catalyzed carbonylation of 2-nitrobenzyl alcohols [see: Nishiyama, Y.; Naitoh, Y.; Sonoda, N. *Synlett* **2004**, 886−888] and iodocyclization of *t*-butyl 2-vinylphenylcarbamates [see: Kobayashi, K.; Fukamachi, S.; Nakamura, D.; Morikava, O.; Konishi, H. *Heterocycles* **2008**, *75*, 95−105].
(10) (a) Yamada, F.; Tamura, M.; Hasegawa, A.; Somei, M. *Chem. Pharm. Bull.* **2002**, *50*, 92–99. (b) Yamada, F.; Tamura, M.; Somei, M. *Heterocycles* **1998**, *49*, 451–457. (c) Sakagami, H.; Ogasawara, K. *Heterocycles* **1999**, *51*, 1131–1135. (d) Nichols, D. E.; Frescas, S. *Synthesis* **1999**, 935–938.
(11) (a) Stoll, A.; Troxler, F.; Peyer, J.; Hofmann, A. *Helv. Chim. Acta* **1955**, *38*, 1452–1472. (b) Hofmann, A.; Heim, R.; Brack, A.; Kobel, H.; Frey, A.; Ott, H.; Petrzilka, T.; Troxler, F. *Helv. Chim. Acta* **1959**, *42*, 1557–1572. (c) Brimblecombe, R. W.; Pinder, R. M. *Hallucinogenic Agents*; Wright-Scientechnica: Bristol, UK, 1975; pp 106−108.
(12) Roby, J.; Voyer, N. *Tetrahedron Lett.* **1997**, *38*, 191–194.
(13) CCDC-675373 (**13**), -703536 (**42**), and -675374 (**57**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

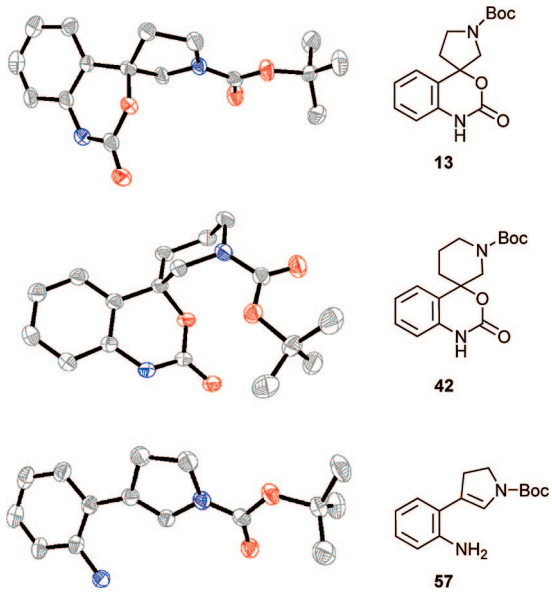
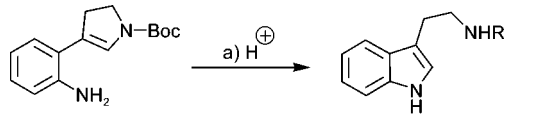


Figure 2. ORTEP drawings of compounds **13**, **42**, and **57** drawn at the 50% probability level.

Scheme 6. Synthesis of Tryptamines **58** and **59**[a]



[a] Reagents and conditions: (a) TFA/CH_2Cl_2 (1:10), 0 → 25 °C, 2 h, **58**, 98%; or HCl (concd, 15−20 μL), CH_2Cl_2, 0 → 25 °C, 2 h, **59**, 98%.

Table 5 demonstrates the application of this methodology to the synthesis of tryptamines, an important class of compounds whose structural motif is often found embedded in naturally occurring molecules and frequently used chemical building blocks. Thus, a diverse array of tryptamines (i.e., **58** and **60**−**72**, entries 1−14) was prepared by exposure of the corresponding spirocarbamates to TFA/CH_2Cl_2 (1:10, 0 → 25 °C). A series of *N*-Boc-protected tryptamines **59** and **73**−**78** was also prepared either by the method described above (concentrated HCl in CH_2Cl_2 at 0 → 25 °C), or, more conveniently, through the use of more dilute TFA in CH_2Cl_2 (1:100), as summarized in Table 5 (entries 1, 3−6, 8, and 11).

The rare chlorine−lithium exchange reaction observed with ortho-chloro *N*-Boc aniline (**26**) mentioned above (Table 2, entry 13), apparently facilitated by the ortho-directing effect of the NLiBoc group, inspired us to attempt selective bromine−lithium exchange on ortho,para-dibromo *N*-Boc aniline (**79**) as shown in Scheme 7. After some experimentation, it was found that treatment of **79** in ether at −10 °C with 1.1 equiv of MeLi followed by sequential addition of 1.2 equiv of *n*-BuLi (at −30 °C), $LaCl_3$·2LiCl (at −70 °C), and *N*-Boc-protected pyrrolidin-3-one (**5**) (−70 → 25 °C), and exposure to catalytic amounts of *t*-BuOK in THF at 70 °C furnished the bromo-substituted spirocycle **81** in 71% overall yield, presumably through the intermediacy of dilithiated species **80**. When subjected to the developed tryptamine forming conditions (*t*-BuOK, TIPSCl; LDA; TFA), the latter compound afforded bromotryptamine **82** in 70% yield. Although bromine−lithium and iodine−lithium exchange reactions to generate ortho-lithiated ArNLiBoc species are known,[14] to the best of our knowledge the regioselective bromine−lithium exchange reported here is unprecedented. Its usefulness to chemical synthesis is apparent, considering the easy access to the starting dibromo *N*-Boc aniline derivatives and the further manipulations of the product that can be easily imagined.

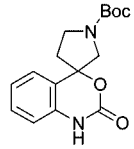
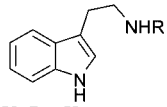
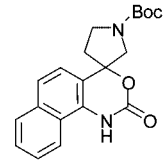
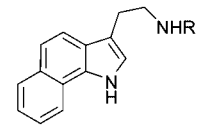
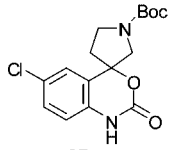
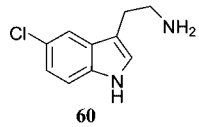
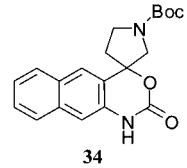
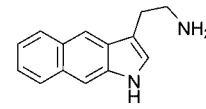
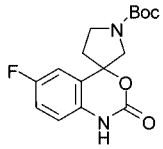
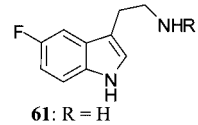
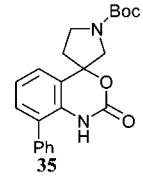
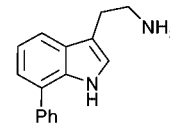
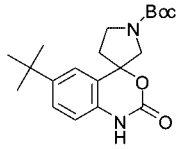
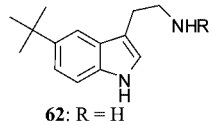
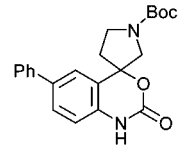
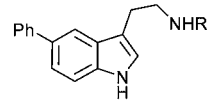
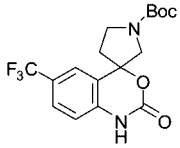
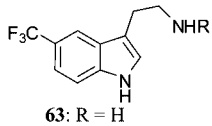
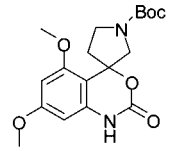
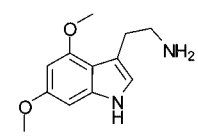
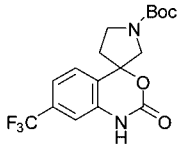
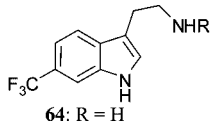
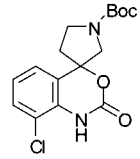
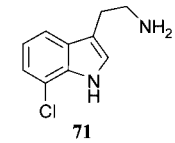
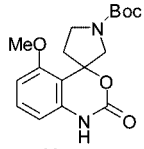
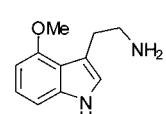
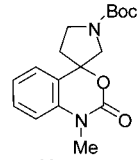
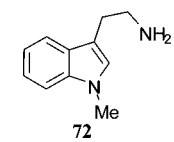
Attempts to apply our fragmentation protocol to the corresponding piperidine derivatives (i.e., **42**, **44**−**50**, Table 3) failed to yield the corresponding homotryptamines (i.e., **85**, Scheme 8). Instead, it was found that capping the carbamate moiety of **42** with BnBr in the presence of KHMDS, followed by treatment with excess of KHMDS, led to formation of the corresponding *N*-Bn-protected piperidinol (**84**) in high yield (Scheme 8).

Applications of the Developed Synthetic Technologies. In a further twist of the developed synthetic technology and taking advantage of the described hydrogen− and halogen−lithium exchange reactions, we reasoned that we could selectively prepare regioisomeric spiroheterocycles and tryptamines starting with the same unsymmetrical *N*-Boc aniline. The successful implementation of this plan employing 3,4-methylenedioxy-substituted *N*-Boc aniline (**86**) is shown in Scheme 9. Thus, following the hydrogen−metal exchange (deprotonative exchange) [*t*-BuLi; $LaCl_3$·2LiCl; ketone **5**; *t*-BuOK cat.; TIPSCl, *t*-BuOK, LDA for fragmentation; TFA for trytamine formation], spirocycle **87** (75% yield) and *N*-Boc-protected tryptamine **88** (63% yield) were obtained sequentially and in good yields. The observed selectivity was expected on the basis of preferred lithiation at position-2 as favored by both the nitrogen and oxygen ortho-directing groups. Position-6, on the other hand, could be activated through regioselective iodination of the starting substrate, a reaction that was regioselectively brought about with I_2/Ag_2SO_4 in ethanol at −30 °C (92%). The selective iodine−lithium exchange with substrate **89** required initial deprotonation of the carbamate group with MeLi, since using other organometallic reagents (e.g., *t*-BuLi, *n*-BuLi, *i*-PrMgCl·LiCl) led to considerable amounts of deiodination, as evidenced by the formation of *N*-Boc aniline **86** upon quenching. This observation can be attributed to faster halogen−metal exchange than deprotonation, followed by self-quenching of the generated ortho-metalated species by the acidic proton remaining at the NHBoc group. The initial anionic species generated by addition of MeLi to **89** was then treated with *i*-PrMgCl·LiCl[15] to effect the intended iodine−metal exchange, and the resulting dimetallic species was processed as before [$LaCl_3$·2LiCl; ketone **5**; *t*-BuOK cat.] to afford regioisomeric spiroheterocycle **90** in 78% yield. The regioisomeric tryptamine **91** was then generated from the latter compound through application of the established protocol [*t*-BuOK, TIPSCl; LDA; TFA, 75% yield].

As another application of the developed synthetic methodology, we describe here an expedient synthesis of 6,7-dimethoxy-1-methyltryptamine (**97**), a building block used by Corey in his elegant synthesis of aspidophytine[16] (Scheme 10). Thus, 2,3-dimethoxy aniline (**92**) was initially converted to iodide **93** by a three-step procedure involving iodination with ICl,[17] followed by *N*-Boc protection (Boc_2O, 4-DMAP, CH_2Cl_2; then *t*-BuOH,

(14) Fleming, I.; Loreto, M. A.; Wallace, I. H. M. *J. Chem. Soc., Perkin Trans. I* **1986**, 349–359.
(15) Krasovskiy, A.; Knochel, P. *Angew. Chem., Int. Ed.* **2004**, *43*, 3333–3336.
(16) He, F.; Bo, Y.; Altom, J. D.; Corey, E. J. *J. Am. Chem. Soc.* **1999**, *121*, 6771–6772.
(17) Mejia-Oneto, J. M.; Padwa, A. *Org. Lett.* **2006**, *8*, 3275–3278.

Table 5. Synthesis of Tryptamines

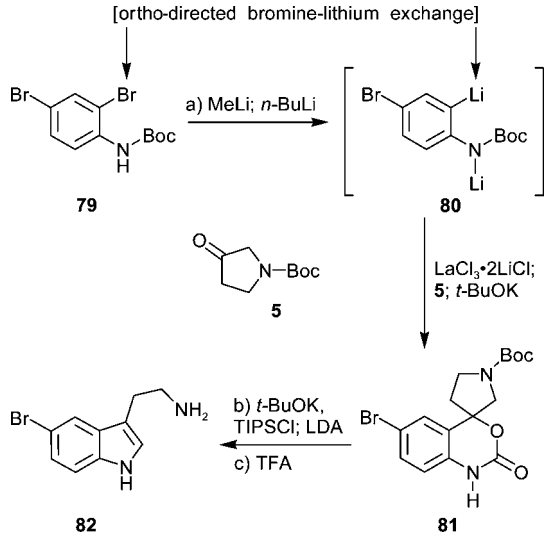
Entry	Spiroheterocycle	Tryptamine[a]	Yield[b] (%)	Entry	Spiroheterocycle	Tryptamine[a]	Yield[b] (%)
1	 **13**	 **58**: R = H **59**: R = Boc	76 77	8	 **33**	 **66**: R = H **77**: R = Boc	41 48
2	 **27**	 **60**	80	9	 **34**	 **67**	65
3	 **28**	 **61**: R = H **73**: R = Boc	71 81	10	 **35**	 **68**	83
4	 **29**	 **62**: R = H **74**: R = Boc	66 72	11	 **36**	 **69**: R = H **78**: R = Boc	87 92
5	 **30**	 **63**: R = H **75**: R = Boc	68 74	12	 **37**	 **70**	41
6	 **31**	 **64**: R = H **76**: R = Boc	77 80	13	 **38**	 **71**	84
7	 **32**	 **65**	84	14	 **39**	 **72**	65

[a] Reactions were carried out on 0.1−0.2 mmol scale. [b] Yield of isolated products from procedures using TFA.

reflux)[18] and methylation (NaH, MeI), in 37% overall yield. A more expedient and efficient process was developed for the preparation of this iodide when we discovered that both the Boc and the Me groups could be introduced in one pot [Boc_2O, 4-DMAP (cat.), THF; then NaH, MeI] and prior to iodination; the latter reaction was then carried out with I_2 in the presence of Ag_2SO_4 in EtOH at −30 °C. This three-bond forming process proceeded in 92% overall yield, providing ready access to the required *N*-Boc aniline **93**. *N*-Boc aniline **93** was then subjected to halogen−metal exchange with *i*-PrMgCl·LiCl[15] in THF at −70 °C (2 h) and then transmetalation with $LaCl_3$·2LiCl (−70 °C, 1 h)[5] before quenching with ketone **5** to afford tertiary alcohol **94** in 78% yield. The standard *t*-BuOK-catalyzed procedure for forming the spiroheterocycle in this case gave a rather low yield (35%) of the desired product **95**. This compound, however, could be obtained in 96% yield from alcohol **94** through the carefully monitored action of TFA in CH_2Cl_2 at 0 °C. The presence of the Me group (as opposed to H) on the nitrogen atom within the molecule apparently had an impact on these events and also influenced the subsequent conversion of spirocycle **95** to enamine **96** and, hence, tryptamine

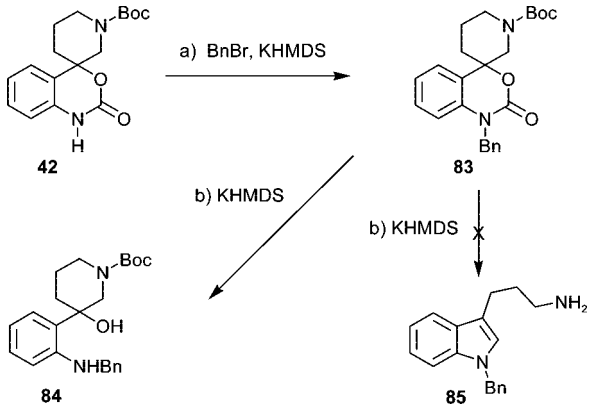
(18) Knoelker, H.-J.; Braxmeier, T.; Schlechtingen, G. *Angew. Chem., Int. Ed.* **1995**, *34*, 2497–2500.

Scheme 7. Synthesis of Bromo-Substituted Spirocycle **81** and Tryptamine **82**[a]



[a] Reagents and conditions: (a) MeLi (1.5 M in ether, 1.1 equiv), Et_2O, −10 °C, 0.5 h; then *n*-BuLi (1.5 M in ether, 1.2 equiv), Et_2O, −50 °C, 2 h; then $LaCl_3$•2LiCl (0.33 M in THF, 1.1 equiv), −70 °C, 5 min; then **5** (1.0 M in THF, 1.2 equiv), −70 → 25 °C, 1 h; then *t*-BuOK (0.1 equiv), THF, 70 °C, 4 h, **81**, 71%; (b) *t*-BuOK (1.2 equiv), TIPSCl (1.2 equiv), THF, 25 °C, 1 h; then LDA (1.0 M in THF, 5.0 equiv), −50 → −30 °C, 2 h; (c) TFA/CH_2Cl_2 (1:10), 0 → 25 °C, 2 h, **82**, 70% over the two steps.

Scheme 8. Attempted Fragmentation of Spiropiperidine **42** to Homotryptamine **85**[a]



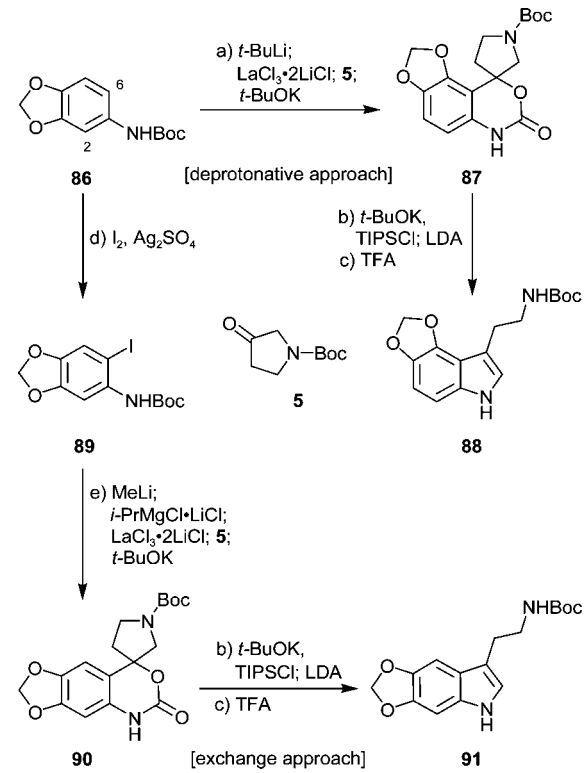
[a] Reagents and conditions: (a) KHMDS (0.5 M in toluene, 2.0 equiv), BnBr (2.0 equiv), THF, −40 → 23 °C, 2 h, 91%; (b) KHMDS (0.5 M in toluene, 5.0 equiv), −50 → 0 °C, 2 h, 83%.

97. Thus, with no hydrogen present on its carbamate moiety, **95** required no capping, and, therefore, direct exposure to LDA induced its rupture to intermediate **96** (92% yield), which was converted to the targeted tryptamine **97** (96% yield) by treatment with TFA at 0 → 25 °C.

Inspired by the successes of this project in constructing heterocycles of type **III**, we developed an alternative and expedient entry into the synthesis of the anti-HIV/AIDS drug efavirenz (**1**, Figure 1). The published process[19] for the manufacture of this reverse transcriptase inhibitor starts with *N*-Boc 4-chloroaniline (**15**, Scheme 11), involves cyclopropyl acetylene, and proceeds through three steps. Shown in Scheme 10, our modified synthesis of efavirenz from the *N*-Boc aniline

(19) Radesca, L. A.; Lo, Y. S.; Moore, J. R.; Pierce, M. E. *Synth. Commun.* **1997**, *27*, 4373–4384.

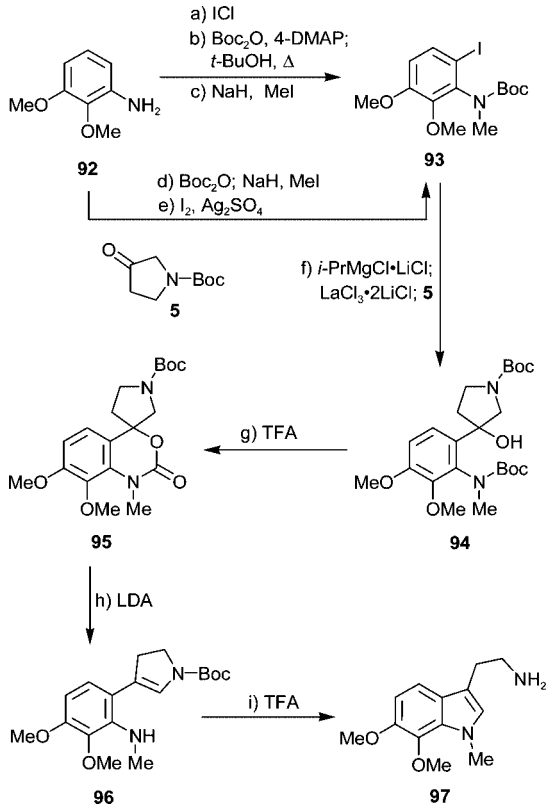
Scheme 9. Synthesis of Regioisomeric Spirocycles **87** and **90** and Tryptamines **88** and **91** Through the Complementary Deprotonative and Exchange Approaches[a]



[a] Reagents and conditions: (a) *t*-BuLi (1.7 M in pentane, 2.4 equiv), Et_2O, −10 °C, 4 h; then $LaCl_3$•2LiCl (0.33 M in THF, 1.1 equiv), −70 °C, 5 min; then **5** (1.0 M in THF, 1.2 equiv), −70 → 25 °C, 1 h; then *t*-BuOK (0.1 equiv), THF, 70 °C, 4 h, **87**, 75% overall yield; (b) *t*-BuOK (1.2 equiv), TIPSCl (1.2 equiv), THF, 25 °C, 1 h; then LDA (1.0 M in THF, 5.0 equiv), −50 → −30 °C, 2 h; (c) TFA/CH_2Cl_2 (1:100), 0 → 25 °C, 2 h, **88**, 63% over two steps; **91**, 75% over two steps; (d) Ag_2SO_4 (1.1 equiv), I_2 (1.05 equiv), EtOH, −30 °C, 3 h, **89**, 92%; (e) MeLi (1.5 M in ether, 1.05 equiv.), THF, −20 °C, 1 h; then *i*-PrMgCl•LiCl (1.0 M in THF, 1.1 equiv), THF, −70 °C, 2 h; then $LaCl_3$•2LiCl (0.33 M in THF, 1.1 equiv), −70 °C, 1 h; then **5** (1 M in THF, 1.0 equiv), −70 → 25 °C, 1 h; then *t*-BuOK (0.1 equiv), THF, 70 °C, 4 h, **90**, 78% overall yield.

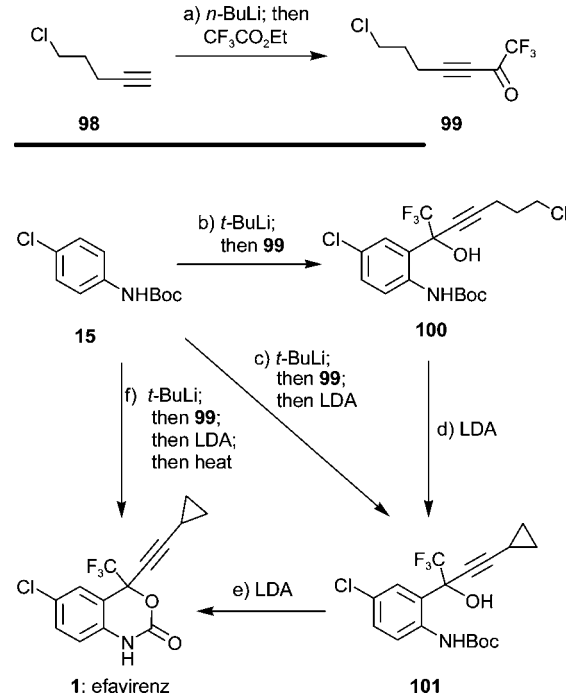
also requires three steps that could easily be combined in one pot. Thus, 5-chloropentyne (**98**) was converted to trifluoroketone **99** in high yield by generating its lithio anion with *n*-BuLi in toluene (−10 °C) and quenching it with trifluoromethyl acetate (96% yield) as shown in Scheme 11. Addition of this trifluoroketone (−60 °C) to bis-metalated 4-chloro-*N*-Boc aniline **15** (*t*-BuLi, ether, −15 °C) followed by addition of excess of LDA (−25 °C) led, upon standard workup, to the known cyclopropyl[19] *N*-Boc intermediate **101** in 71% yield, presumably through the intermediacy of the trilithiated species of **100**. Exposure of the latter intermediate to LDA in refluxing toluene according to the known procedure[19] furnished efavirenz in 95% yield. Intermediate **100** could be isolated in 82% yield before the addition of the third equivalent of base, upon standard workup. This intermediate could be subsequently converted to **101** by treatment with LDA (5.0 equiv, THF) in 94% yield. A one-pot procedure from 4-chloro *N*-Boc aniline **15** involving sequential addition of *t*-BuLi (2.2 equiv), trifluoroketone **99** (0.9 equiv), LDA (6.0 equiv), and heating (toluene, reflux) also proved successful, furnishing efavirenz (**1**) in 38% overall yield. Starting with ketone **99**, however, and proceeding via isolated **101** as described above resulted in improvement in the yield of efavirenz to 68% over three steps from **15**. This process has

Scheme 10. Construction of Corey's Aspidophytine Tryptamine (**97**)[a]



[a] Reagents and conditions: (a) ICl (1.1 equiv), $CHCl_3$; (b) Boc_2O (1.2 equiv), 4-DMAP (1.0 equiv), CH_2Cl_2, 25 °C, 2 h; then reflux in *t*-BuOH, 6 h; (c) NaH (1.5 equiv), MeI (2.0 equiv), THF, 25 °C, 2 h, **93**, 37% over three steps; (d) Boc_2O (1.2 equiv), 4-DMAP (0.01 equiv), THF, 25 °C, 12 h; then NaH (3.0 equiv), MeI (3.0 equiv); (e) Ag_2SO_4 (1.10 equiv), I_2 (1.05 equiv), EtOH, −30 °C, 3 h, **93**, 92% over two steps; (f) *i*-PrMgCl•LiCl (1.0 M in THF, 1.1 equiv), THF, −70 °C, 2 h; then $LaCl_3$•2LiCl (0.33 M in THF, 1.1 equiv), −70 °C, 1 h; then **5** (1.0 M in THF, 1.0 equiv), −70 → 25 °C, 1 h, **94**, 78%; (g) TFA (0.1 equiv), CH_2Cl_2, 0 °C, 1 h, **95**, 96%; (h) LDA (1.0 M in THF, 1.1 equiv), −50 → −30 °C, 3 h, **96**, 92%; (i) TFA (0.1 equiv), CH_2Cl_2, 0 → 25 °C, 2 h, **97**, 96%.

Scheme 11. Synthesis of Efavirenz **1**[a]



[a] Reagents and conditions: (a) *n*-BuLi (2.5 M in hexanes, 1.0 equiv), toluene, −10 °C, 0.5 h; then CF_3CO_2Et (1.0 equiv), −30 → 25 °C, 1.5 h, **99**, 96%; (b) *t*-BuLi (1.5 M in pentane, 2.1 equiv), Et_2O, −15 °C, 2 h; then **99** (0.9 equiv), −60 °C, 1 h, **100**, 82%; (c) *t*-BuLi (1.5 M in pentane, 2.1 equiv), Et_2O, −15 °C, 2 h; then **99** (0.9 equiv), −60 °C, 1 h; then LDA (1.0 M in THF, 6.0 equiv), −25 °C, 12 h, **101**, 71%; (d) LDA (1.0 M in THF, 5.0 equiv), −25 °C, 3 h, **101**, 94%; (e) LDA (1.0 M in THF, 2.0 equiv), toluene, reflux, 1 h, **1**, 95%; (f) *t*-BuLi (1.5 M in pentane, 2.2 equiv), Et_2O, −15 °C, 2 h; then **99** (0.9 equiv), −60 °C, 1 h; then LDA (1.0 M in pentane, 6.0 equiv), −10 °C, 3 h; toluene, reflux, 1 h, **1**, 38%.

the obvious virtues of brevity and stability of both starting materials **15** and **99**. Its main advantage, however, lies in the convenient handling of the trifluoro component (**99**), which does not suffer from the volatility of the cyclopropyl acetylene employed in previous processes.[19]

Conclusion

The described synthetic technologies expand the uses of anilines and their derivatives as versatile starting materials for chemical synthesis and offer rapid access to novel heterocycles, including spirosystems and tryptamines, all relevant molecular entities to biology and medicine. The expediency and efficiency of these metalation-based processes, combined with their flexibility to produce selectively different regioisomeric products, recommend them as valuable synthetic tools. Further applications of this chemistry to the construction of both natural and designed molecules are anticipated, and so are variations and extensions of the reported methods.

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Supporting Information Available: Experimental procedures, spectroscopic data, and analytical data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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