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General One-Pot Reductive *gem*-Bis-Alkylation of Tertiary Lactams/Amides: Rapid Construction of 1-Azaspirocycles and Formal Total Synthesis of (±)-Cephalotaxine

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Abstract: Amides are a class of highly stable and readily available compounds. The amide functional group constitutes a class of powerful directing/activating and protecting group for C–C bond formation. Tertiary *tert*-alkylamine, including 1-azaspirocycle is a key structural feature found in many bioactive natural products and pharmaceuticals. The transformation of amides into *tert*-alkylamines generally requires several steps. In this paper, we report the full details of the first general method for the direct transformation of tertiary lactams/amides into *tert*-alkylamines. The method is based on in situ activation of amide with triflic anhydride/2,6-di-*tert*-butyl-4-methylpyridine (DTBMP), followed by successive addition of two organometallic reagents of the same or different kinds to form two C–C bonds. Both alkyl and functionalized organometallic reagents and enolates can be used as the nucleophiles. The method displayed excellent 1,2- and good 1,3-asymmetric induction. Construction of 1-azaspirocycles from lactams required only two steps or even one-step by direct spiroannelation of lactams. The power of the method was demonstrated by a concise formal total synthesis of racemic cephalotaxine.

Keywords: alkylation · C–C bond formation · lactams · reduction · synthetic methods

Introduction

Simplicity is one of the major pursuits of organic synthesis.[1] The development of general synthetic methods using simple and stable starting materials[2] and multicomponent reactions leading to the formation of two or more carbon–carbon bonds in a one-pot process[3] are two powerful strategies directed at this goal. Tertiary *tert*-alkylamine, particularly 1-azaspirocyclic motif **A** (Figure 1), is a salient structural feature of many bioactive natural products and medicinal agents. Representative bioactive alkaloids containing 1-azaspirocycles are shown in Figure 1.[4] Although much effort has been made to construct such structural motif,[5,6] the transformation of lactams and amides into the corresponding *tert*-alkylamines by one-pot reductive bis-alkylation with different organometallic reagents (Scheme 1) is both a highly desirable and a challenging objective.[6] The merit of this transformation is also linked to the high stability of lactams/amides, the powerful directing ability of lactams/amides for metallation[7] and C–H activation,[8] as well as the ready availability of both lactams/amides[9] and Grignard/organolithium reagents.[10]

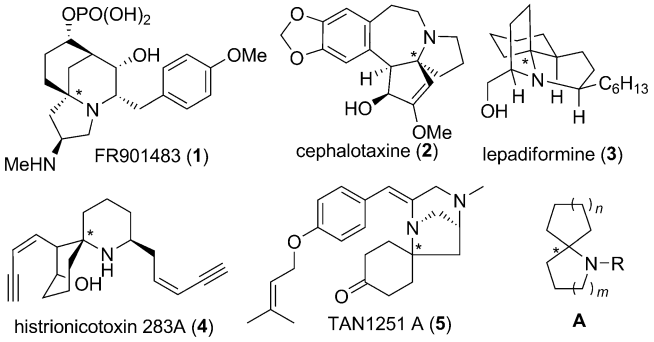
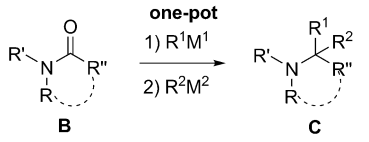


Figure 1. Selected alkaloids containing the 1-azaspirocyclic motif **A**.



Scheme 1. One-pot transformation of lactams/amides to *tert*-alkylamines with cleavage of the C=O bond and the formation of two C–C bonds.

The challenges for the one-pot reductive bis-alkylation of an amide to give an α-*tert*-alkylamine are threefold: first, the low reactivity of an amide requires the use of highly reactive organometallic reagents as the nucleophiles and harsh reaction conditions; second, the chemoselective formation

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of an iminium ion intermediate instead of a more probable ketone; third, chemoselective and stereoselective addition of two different nucleophiles to form a new chiral centre at the α-carbon to the nitrogen atom. Due to these formidable challenges, only direct reductive dimethylation,[11] diallylation[12] of lactams and cyclopropanation (intramolecular Kulinkovich–de Meijere reactions)[13] of amides have been reported. To achieve the desired transformation, three indirect tactics have been developed.

The first one involves the conversion of lactams to lactim ethers, however, the method is limited to the introduction of two same alkyl groups to lactams.[14] The second tactic is based on activation of amide by conversion to *N*-carbamoyl lactam derivatives, followed by stepwise transformations such as organometallic reagents addition and α-amidoalkylation of the resulting *N*-acyliminium ion precursors.[4,6] The third one, developed by Murai[15] and Renaud,[16] consists of transforming amides/lactams into thioamide or selenoamide derivatives, followed by in situ activation by using *S*-methylation and the addition of organometallic reagents. On the basis of the latter work, Renaud and co-workers have thus established a flexible approach to 1-azaspirocycles.[16]

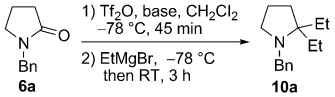
To develop a more convenient and less noxious general method, the direct use of readily available lactams and amides is highly desirable (Scheme 1). In this regard, de Meijere and co-workers recently reported a Ti(O-*i*Pr)$_4$/trimethylsilyl chloride (TMSCl)-mediated addition to formamides, but their method is restricted to *N*,*N*-dialkylformamides.[17]

In connection with our longstanding interest in the synthesis of bioactive alkaloids[18] and the development of related synthetic methodologies,[19] we have embarked on a program to develop a general one-pot method for the direct conversion of lactams and amides into tertiary *tert*-alkylamines.[20,21] We now report the full account of this investigation, which includes the application of this method to the synthesis of 1-azaspirocycles and a formal racemic synthesis of alkaloid cephalotaxine (**2**).

Results and Discussion

Reductive bis-alkylation of tertiary lactams/amides: We first investigated the reductive bis-alkylation of lactams by introduction of two same alkyl groups. To achieve the required one-pot reaction under mild conditions, triflic anhydride (Tf_2O)[22] was selected as an amide activator.[23] As demonstrated by many Tf_2O-mediated transformations,[22] the addition of a base additive is usually necessary. Thus, a screening of base additives was undertaken with lactam **6a** as the substrate, Tf_2O as the activating reagent, and EtMgBr as the nucleophile. In the event, Tf_2O (1.2 equiv) was added to a dichloromethane solution of lactam **6a** (1.0 equiv) and base additive (1.2 equiv) at −78 °C. After stirring for 45 min, EtMgBr (3.0 equiv) was added, and the mixture was stirred at RT for 3 h. The results are summarized in Table 1. As can be seen from Table 1, among the bases tested (triethylamine, Hünig base, pyridine, 2,6-lutidine, 2-chloropyridine, 2-fluropyridine, and 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP),[22d,24] DTBMP afforded the best result, providing the desired 2,2-diethylpyrrolidine **10a** in 87% yield (Table 1, entry 7). The success with DTBMP may be attributed to the appropriate basicity and low nucleophilicity of DTBMP as well as the low electrophilicity of the plausible pyridinium ion intermediate.

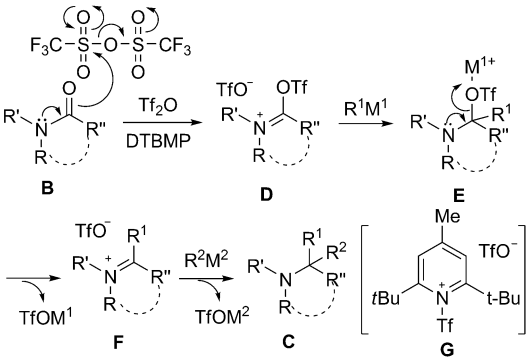
Table 1. Screen of base additives for the direct reductive diethylation of lactam **6a**.[a]



Entry	Base	Product yield[%][b]
1	Et_3N	9
2	iPr_2NEt	5
3	pyridine	20
4	2-chloropyridine	38
5	2-fluoropyridine	15
6	2,6-lutidine	57
7	DTBMP	87
8	none	63

[a] Reaction conditions (procedure A): 1) lactam **6a** (1.0 equiv), base (1.2 equiv), Tf_2O (1.2 equiv), CH_2Cl_2, −78 °C, 45 min; 2) EtMgBr (3.0 equiv), −78 °C, then RT, 3 h; [b] Yield of the isolated product. Bn = benzyl; Tf_2O = trifluoromethanesulfonic anhydride; DTBMP = 2,6-di-*tert*-butyl-4-methylpyridine.

It is worth noting that a reasonable yield (63%) was also obtained in the absence of base additive (Table 1, entry 8). The result made us have a reconsideration of the mechanism of the reaction. In our preliminary communication,[20] the pyridinium intermediate **G** (Scheme 2) was suggested as a plausible intermediate. The fact here, however, seemed to preclude the role of DTBMP as a nucleophile to first react with triflic anhydride. Indeed, it has been reported that due to its steric hindrance, DTBMP does not react with triflic anhydride to generate the reactive pyridinium intermediate **G**.[22a] Thus, although the exact role of DTBMP is not yet clear at this stage, a new plausible mechanism for the Tf_2O-activated addition of organometallic reagents to lactams and



Scheme 2. Proposed reaction mechanism.

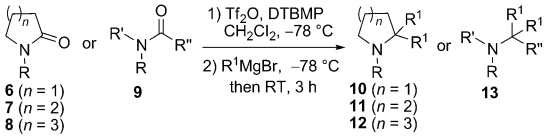
amides is proposed as shown in Scheme 2. The amide carbonyl reacts with triflic anhydride to form highly electrophilic triflyloxyiminium intermediate **D**, which reacts with one molecule of R^1M^1 to give *O*-triflyl aminal **E**. The subsequent elimination of $^-$OTf, assisted by the nitrogen lone pair and metal cation, leads to the formation of iminium ion **F**, which is trapped by a second molecule of nucleophile (R^2M^2) to give amine **C**.

We next investigated the scope of the reaction. Successive treatment of lactam **6a** with Tf_2O/DTBMP (−78 °C, 45 min) and *n*-BuMgBr (3.0 equiv) gave the desired amine **10b** in 83 % yield (Table 2, entry 1). Use of BnMgBr as the Grignard reagent produced amine **10c** in 71 % (Table 2, entry 2). Similarly, reductive alkylation of lactam **7** and **8** with EtMgBr, *n*-BuMgBr and BnMgBr produced the corresponding dialkylated cyclic amines **11a–12c** in 60–81 % (Table 2, entries 3–8). Mention should be made that to ensure complete lactam activation, the activation time may be prolonged to 2 h, or the reaction temperature may rise from −78 to 0 °C before cooling back to −78 °C for Grignard reagent addition.

The method was successfully extended to the reductive bis-alkylation of amides. Reductive dialkylation of amide **9a** with EtMgBr and BnMgBr yielded smoothly the desired amines **13a** and **13b** in 86 and 90 % yield, respectively (Table 2, entries 9 and 10). Reductive diphenylation of *N,N*-dimethylformamide gave the desired amine in 93 % yield (Table 2, entry 11). The dialkylation reaction of sterically hindered amide **9c** with BnMgBr afforded the dibenzylated amine **13d** in 81 % yield (Table 2, entry 12).

It is worth mentioning that higher yields were obtained with amides than lactams. This may be ascribed to the easier formation of activation intermediates from amides than lactams.

Table 2. Scope of the Tf_2O-activated direct reductive dialkylation of lactams and amides.[a]

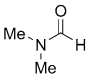
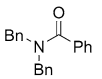
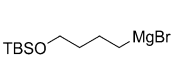
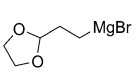
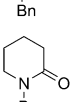
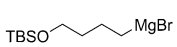
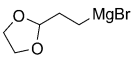


6 (*n* = 1)
7 (*n* = 2)
8 (*n* = 3)

9

10 (*n* = 1)
11 (*n* = 2)
12 (*n* = 3)

13

Entry	Substrate		R^1MgX	Product yield [%][b]	Entry	Substrate		R^1MgX		Product yield [%][b]
1		**6a**	*n*-BuMgBr	**10b** (83)	11		**9b**	PhMgBr		**13c** (93)
2		**6a**	BnMgBr	**10c** (71)	12		**9c**	BnMgBr		**13d** (81)
3		**7**	EtMgBr	**11a** (74)	13		**6a**			**10d** (85)
4		**7**	*n*BuMgBr	**11b** (70)	14		**6a**		**14**	**10e** (64)
5		**7**	BnMgBr	**11c** (60)	15		**6a**		**15**	**10f** (76)
6		**8**	EtMgBr	**12a** (81)	16		**6a**			**10g** (trace)
7		**8**	*n*BuMgBr	**12b** (80)	17		**6a**			**10h** (trace)
8		**8**	BnMgBr	**12c** (68)	18		**7**			**11d** (75)
9		**9a**	EtMgBr	**13a** (86)	19		**7**		**14**	**11e** (60)
10		**9a**	BnMgBr	**13b** (90)	20		**7**		**15**	**11f** (78)

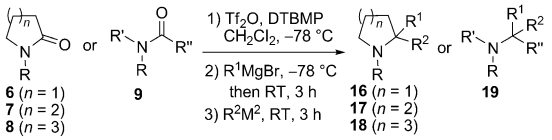
[a] Reaction conditions (Procedure A): 1) amide (1.0 equiv), DTBMP (1.2 equiv), Tf_2O (1.2 equiv), CH_2Cl_2, −78 °C, 45 min; 2) R^1MgBr (3.0 equiv), −78 °C, then RT, 3 h; [b] Yield of the isolated product. TBS = *tert*-butyldimethylsilyl.

The methodology was further extended to the addition of functionalized Grignard reagents. As can be seen from Table 2, not only allylmagnesium bromide (entries 13 and 18) and TBSO-containing Grignard reagent **14** (entries 14 and 19) can be used, but also acetal-containing Grignard reagent **15** can be tolerated (entries 15 and 20). However, the reaction failed with less reactive vinylmagnesium bromide and ethynylmagnesium bromide (Table 2, entries 16 and 17).

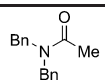
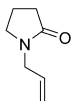
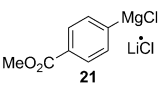
Reductive bis-alkylation with two different organometallic reagents: We next turned our attention to the more demanding and also more challenging task, namely, the introduction of two different substituents by sequential reaction with two different organometallic reagents. For this purpose, a CH_2Cl_2 solution of lactam **6a** and DTBMP (1.2 equiv) was successively treated with 1.2 molar equivalents of Tf_2O (−78 °C, 45 min), 1.0 molar equivalent of ethylmagnesium bromide (−78 °C, then warmed-up to RT, 1 h), and 2.0 molar equivalents of *n*-butylmagnesium bromide (−78 °C, 3 h). Pyrrolidine **16a** bearing two different alkyl groups (Et, *n*-Bu) was obtained in 75% yield, along with 9% of pyrrolidine **10b** arising from the addition of two molecules of *n*-butylmagnesium bromide (Table 3, entry 1). To avoid the dialkylation with the first Grignard reagent, it is beneficial to add the first Grignard reagent as a $\leq$0.5 M solution. Similarly, use of benzylmagnesium bromide and allylmagnesium bromide as the second nucleophile provided the desired bis-alkylation products **16b** and **16c** in 71 and 74% yield, respectively (Table 3, entries 2 and 3). Organolithium reagents such as *n*-butyllithium can also be used as the second addition nucleophiles (Table 3, entry 4). The sequential one-pot reductive bis-alkylation with two different organometallic reagents can be extended to other lactams as well as amides (Table 3, entries 5–9).

Employment of functionalized nucleophiles as the second addition nucleophiles was also investigated. To our delight, sp^2- and sp-hybridized carbon nucleophiles, such as vinylmagnesium bromide, ethynylmagnesium bromide, and phenylethynyllithium, could serve as effective second addition nucleophiles (Table 3, entries 10–12), although they had previously failed to give the reductive dialkylation products (Table 2, entries 16 and 17). In these cases, products arising from the addition of two molecules of the first Grignard reagent were not detected. In view of enolates as versatile nucleophiles, we also carried out the one-pot sequential reductive bis-alkylation of 2-pyrrolidinone **6a** with ethylmagnesium bromide and lithium enolate **20**. The desired pyrrolidine **16f** was produced in 73% yield (Table 3, entry 13). Knochel's functional arylmagnesium reagents,[25] a new class of versatile nucleophiles, were also tested. Thus, successive treatment of 2-pyrrolidinone **6a** with triflic anhydride, isopropylmagnsium bromide, and Knochel's functional aryl-

Table 3. Tf_2O-Activated sequential addition of two organometallic reagents to lactams/amides.[a]



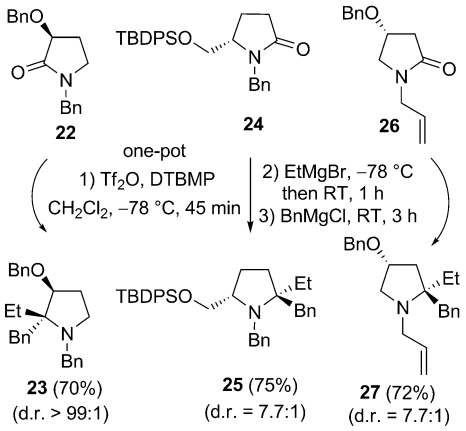
6 (*n* = 1) **7** (*n* = 2) **8** (*n* = 3) | **9** | **16** (*n* = 1) **17** (*n* = 2) **18** (*n* = 3) | **19**

Entry	Substrate		R^1MgBr	R^2M^2	Product yield [%][b]	Entry	Substrate		R^1MgBr	R^2M^2	Product yield [%][b]
1		**6a**	EtMgBr	*n*-BuMgBr	**16a** (75) **10b** (9)	8		**9a**	*n*BuMgBr	EtMgBr	**19a** (78) **13a** (8)
2		**6a**	EtMgBr	BnMgBr	**16b** (71) **10c** (8)	9		**9a**	*n*BuMgBr	BnMgBr	**19b** (74) **13b** (7)
3		**6a**	EtMgBr	allylMgBr	**16c** (74) **10d** (8)	10		**7**	*n*BuMgBr		**17d** (65)
4		**6a**	EtMgBr	*n*BuLi	**16a** (76) **10b** (9)	11		**6b**	EtMgBr		**16d** (72)
5		**7**	*n*BuMgBr	EtMgBr	**17a** (66) **11a** (6)	12		**6a**	EtMgBr		**16e** (70)
6		**7**	EtMgBr	BnMgBr	**17b** (63) **11c** (4)	13		**6a**	EtMgBr		**16f** (73)
7		**7**	EtMgBr	AllylMgBr	**17c** (68) **11d** (7)	14		**6a**	*i*PrMgBr		**16g** (70)

[a] Reaction conditions (Procedure B): 1) amide (1.0 equiv), DTBMP (1.2 equiv), Tf_2O (1.2 equiv), CH_2Cl_2, −78 °C, 45 min; 2) R^1MgBr (1.0 equiv), −78 °C, then RT, 1 h; 3) R^2M^2, RT, 3 h; [b] Yield of the isolated product.

magnesium reagent **21**, prepared in situ from methyl *p*-iodobenzoate,[25] furnished the expected pyrrolidine **16g** in 70% yield (Table 3, entry 14).

1,3-Asymmetric induction in the reductive bis-alkylation: To explore the use of this method for asymmetric synthesis, the reductive bis-alkylation of the chiral ring systems **22**, **24**, and **26** have been investigated. Following the procedure for the sequential reductive bis-alkylation of lactams/amides, (*S*)-3-benzyloxy-2-pyrrolidinone **22**[26] was treated successively with triflic anhydride, ethylmagnsium bromide, and benzylmagnesium chloride to produce pyrrolidine **23** as the only diastereomer in 70% yield (Scheme 3). The Tf_2O-activated



Scheme 3. 1,2 and 1,3-asymmetric induction in the sequential reductive bis-alkylation of lactams.

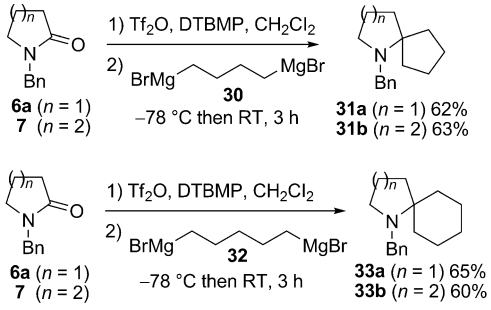
sequential ethylation and benzylation of (*S*)-glutamic acid derived 2-pyrrolidinone **24**[27] also proceeded with good 1,3-asymmetric induction, yielding pyrrolidine **25** and its diastereomer in a ratio of 7.7:1 (HPLC) with 75% combined yield. Similarly, the Tf_2O-activated sequential ethylation and benzylation of (*S*)-malimide derived 2-pyrrolidinone **26**[28] exhibited good 1,3-asymmetric induction, giving pyrrolidine **27** and its diastereomer in 7.7: 1 ratio (HPLC) with 72% combined yield.

The configurations of the newly formed quaternary stereocenters in pyrrolidines **23**, **25**, and **27** were determined by using nuclear Overhauser effect spectroscopy (NOESY) experiments. In all cases, the second alkyl groups (benzyl group) are *trans* to the substituents originally existing in the starting materials. The results are in agreement with the proposed mechanism shown in Scheme 2. Namely, to avoid the steric hindrance, the second Grignard reagent (benzylmagnesium chloride) approaches the cyclic iminium ion intermediate **F** from the direction opposite to the existing substituent at the ring.

Two-step construction of 1-azaspirocycles by reductive bis-alkylation and ring-closing metathesis (RCM): In view of 1-azaspirocyclic ring system **A** as a salient structural feature in many bioactive natural products[4] (Figure 1), we next turned our attention to the construction of such ring systems. Although the introduction of two functionalized side chains such as those shown in entries 14, 15, 19, and 20 in Table 2 would serve well for this purpose, we envisioned that the introduction of two olefinic side chains would afford a more concise approach by means of RCM.[29] Thus the hydrochloride salt of the reductive di-allylation product **10d** (Table 2, entry 13) was treated[12,16,30] with the Grubbs second-generation catalyst,[30] and the *N*-α-spiro-pyrrolidine **28a** was obtained in excellent yield (90%, Table 4, entry 1). Encouraged by this result, the protocol was extended to other lactams/amides and alkenyl Grignard reagents. As outlined in Table 4, the desired *N*-α-spiro-pyrrolidines were provided in good overall yields (Table 4, entries 2–8).

By varying two different alkenyl groups, the spiro-cyclic alkenes could be built with C=C double bonds located at different positions (Table 5).

Direct one-step spiroannelation of lactams: For the construction of the *N*-α-spiro ring systems, an even more direct access would be the one-pot reductive bis-alkylation of lactams by α,ω-bis-Grignard reagent.[31] Thus lactams **6a** and **7** were treated with Grignard reagent **30**, which produced the *N*-α-spiro ring systems **31a** and **31b** in 62 and 63% yield, respectively (Scheme 4). Similarly, bis-alkylation of lactams **6a** and **7** with α,ω-bis-Grignard reagent **32** afforded compounds **33a** and **33b** in 65 and 60% yield, respectively.

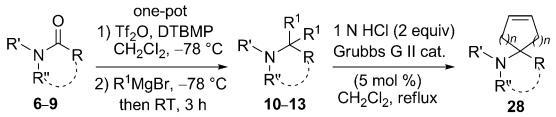


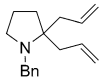
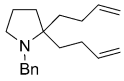
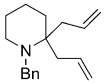
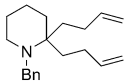
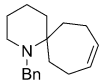
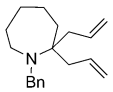
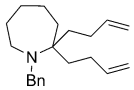
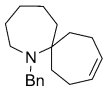
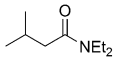
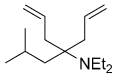
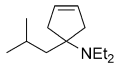
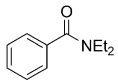
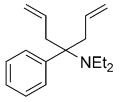
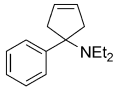
Scheme 4. One-pot approach to 1-azaspirocycles starting from lactams.

Formal synthesis of racemic cephalotaxine (2): The synthesis of racemic cephalotaxine (**2**),[32] a member of the *cephalotaxus* family of cytotoxic alkaloids,[33] was then undertaken. The requisite lactam **36** was prepared from 2-arylethanol **34** in a total yield of 65%, through succinimide formation under the Mitsunobu conditions (PPh_3, diisopropyl azodicarboxylate (DIAD), RT, 4 h),[34] followed by partial reduction of the crude succinimide **35** with sodium borohydride in $CHCl_3$/MeOH, and reductive dehydroxylation of the resulting hemiaminal (Scheme 5).

Successive treatment of lactam **36** with DTBMP (1.2 equiv), Tf_2O (1.1 equiv, CH_2Cl_2, −78 °C, 45 min), buten-

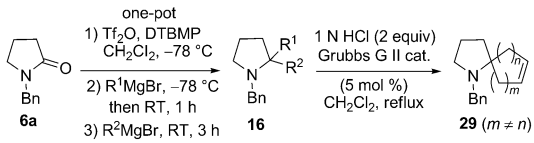
Table 4. Two-step synthesis of 1-azaspirocycles **28a–f** and aminocyclopentenes **28g** and **h** from amides/lactams.[a,b]

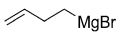
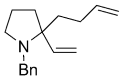
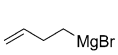


Entry	Substrate		R^1MgX	Product yield [%][c]		*N*-α-spiro-amines **28** yield [%][c]	
1		**6a**			**10d** (85)		**28a** (90)
2		**6a**			**10i** (72)		**28b** (85)
3		**7**			**11d** (75)		**28c** (91)
4		**7**			**11g** (75)		**28d** (88)
5		**8**			**12d** (77)		**28e** (91)
6		**8**			**12e** (70)		**28f** (87)
7		**9d**			**13e** (76)		**28g** (83)
8		**9e**			**13f** (65)		**28h** (87)

[a] Reaction conditions (Procedures A and D): 1) amide (1.0 equiv), DTBMP (1.2 equiv), Tf_2O (1.2 equiv), CH_2Cl_2, −78 °C, 45 min; 2) R^1MgBr (3.0 equiv), −78 °C, then RT, 3 h; [b] 1) amine (1.0 equiv), AcCl (2.0 equiv), MeOH; 2) Grubbs G II cat. (5 mol %), CH_2Cl_2, reflux, 2 h; [c] Yield of the isolated product.

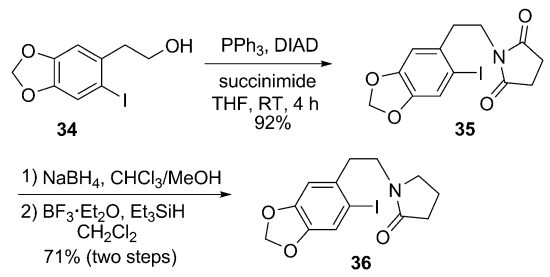
Table 5. Two step synthesis of 1-azaspirocycles **29** from lactams **6a**.[a,b]



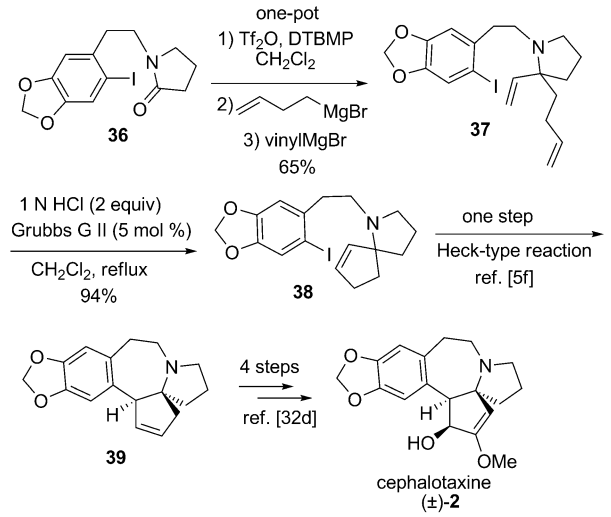
Entry	R^1MgX	R^2MgBr	Product **16** Yield [%][c]		*N*-α-spiropyrrolidines **29** [%][c]	
1				**16h** (75)		**29a** (85)
2				**16i** (71)		**29b** (89)
3				**16j** (75)		**29c** (90)

[a] Reaction conditions (Procedures B and D): 1) lactam **6a** (1.0 equiv), DTBMP (1.2 equiv), Tf_2O (1.2 equiv), CH_2Cl_2, −78 °C, 45 min; 2) R^1MgBr (1.0 equiv), −78 °C, then RT, 1 h; 3) R^2MgBr, RT, 3 h; [b] 1) amine **16** (1.0 equiv), AcCl (2.0 equiv), MeOH; 2) Grubbs G II cat. (5 mol %), CH_2Cl_2, reflux, 2 h; [c] Yield of the isolated product.

1-ylmagnesium bromide (1.0 equiv, −78 °C, then warmed up to RT, 1 h), and vinylmagnesium bromide (3.0 equiv) produced the desired pyrrolidine **37** in 65% yield (Scheme 6). Subjection of the hydrochloride salt of the dienic pyrrolidine **37** to the RCM conditions (Grubbs generation II catalyst, CH_2Cl_2, reflux, 2 h) produced the known spiro-pyrrolidine **38** in a high yield (94%). The spectral data (^1H and ^{13}C NMR spectroscopic analysis) of compound **38** are in agreement with those reported.[5f] The palladium-catalyzed Heck-type cyclization of **38** (and also the bromo analogue of **38**) to give compound **39** has been achieved by the groups of Yoshida[5f] and Tietze,[32e,f] and the conversion of **39** into cephalotaxine (**2**) has been reported by Isono and Mori.[32d] Our synthesis of compound **38** thus constitutes a formal synthesis of racemic cephalotaxine (**2**).



Scheme 5. Preparation of lactam **36**.



Scheme 6. Concise synthesis of racemic cephalotaxine (**2**).

Conclusion

By taking advantage of both the high electrophilicity of Tf_2O and excellent leaving group ability of ^-OTf, we have developed a highly efficient and general one-pot method for the synthesis of *tert*-alkylamines from lactams/amides. The advantages of this method are: 1) this is a multicomponent reaction with two C–C bond formations in one pot; 2) both lactams and amides can be used as substrates; 3) two different Grignard reagents can be used in the one-pot process; 4) both Grignard reagents and organolithium reagents can be used in the one-pot process; 5) for the second addition, either sp^3, sp^2-, or sp-hybridized carbon nucleophiles, functionalized carbon nucleophiles such as enolates, and Knochel's functional arylmagnesium reagent can be used; 6) the sequential addition afforded excellent 1,2- and 1,3-asymmetric induction in substituted γ-lactams; 7) the method provides a versatile entry to 1-azaspirocycles, a key structural feature of many bioactive alkaloids. The high stability of lactams/amides combined with the ready availability of both lactams/amides and Grignard/organolithium reagents make this a general method for the synthesis of various *tert*-alkylamines from amides and lactams. The power of this method is demonstrated by a concise formal total synthesis of racemic cephalotaxine. It is worth mentioning that this method has found applications in the synthesis of azacycles[35] and alkaloid FR901483 (**1**).[18b]

Experimental Section

General methods: Unless otherwise stated, reactions were performed in oven-dried glassware under a nitrogen atmosphere. Dichloromethane was distilled over calcium hydride under a nitrogen atmosphere. Ether and THF were distilled over sodium benzophenone ketyl under a nitrogen atmosphere. Silica gel (300–400 mesh) was used for flash column chromatography, eluting (unless otherwise stated) with ethyl acetate (EtOAc)/hexane. Melting points were uncorrected. Infrared spectra were measured using film KBr pellet techniques. ^1H NMR spectra were recorded in $CDCl_3$ with tetramethylsilane as an internal standard. Chemical shifts are expressed in δ (ppm) units downfield from TMS. Mass spectra were obtained using electrospray ionization and an FT-ICR analyzer (ESI-MS) for high resolution mass spectra (HRMS). Tf_2O was distilled over phosphorous pentoxide and was stored for use within a week. All the Grignard reagents were titrated before use.[36] All other commercially available compounds were used as received.

General procedure for the Tf_2O-activated one-pot reductive di-alkylation of lactams/amides: *General procedure A*: *use of only one kind of organometallic reagent*: Tf_2O (1.2 mmol) was added dropwise to a cooled (−78 °C) CH_2Cl_2 (10 mL) solution of a lactam/amide (1.0 mmol) and DTBMP (1.2 mmol). After the resulting mixture was stirred at −78 °C for 45 min, a solution of an organometallic reagent (3.0 mmol) was added dropwise. The mixture was allowed warming slowly to RT and stirred for 3 h. The reaction was quenched with a saturated ammonium chloride solution and extracted with CH_2Cl_2 (5×4 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (EtOAc/hexane) on silica gel to give the desired amine.

General procedure for the Tf_2O-activated one-pot reductive bis-alkylation of lactams/amides: *General procedure B*: *use of two different organometallic reagents*: Tf_2O (1.2 mmol) was added dropwise to a cooled (−78 °C) CH_2Cl_2 (10 mL) solution of a lactam/amide (1.0 mmol) and DTBMP (1.2 mmol). After the resulting mixture was stirred at −78 °C for 45 min, a solution of an organometallic reagent (1.0 mmol) was added dropwise. The mixture was allowed warming slowly to RT and stirred for 1 h. A solution of another organometallic reagent (2.0 mmol) was added dropwise to this mixture and then stirred for 3 h. The reaction was quenched with a saturated ammonium chloride solution and extracted with CH_2Cl_2 (5×4 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (EtOAc/hexane) on silica gel to give the desired amine.

General procedure for the direct synthesis of 1-azaspirocycles from lactams/amides: *General procedure C*: *use of α,ω-dinucleophilic organometallic reagent*: Tf_2O (1.2 mmol) was added dropwise to a cooled (−78 °C) CH_2Cl_2 (10 mL) solution of a lactam (1.0 mmol) and DTBMP (1.2 mmol). After being stirred at −78 °C for 45 min, a solution of α,ω-dinucleophilic organometallic reagent (1.0 mmol) was added dropwise. The mixture was allowed to warm slowly to RT and stirred for 3 h. The reaction was quenched with saturated ammonium chloride solution and extracted with CH_2Cl_2 (5×4 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (EtOAc/hexane) on silica gel to give the desired 1-azaspirocycle.

General procedure for the ring closing metathesis of dienic amines: *General procedure D*: Acetyl chloride (71 μL, 1 mmol) was added at 0 °C to MeOH (4 mL). The mixture was stirred for 5 min and a dienic amine (0.5 mmol) was added. After being stirred at RT for 30 min, the resulting mixture was concentrated under reduced pressure. The residue was used in the next step without further purification.

To a solution of the foregoing residue (0.5 mmol estimated based on a 100% yield) in CH_2Cl_2 (50 mL) at RT was added Grubbs II catalyst (21 mg, 0.025 mmol), and the mixture was heated at reflux for 2 h. The reaction was quenched with a saturated aqueous solution of $NaHCO_3$ and extracted with CH_2Cl_2 (5×10 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (EtOAc/hexane) on silica gel to give the corresponding 1-azaspirocycle.

1-Benzyl-2,2-bis(4-(*tert*-butyldimethylsilyloxy)butyl)pyrrolidine (10e): Following the general procedure A, addition of Grignard Reagent **14** to 1-benzylpyrrolidin-2-one (120 mg, 0.69 mmol) gave, after flash column chromatography on silica gel (eluent: EtOAc/hexane = 1:20), pyrrolidine **10e** (235 mg, yield: 64%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.06 (s, 12H), 0.90 (s, 18H), 1.32–1.54 (m, 12H), 1.58–1.70 (m, 4H), 2.60 (t, J = 6.4 Hz, 2H), 3.60 (s, 2H), 3.63 (t, J = 6.4 Hz, 4H), 7.15–7.33 ppm (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = −5.2 (4C), 18.4, 20.8 (2C), 21.9, 26.0 (6C), 33.0, 33.9 (2C), 35.4, 50.8, 52.2, 63.3, 64.5, 126.3, 128.1 (2C), 128.2 (2C), 141.4 ppm; IR (film): $\tilde{\nu}$ = 3064, 3027, 2953, 2928, 2857, 2791, 1471, 1462, 1255, 1102, 836, 774 cm^{-1}; HRMS (ESI) m/z calcd for $C_{31}H_{60}NO_2Si_2$: 534.4157 $[M+H]^+$; found: 534.4165.

1-Benzyl-2,2-bis(4-(*tert*-butyldimethylsilyloxy)butyl)piperidine (11e): Following the general procedure A, addition of Grignard reagent **14** to 1-benzylpiperidin-2-one (130 mg, 0.69 mmol) gave, after flash column chromatography on silica gel (eluent: EtOAc/hexane = 1:40), piperidine **11e** (226 mg, yield: 60%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.04 (s, 12H), 0.90 (s, 18H), 1.30–1.54 (m, 16H), 1.68–1.78 (m, 2H), 2.38 (t, J = 5.2 Hz, 2H), 3.52 (s, 2H), 3.61 (t, J = 6.4 Hz, 4H), 7.15–7.33 ppm (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = −5.2 (4C), 18.3, 19.8 (2C), 20.8, 26.0 (6C), 26.3, 31.5, 33.4, 33.9 (2C), 45.8, 52.8, 57.6, 63.2 (2C), 126.2, 128.0 (2C), 128.1 (2C), 141.5 ppm; IR (film): $\tilde{\nu}$ = 3062, 3025, 2948, 2929, 2857, 2974, 1470, 1255, 1101, 836, 775 cm^{-1}; HRMS (ESI): m/z calcd for $C_{32}H_{62}NO_2Si_2$: 548.4314 $[M+H]^+$; found: 548.4317.

2,2-Bis(2-(1,3-dioxolan-2-yl)ethyl)-1-benzylpyrrolidine (10f): Following the general procedure A, addition of Grignard Reagent **15** to 1-benzylpyrrolidin-2-one (140 mg, 0.80 mmol) gave, after flash column chromatography on silica gel (eluent: EtOAc/hexane = 1:5), pyrrolidine **10f** (220 mg, yield: 76%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.54–1.75 (m, 10H), 1.78–1.89 (m, 2H), 2.61 (t, J = 6.4 Hz, 2H), 3.62 (s, 2H), 3.82–3.90 (m, 4H), 3.92–4.00 (m, 4H), 4.86 (t, J = 4.7 Hz, 2H), 7.16–7.34 ppm (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.8, 29.0 (4C), 32.6, 50.4, 51.8, 63.6, 64.8 (2C), 64.9 (2C), 105.1 (2C), 126.4, 128.1 (2C), 128.2 (2C), 141.0 ppm; IR (film): $\tilde{\nu}$ = 2953, 2882, 1454, 1408, 1363, 1141, 1033, 943, 731, 702 cm^{-1}; HRMS (ESI): m/z calcd for $C_{21}H_{32}NO_4$: 362.2326 $[M+H]^+$; found: 362.2324.

2,2-Bis(2-(1,3-dioxolan-2-yl)ethyl)-1-benzylpiperidine (11f): Following the general procedure A, addition of Grignard Reagent **15** to 1-benzylpiperidin-2-one (151 mg, 0.80 mmol) gave, after flash column chromatography on silica gel (eluent: EtOAc/hexane = 1:5), piperidine **11f** (234 mg, yield: 78%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.40–1.54 (m, 8H), 1.64–1.80 (m, 4H), 1.86–1.96 (m, 2H), 2.41 (t, J = 5.7 Hz, 2H), 3.56 (s, 2H), 3.79–3.88 (m, 4H), 3.92–3.98 (m, 4H), 4.84 (t, J = 4.8 Hz, 2H), 7.15–7.36 ppm (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.5, 26.1, 27.2 (2C), 28.0 (2C), 31.3, 45.6, 52.5, 56.8, 64.8 (2C), 64.8 (2C), 105.1 (2C), 126.2, 127.9 (2C), 128.1 (2C), 141.0 ppm; IR (film): $\tilde{\nu}$ = 3025, 2940, 2878, 2795, 1452, 1406, 1139, 1037, 972, 943, 732, 700 cm^{-1}; HRMS (ESI): m/z calcd for $C_{22}H_{34}NO_4$: 376.2482 $[M+H]^+$; found: 376.2486.

2,2-Diallyl-1-benzylpyrrolidine (10d): Following the general procedure A, addition of allylmagnesium bromide to 1-benzylpyrrolidin-2-one (140 mg, 0.8 mmol) gave, after flash column chromatography on silica gel (eluent: EtOAc/hexane = 1:20), pyrrolidine **10d** (141 mg, yield: 85%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.61–1.78 (m, 4H), 2.22 (dd, J = 13.9, 7.8 Hz, 2H), 2.30 (dd, J = 13.9, 6.8 Hz, 2H), 2.62 (t, J = 7.0 Hz, 2H), 3.67 (s, 2H), 5.03–5.12 (m, 4H), 5.87–6.01 (m, 2H), 7.16–7.35 ppm (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.2, 32.6, 39.9 (2C), 50.8, 52.1, 64.6, 116.9 (2C), 126.5, 128.1 (2C), 128.3 (2C), 135.8 (2C), 140.9 ppm; IR (film): $\tilde{\nu}$ = 3073, 2965, 2792, 1637, 1494, 1453, 1154, 1027, 910, 732, 697 cm^{-1}; HRMS (ESI): m/z calcd for $C_{17}H_{24}N$ $[M+H]^+$: 242.1903; found: 242.1915.

1-Benzyl-2,2-di(but-3-en-1-yl)pyrrolidine (10i): Following the general procedure A, addition of 3-butenylmagnesium bromide to 1-benzylpyrrolidin-2-one (120 mg, 0.68 mmol) gave, after flash column chromatography on silica gel (eluent: EtOAc/hexane = 1:20), pyrrolidine **10i** (132 mg, yield: 72%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.46–1.61 (m, 4H), 1.62–1.76 (m, 4H), 2.01–2.14 (m, 2H), 2.20–2.32 (m, 2H), 2.62 (t, J = 6.5 Hz, 2H), 3.62 (s, 2H), 4.92–5.06 (m, 2H), 5.03 (dd, J = 17.1, 1.7 Hz, 2H), 5.80–5.92 (m, 2H), 7.18–7.36 ppm (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.9, 28.9, 32.8, 34.6, 50.6, 52.0, 64.2, 113.9 (2C), 126.4, 128.1 (2C), 128.2 (2C), 139.6 (2C), 141.1 ppm; IR (film): $\tilde{\nu}$ = 3058, 2931, 1601, 1450, 735, 696 cm^{-1}; HRMS (ESI): m/z calcd for $C_{19}H_{28}N$: 270.2216 $[M+H]^+$; found: 270.2224.

2,2-Diallyl-1-benzylpiperidine (11d): Following the general procedure A, addition of allylmagnesium bromide to 1-benzylpiperidin-2-one (129 mg, 0.68 mmol) gave, after flash chromatography on silica gel (eluent: EtOAc/hexane = 1:40), piperidine **11d** (139 mg, yield: 75%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.42–1.57 (m, 6H), 2.11 (ddt, J = 14.2, 7.6, 1.2 Hz, 2H), 2.41 (t, J = 5.5 Hz, 2H), 2.60 (ddt, J = 14.2, 7.0, 1.2 Hz, 2H), 3.61 (s, 2H), 5.01–5.09 (m, 4H), 5.88–6.02 (m, 2H), 7.17–7.39 ppm (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.5, 26.2, 32.3, 38.0, 46.0, 52.9, 58.2, 116.8 (2C), 126.3, 128.1 (2C), 128.2 (2C), 135.3 (2C), 140.9 ppm; IR (film): $\tilde{\nu}$ = 3073, 2930, 2794, 1450, 1382, 909, 725, 696 cm^{-1}; HRMS (ESI): m/z calcd for $C_{18}H_{26}N$: 256.2060 $[M+H]^+$; found: 256.2067.

1-Benzyl-2,2-di(but-3-enyl)piperidine (11g): Following the general procedure A, addition of 3-butenylmagnesium bromide to 1-benzylpiperidin-2-one (129 mg, 0.68 mmol) gave, after flash chromatography on silica gel (eluent: EtOAc/hexane = 1:40), piperidine **11g** (144 mg, yield: 75%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.36–1.51 (m, 6H), 1.52–1.57 (m, 2H), 1.78–1.92 (m, 2H), 2.01–2.21 (m, 4H), 2.41 (t, J = 5.2 Hz, 2H), 3.55 (s, 2H), 4.89–4.95 (m, 2H), 4.96–5.04 (ddd, J = 17.1, 3.5, 1.5 Hz, 2H), 5.77–5.91 (m, 2H), 7.16–7.36 ppm (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.7, 26.2, 27.9, 31.3, 32.8, 45.8, 52.6, 57.4, 113.9 (2C), 126.3, 127.9 (2C), 128.2 (2C), 139.7 (2C), 141.1 ppm; IR (film): $\tilde{\nu}$ = 3075, 2936, 2795, 1639, 1451, 1067, 907, 696 cm^{-1}; HRMS (ESI): m/z calcd for $C_{20}H_{30}N$ $[M+H]^+$: 284.2373; found: 284.2379.

2,2-Diallyl-1-benzylazepane (12d): Following the general procedure A, addition of allylmagnesium bromide to 1-benzylazepan-2-one (112 mg, 0.55 mmol) gave, after flash column chromatography on silica gel (eluent: EtOAc/hexane = 1:80), azepane **12d** (114 mg, yield: 77%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.27–1.33 (m, 2H), 1.37–1.45 (m, 2H), 1.62–1.73 (m, 4H), 2.29 (dd, J = 14.0, 7.8 Hz, 2H), 2.44 (ddt, J = 14.0, 7.2, 1.2 Hz, 2H), 2.61–2.68 (m, 2H), 3.82 (s, 2H), 5.01–5.10 (m, 4H), 5.91–6.04 (m, 2H), 7.16–7.45 ppm (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.7, 30.0, 31.9, 37.2, 42.8, 48.7, 54.8, 61.2, 116.9 (2C), 126.4, 127.9 (2C), 128.4 (2C), 136.1 (2C), 142.3 ppm; IR (film): $\tilde{\nu}$ = 2975, 2926, 1493, 1450, 909, 697 cm^{-1}; HRMS (ESI): m/z calcd for $C_{19}H_{28}N$: 270.2216 $[M+H]^+$; found: 270.2220.

1-Benzyl-2,2-di(but-3-en-1-yl)azepane (12e): Following the general procedure A, addition of 3-butenylmagnesium bromide to 1-benzylazepan-2-one (140 mg, 0.69 mmol) gave, after flash chromatography on silica gel (eluent: EtOAc/hexane = 1:80), azepane **12e** (143 mg, yield: 70%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.30–1.37 (m, 2H), 1.39–1.47 (m, 2H), 1.55–1.75 (m, 8H), 2.05–2.25 (m, 4H), 2.61–2.68 (m, 2H), 3.74 (s, 2H), 4.90–5.06 (m, 4H), 5.76–5.89 (m, 2H), 7.17–7.44 ppm (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 23.1, 29.2, 30.0, 31.4, 37.2, 37.5, 48.2, 54.2, 60.1, 113.9 (2C), 126.3, 128.0 (2C), 128.4 (2C), 139.6 (2C), 142.4 ppm; IR (film): $\tilde{\nu}$ = 2928, 2852, 1493, 1451, 908, 697 cm^{-1}; HRMS (ESI): m/z calcd for $C_{21}H_{32}N$: 298.2529 $[M+H]^+$; found: 298.2528.

***N,N*-Diethyl-4-isobutylhepta-1,6-dien-4-amine (13e)**: Following the general procedure A, addition of allylmagnesium bromide to *N,N*-diethyl-3-methylbutanamide (116 mg, 0.74 mmol) gave, after flash column chromatography on silica gel (eluent: EtOAc/hexane = 1:10), diene **13e** (125 mg, yield: 76%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.94 (d, J = 6.7 Hz, 6H), 1.01 (t, J = 7.1 Hz, 6H), 1.33 (d, J = 5.3 Hz, 2H), 1.75–1.88 (m, 1H), 2.22 (dd, J = 14.4, 7.2 Hz, 2H), 2.32 (dd, J = 14.4, 7.2 Hz,

2H), 2.67 (q, $J=7.1$ Hz, 4H), 4.98–5.07 (m, 4H), 5.82–5.94 ppm (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=17.9$ (2C), 23.7, 25.1 (2C), 40.5 (2C), 43.7 (2C), 44.4, 62.4, 116.5 (2C), 136.3 ppm (2C); IR (film): $\tilde{\nu}=2959$, 2925, 1611, 1258, 910 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{15}H_{30}N$: 224.2373 $[M+H]^+$; found: 224.2374.

***N,N*-Diethyl-4-phenylhepta-1,6-dien-4-amine (13f)**: Following the general procedure A, addition of allylmagnesium bromide to *N,N*-diethylbenzamide (110 mg, 0.62 mmol) gave, after flash chromatography on silica gel (eluent: EtOAc/ hexane = 1:30), diene **13f** (98 mg, yield: 65%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=1.01$ (t, $J=7.1$ Hz, 6H), 2.60 (dd, $J=13.6$, 6.9 Hz, 2H), 2.65 (q, $J=7.1$ Hz, 4H), 2.71 (dd, $J=13.6$, 7.4 Hz, 2H), 4.94–5.05 (m, 4H), 5.56–5.66 (m, 2H), 7.14–7.50 ppm (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=18.1$ (2C), 40.9 (2C), 45.3 (2C), 65.8, 117.1 (2C), 125.9, 127.4 (2C), 127.5 (2C), 135.7 (2C), 147.3 ppm; IR (film): $\tilde{\nu}=3074$, 2966, 2924, 1637, 1470, 1444, 911, 699 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{17}H_{26}N$: 244.2060 $[M+H]^+$; found: 244.2057.

1-Benzyl-2-(but-3-en-1-yl)-2-vinylpyrrolidine (16h): Following the general procedure B, sequential addition of 3-butenylmagnesium bromide and vinylmagnesium bromide to 1-benzylpyrrolidin-2-one (123 mg, 0.7 mmol) gave, after flash column chromatography on silica gel (eluent: EtOAc/ hexane = 1:20), pyrrolidine **16h** (127 mg, yield: 75%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=1.61$–1.90 (m, 6H), 2.06–2.25 (m, 2H), 2.39–2.48 (m, 1H), 2.79–2.87 (m, 1H), 3.31 (d, $J=13.3$ Hz, 1H), 3.82 (d, $J=13.3$ Hz, 1H), 4.95–5.01 (m, 1H), 5.03–5.15 (m, 2H), 5.23 (dd, $J=10.9$, 1.2 Hz, 1H), 5.80–5.97 (m, 2H), 7.20–7.38 ppm (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=21.1$, 29.1, 33.9, 35.0, 50.7, 52.8, 66.3, 113.9 (2C), 126.5, 128.1 (2C), 128.4 (2C), 139.4, 140.2, 140.9 ppm; IR (film): $\tilde{\nu}=3077$, 3026, 2961, 2922, 2797, 1640, 1602, 1450, 912, 697 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{17}H_{24}N$: 242.1903 $[M+H]^+$; found: 242.1909.

2-Allyl-1-benzyl-2-(but-3-enyl)pyrrolidine (16i): Following the general procedure B, sequential addition of 3-butenylmagnesium bromide and allylmagnesium bromide to 1-benzylpyrrolidin-2-one (123 mg, 0.7 mmol) gave, after flash column chromatography on silica gel (eluent: EtOAc/ hexane = 1:20), pyrrolidine **16i** (127 mg, yield: 71%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=1.48$–1.80 (m, 6H), 2.02–2.31 (m, 4H), 2.48–2.60 (m, 1H), 2.64–2.74 (m, 1H), 3.56 (d, $J=13.3$ Hz, 1H), 3.71 (d, $J=13.3$ Hz, 1H), 4.91–5.11 (m, 4H), 5.80–6.01 (m, 2H), 7.17–7.35 ppm (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=21.5$, 28.7, 32.6, 34.8, 39.8, 50.7, 52.0, 64.4, 113.9, 116.9, 126.5, 128.1 (2C), 128.2 (2C), 136.0, 139.6, 141.0 ppm; IR (film): $\tilde{\nu}=3022$, 2922, 1602, 1452, 1362, 1028, 696 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{18}H_{26}N$:256.2060 $[M+H]^+$; found: 256.2068.

1-Benzyl-2-(pent-4-en-1-yl)-2-vinylpyrrolidine (16j): Following the general procedure B, sequential addition of pent-4-en-1-ylmagnesium bromide and vinylmagnesium bromide to 1-benzylpyrrolidin-2-one (436 mg, 2.49 mmol) gave, after flash column chromatography on silica gel (eluent: EtOAc/hexane = 1:100), pyrrolidine **16j** (475 mg, yield: 75%) as a pale yellow oil.; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=1.36$–1.56 (m, 3H), 1.65–1.89 (m, 5H), 2.08 (dd, $J=14.0$, 7.2 Hz, 2H), 2.34–2.44 (m, 1H), 2.74–2.82 (m, 1H), 3.26 (d, $J=13.2$ Hz, 1H), 3.78 (d, $J=13.2$ Hz, 1H), 4.93–5.22 (m, 4H), 5.74–5.88 (m, 2H), 7.17–7.33 ppm (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=21.0$, 24.1, 33.9, 34.5, 35.3, 50.7, 52.9, 66.4, 113.8, 114.5, 126.5, 128.1 (2C), 128.4 (2C), 139.0, 140.3, 141.0 ppm; IR (film): $\tilde{\nu}=3066$, 3023, 2971, 2902, 2794, 1637, 1493, 1451, 1126, 910, 725, 697 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{18}H_{26}N$: 256.2060 $[M+H]^+$; found: 256.2060.

1-Benzyl-1-azaspiro[4.4]non-7-ene (28a): Following the general procedure D, the Grubbs generation II (21 mg, 0.025 mmol) -catalyzed RCM of azepine hydrochloride salt **10d** (139 mg, 0.5 mmol) gave, after flash column chromatography on silica gel (eluent: EtOAc/hexane = 1:5), spiro-pyrrolidine **28a** (96 mg, yield: 90%) as a pale-yellow oil.; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=1.73$–1.85 (m, 2H), 1.90–1.99 (m, 2H), 2.21–2.34 (m, 2H), 2.58–2.68 (m, 4H), 3.48 (s, 2H), 5.75 (s, 2H), 7.21–7.41 ppm (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=20.5$, 39.3, 40.3, 50.4, 53.3, 70.8, 126.5, 128.1 (2C), 128.6 (2C), 129.3 (2C), 140.6 ppm; IR (film): $\tilde{\nu}=3052$, 2950, 2841, 2790, 1619, 1611, 1432, 1363, 1260, 1027, 947, 698 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{15}H_{20}N$: 214.1590 $[M+H]^+$; found: 214.1600.

1-Benzyl-1-azaspiro[4.6]undec-8-ene (28b): Following the general procedure D, the Grubbs generation II (17 mg, 0.02 mmol) -catalyzed RCM of azepine hydrochloride salt **10i** (122 mg, 0.4 mmol) gave, after flash column chromatography on silica gel (eluent: EtOAc/ hexane = 1:5), spiro-pyrrolidine **28b** (82 mg, yield: 85%) as a pale-yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=1.56$–1.84 (m, 8H), 2.01–2.13 (m, 2H), 2.14–2.28 (m, 2H), 2.62 (t, $J=6.8$ Hz, 2H), 3.60 (s, 2H), 5.79 (s, 2H), 7.15–7.36 ppm (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=20.7$, 24.6, 29.7, 34.0, 34.5, 50.6, 52.7, 66.3, 126.4, 128.1 (2C), 128.4 (2C), 131.9 (2C), 141.3 ppm; IR (film): $\tilde{\nu}=3021$, 2923, 2848, 2789, 1598, 1493, 1452, 1363, 1113, 737, 698 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{17}H_{24}N$: 242.1903 $[M+H]^+$; found: 242.1909.

6-Benzyl-6-azaspiro[4.5]dec-2-ene (28c): Following the general procedure D, the Grubbs generation II (21 mg, 0.025 mmol) -catalyzed RCM of azepine hydrochloride salt **11d** (146 mg, 0.5 mmol) gave, after flash column chromatography on silica gel (eluent: EtOAc/hexane = 1:5), spiro-piperidine **28c** (103 mg, yield: 91%) as a pale-yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=1.43$–1.54 (m, 4H), 1.67–1.73 (m, 2H), 2.15–2.24 (m, 2H), 2.32–2.40 (m, 2H), 2.56–2.65 (m, 2H), 3.31 (s, 2H), 5.67 (s, 2H), 7.15–7.38 ppm (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=22.0$, 26.3, 40.5, 48.2, 54.5, 65.1, 126.3, 128.0 (2C), 128.3 (2C), 129.3 (2C), 141.2 ppm; IR (film): $\tilde{\nu}=3041$, 2925, 2848, 1451, 730, 696 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{16}H_{22}N$: 228.1747 $[M+H]^+$; found: 228.1751.

1-Benzyl-1-azaspiro[5.6]dodec-9-ene (28d): Following the general procedure D, the Grubbs generation II (17 mg, 0.02 mmol) -catalyzed RCM of azepine hydrochloride salt **11g** (128 mg, 0.4 mmol) gave, after flash column chromatography on silica gel (eluent: EtOAc/hexane = 1:5), spiro-piperidine **28d** (90 mg, yield: 88%) as a pale-yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=1.41$–1.52 (m, 4H), 1.58–1.64 (m, 2H), 1.76–1.93 (m, 4H), 2.05–2.16 (m, 2H), 2.17–2.29 (m, 2H), 2.44 (t, $J=5.4$ Hz, 2H), 3.63 (s, 2H), 5.62–5.71 (m, 2H), 7.15–7.40 ppm (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=20.3$, 24.4 (2C), 25.5, 33.4, 46.5, 52.7, 57.7, 126.3, 128.0 (2C), 128.2 (2C), 130.8 (2C), 142.1 ppm; IR (film): $\tilde{\nu}=2926$, 2851, 2792, 1492, 1451, 1130, 732, 697 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{18}H_{26}N$: 256.2060 $[M+H]^+$; found: 256.2067.

6-Benzyl-6-azaspiro[4.6]undec-2-ene (28e): Following the general procedure D, the Grubbs generation II (13 mg, 0.015 mmol) -catalyzed RCM of azepine hydrochloride salt **12d** (92 mg, 0.3 mmol) gave, after flash column chromatography on silica gel (eluent: EtOAc/hexane = 1:10), spiro-azepane **28e** (66 mg, yield: 91%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=1.37$–1.45 (m, 2H), 1.48–1.55 (m, 2H), 1.66–1.74 (m, 2H), 1.76–1.82 (m, 2H), 2.16–2.29 (m, 2H), 2.47–2.64 (m, 4H), 3.49 (s, 2H), 5.65 (s, 2H), 7.15–7.44 ppm (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=22.9$, 29.7, 31.2, 43.8, 44.0, 48.3, 55.4, 68.2, 126.3, 127.9 (2C), 128.4 (2C), 129.4 (2C), 142.1 ppm; IR (film): $\tilde{\nu}=3048$, 2926, 1451, 1261, 697 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{17}H_{24}N$: 242.1903 $[M+H]^+$; found: 242.1903.

1-Benzyl-1-azaspiro[6.6]tridec-10-ene (28f): Following the general procedure D, the Grubbs generation II (6 mg, 0.0075 mmol) -catalyzed RCM of azepine hydrochloride salt **12e** (50 mg, 0.15 mmol) gave, after flash column chromatography on silica gel (eluent: EtOAc/hexane = 1:10), spiro-azepane **28f** (35 mg, yield: 87%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=1.29$–1.35 (m, 2H), 1.43–1.50 (m, 2H), 1.60–1.72 (m, 6H), 1.86–1.94 (m, 2H), 2.04–2.24 (m, 4H), 2.58 (t, $J=5.3$ Hz, 2H), 3.76 (s, 2H), 5.61–5.71 (m, 2H), 7.15–7.45 ppm (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=21.9$, 24.7, 29.6, 30.7, 35.0, 37.2, 46.8, 53.8, 60.9, 126.2, 127.9 (2C), 128.4 (2C), 130.9 (2C), 142.8 ppm; IR (film): $\tilde{\nu}=3017$, 2925, 1450, 1260, 734, 697 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{19}H_{28}N$: 270.2216 $[M+H]^+$; found: 270.2218.

***N,N*-Diethyl-1-isobutylcyclopent-3-enamine (28g)**: Following the general procedure D, the Grubbs generation II (7 mg, 0.008 mmol) -catalyzed RCM of azepine hydrochloride salt **13e** (41 mg, 0.16 mmol) gave, after flash column chromatography on silica gel (eluent: EtOAc/hexane = 1:2), aminocyclopentene **28g** (26 mg, yield: 83%) as a pale-yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=0.91$ (d, $J=6.7$ Hz, 6H), 1.06 (t, $J=7.2$ Hz, 6H), 1.38 (d, $J=5.4$ Hz, 2H), 1.59–1.70 (m, 1H), 2.20–2.30 (m, 2H), 2.41–2.65 (m, 6H), 5.63 ppm (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=16.7$, 24.4, 25.3, 43.5, 45.0, 46.6, 69.9, 129.7 ppm; IR (film): $\tilde{\nu}=2956$,

2923, 1615, 1260, 798 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{13}H_{26}N$ $[M+H]^+$: 196.2060; found: 196.2062.

***N,N*-Diethyl-1-phenylcyclopent-3-enamine (28h):** Following the general procedure D, the Grubbs generation II (11 mg, 0.0135 mmol) -catalyzed RCM of azepine hydrochloride salt **13f** (75 mg, 0.27 mmol) gave, after flash column chromatography on silica gel (eluent: EtOAc/hexane = 1:10), aminocyclopentene **28h** (50 mg, yield: 87%) as a pale-yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.02 (t, J = 7.1 Hz, 6H), 2.46 (q, J = 7.1 Hz, 4H), 2.59 (d, J = 15.6 Hz, 2H), 2.80 (d, J = 15.6 Hz, 2H), 5.69 (s, 2H), 7.15–7.51 ppm (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 16.9 (2C), 42.8 (2C), 45.6 (2C), 73.5, 125.8, 126.4 (2C), 127.8 (2C), 129.2 (2C), 150.1 ppm; IR (film): $\tilde{\nu}$ = 2965, 2925, 2856, 1467, 1295, 700, 671 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{15}H_{22}N$ $[M+H]^+$: 216.1747; found: 216.1750.

1-Benzyl-1-azaspiro[4.4]non-6-ene (29a): Following the general procedure D, the Grubbs generation II catalyst (14 mg, 0.0165 mmol) -catalyzed RCM of azepine hydrochloride salt **16h** (91 mg, 0.33 mmol) gave, after flash column chromatography on silica gel (eluent: EtOAc/hexane = 1:5), spiro-pyrrolidine **29a** (60 mg, yield: 85%) as a pale-yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.64–1.72 (m, 1H), 1.74–1.84 (m, 3H), 1.85–1.94 (m, 1H), 1.99–2.08 (m, 1H), 2.30–2.42 (m, 2H), 2.50–2.58 (m, 1H), 2.64–2.73 (m, 1H), 3.36 (d, J = 13.1 Hz, 1H), 3.51 (d, J = 13.1 Hz, 1H), 5.63–5.68 (m, 1H), 5.85–5.90 (m, 1H), 7.16–7.36 ppm (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.4, 29.8, 31.6, 38.3, 51.1, 53.5, 77.5, 126.4, 128.1 (2C), 128.5 (2C), 132.1, 135.3, 140.9 ppm; IR (film): $\tilde{\nu}$ = 3047.8, 2849, 2790, 1611, 1493, 1452, 732, 697 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{15}H_{20}N$: 214.1590 $[M+H]^+$; found: 214.1595.

1-Benzyl-1-azaspiro[4.5]dec-7-ene (29b): Following the general procedure D, the Grubbs generation II (15 mg, 0.018 mmol) -catalyzed RCM of azepine hydrochloride salt **16i** (105 mg, 0.36 mmol) gave, after flash column chromatography on silica gel (eluent: EtOAc/hexane = 1:5), spiro-pyrrolidine **29b** (73 mg, yield: 89%) as a pale-yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.45–1.55 (m, 1H), 1.66–1.77 (m, 5H), 1.80–1.88 (m, 1H), 2.10–2.30 (m, 3H), 2.57–2.67 (m, 1H), 2.68–2.79 (m, 1H), 3.54 (d, J = 13.1 Hz, 1H), 3.66 (d, J = 13.1 Hz, 1H), 5.55–5.75 (m, 2H), 7.18–7.35 ppm (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.8, 24.9, 29.6, 31.5, 35.1, 50.9, 52.8, 61.4, 126.3, 126.5, 126.6, 128.1 (2C), 128.5 (2C), 141.1 ppm; IR (film): $\tilde{\nu}$ = 3022, 2922, 2790, 1602, 1452, 1260, 696 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{16}H_{22}N$: 228.1747 $[M+H]^+$; found: 228.1750.

1-Benzyl-1-azaspiro[4.5]dec-6-ene (29c): Following the general procedure D, the Grubbs generation II (9 mg, 0.0105 mmol) -catalyzed RCM of azepine hydrochloride salt **16j** (61 mg, 0.21 mmol) gave, after flash column chromatography on silica gel (eluent: EtOAc/hexane = 1:5), spiro-pyrrolidine **29c** (43 mg, yield: 90%) as a pale-yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.57–1.81 (m, 8H), 1.94–2.03 (m, 2H), 2.55–2.66 (m, 1H), 2.69–2.78 (m, 1H), 3.49 (d, J = 13.3 Hz, 1H), 3.63 (d, J = 13.3 Hz, 1H), 5.54–5.62 (m, 1H), 5.75–5.85 (m, 1H), 7.16–7.35 ppm (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.2, 21.4, 25.3, 28.9, 38.4, 50.3, 53.5, 63.4, 126.4, 128.1 (2C), 128.4 (2C), 128.9, 133.9, 141.2 ppm; IR (film): $\tilde{\nu}$ = 2917, 2848, 2792, 1578, 1493, 1124, 734, 697 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{16}H_{22}N$: 228.1747 $[M+H]^+$; found: 228.1752.

1-Benzyl-1-azaspiro[4.4]nonane (31a): Following the general procedure C, addition of Grignard reagent **30** to 1-benzylpyrrolidin-2-one (174 mg, 1.0 mmol) gave, after flash column chromatography on silica gel (eluent: EtOAc/hexane = 1:50), spiro-pyrrolidine **31a** (133 mg, yield: 62%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.40–1.46 (m, 2H), 1.57–1.79 (m, 10H), 2.57 (t, J = 6.8 Hz, 2H), 3.54 (s, 2H), 7.18–7.34 ppm (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.8, 24.3 (2C), 32.0 (2C), 39.7, 51.7, 53.3, 72.2, 126.5, 128.1 (2C), 128.6 (2C), 140.8 ppm; IR (film): $\tilde{\nu}$ = 3062, 3026, 2956, 2930, 2791, 1493, 1454, 1162, 1067 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{15}H_{22}N$: 216.1747 $[M+H]^+$; found: 216.1747.

6-Benzyl-6-azaspiro[4.5]decane (31b): Following the general procedure C, addition of Grignard reagent **30** to 1-benzylpiperidin-2-one (214 mg, 1.13 mmol) gave, after flash column chromatography on silica gel (eluent: EtOAc/hexane = 1:40), spiro-piperidine **31b** (162 mg, yield: 63%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.39–1.69 (m, 12H), 1.74–1.86 (m, 2H), 2.35 (t, J = 6.7 Hz, 2H), 3.47 (s, 2H), 7.16–7.38 ppm (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.3, 25.5, 25.9 (2C), 33.6 (2C), 39.0, 48.9, 54.4, 66.6, 126.3, 128.0 (2C), 128.3 (2C), 141.5 ppm; IR (film): $\tilde{\nu}$ = 3062, 3025, 2936, 2877, 2794, 1493, 1451, 1127, 1067 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{16}H_{24}N$: 230.1903 $[M+H]^+$; found: 230.1906.

1-Benzyl-1-azaspiro[4.5]decane (33a): Following the general procedure C, addition of Grignard reagent **32** to 1-benzylpyrrolidin-2-one (218 mg, 1.24 mmol) gave, after flash column chromatography on silica gel (eluent: EtOAc/hexane = 1:30), spiro-pyrrolidine **33a** (185 mg, yield: 65%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.28–1.50 (m, 7H), 1.61–1.78 (m, 7H), 2.64 (t, J = 6.8 Hz, 2H), 3.59 (s, 2H), 7.17–7.36 ppm (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 21.0, 24.4 (2C), 26.4, 32.6 (2C), 34.3, 50.6, 52.5, 63.1, 126.4, 128.1 (2C), 128.5 (2C), 141.4 ppm; IR (film): $\tilde{\nu}$ = 3063, 3026, 2964, 2933, 2861, 2791, 1494, 1454, 1165, 1067 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{16}H_{24}N$: 230.1903 $[M+H]^+$; found: 230.1905.

1-Benzyl-1-azaspiro[5.5]undecane (33b): Following the general procedure C, addition of Grignard reagent **32** to 1-benzylpiperidin-2-one (200 mg, 1.06 mmol) gave, after flash column chromatography on silica gel (eluent: EtOAc/hexane = 1:30), spiro-piperidine **33b** (154 mg, yield: 60%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.30–1.68 (m, 16H), 2.50 (t, J = 5.4 Hz, 2H), 3.63 (s, 2H), 7.16–7.38 ppm (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.3, 22.3 (2C), 24.9, 26.6, 31.4 (2C), 32.1, 46.1, 52.0, 55.2, 126.2, 128.0 (2C), 128.2 (2C), 142.3 ppm; IR (film): $\tilde{\nu}$ = 3063, 3025, 2930, 2876, 2862, 2792, 1494, 1454, 1126, 1067 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{17}H_{26}N$: 244.2060 $[M+H]^+$; found: 224.2066.

1-(2-(6-Iodobenzo[*d*][1,3]dioxol-5-yl)ethyl)pyrrolidine-2,5-dione (35): DIAD (0.34 mL, 1.69 mmol) was added to a solution of alcohol **34** (446 mg, 1.53 mmol), PPh_3 (442 mg, 1.69 mmol), and succinimide (152, 1.53 mmol) in THF (6.0 mL) under N_2 at RT. After being stirred at RT for 4 h, the solid was filtered off and washed with Et_2O to give compound **35** (526 mg, yield: 92%) as a white solid without further purification. M.p. 212–214 °C (Et_2O); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.67 (s, 4H), 2.94 (t, J = 7.30 Hz, 2H), 3.72 (t, J = 7.30 Hz, 2H), 5.94 (s, 2H), 6.74 (s, 1H), 7.20 ppm (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 28.1 (2C), 38.1, 38.8, 87.7, 101.6, 109.6, 118.7, 134.3, 147.4, 148.7, 176.8 ppm (2C); IR (film): $\tilde{\nu}$ = 2978, 2917, 1698, 1499, 1142, 919, 757, 663 cm^{-1} HRMS (ESI): *m/z* calcd for $C_{13}H_{12}INO_4Na$: 395.9703 $[M+Na]^+$; found: 395.9708.

1-(2-(6-Iodobenzo[*d*][1,3]dioxol-5-yl)ethyl)pyrrolidin-2-one (36): $NaBH_4$ (291 mg, 7.67 mmol) was added portion-wise to a solution of cyclic imide **35** (286 mg, 0.767 mmol) in $CHCl_3$ and MeOH (40 mL) at 0 °C. The resulting suspension was stirred at 0 °C for 2 h before quenching with a saturated aqueous solution of $NaHCO_3$. After completion of the addition, the mixture was stirred for 30 min and then filtered through Celite. The filter was concentrated under reduced pressure. The residue was extracted with $CHCl_3$ (3 × 10 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was dissolved in anhydrous CH_2Cl_2 (80 mL) under nitrogen. Triethylsilane (1.21 mL, 7.67 mmol) and boron trifluoride etherate (0.28 mL, 2.30 mmol) were added dropwise at −78 °C to the resulting solution. After being stirred at −78 °C for 2 h, the reaction mixture was allowed to warm to RT and stirred overnight. The reaction was quenched with a saturated aqueous solution of $NaHCO_3$ and extracted with CH_2Cl_2 (4 × 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (eluent: EtOAc/hexane = 2:1) to give compound **36** (195 mg, yield: 71%) as a white solid. M.p. 136–138 °C (EtOAc/hexane). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.92–2.04 (m, 2H), 2.36 (t, J = 8.0 Hz, 2H), 2.84–2.91 (m, 2H), 3.33 (t, J = 7.0 Hz, 2H), 3.40–3.46 (m, 2H), 5.94 (s, 2H), 6.78 (s, 1H), 7.21 ppm (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 18.0, 31.0, 38.3, 42.9, 47.8, 87.6, 101.6, 109.7, 118.6, 134.7, 147.2, 148.6, 174.9 ppm; IR (film): $\tilde{\nu}$ = 2917, 1679, 1501, 1475, 1260, 1227, 1035, 928 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{13}H_{14}INO_3Na$: 381.9911 $[M+Na]^+$; found: 381.9917.

2-(But-3-en-1-yl)-1-(2-(6-iodobenzo[*d*][1,3]dioxol-5-yl)ethyl)-2-vinylpyrrolidine (37): Following the general procedure B, sequential addition of 3-butenylmagnesium bromide and vinylmagnesium bromide to lactam **36** (83 mg, 0.23 mmol) gave, after flash column chromatography on silica gel

(eluent: EtOAc/hexane = 1:5), pyrrolidine **37** (63 mg, yield: 65%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.42–1.52 (m, 1H), 1.65–1.84 (m, 5H), 1.91–2.06 (m, 2H), 2.29–2.39 (m, 1H), 2.54–2.64 (m, 1H), 2.65–2.86 (m, 3H), 3.14–3.22 (m, 1H), 4.85–5.05 (m, 3H), 5.12 (dd, J = 11.0, 1.4 Hz, 1H), 5.69 (dd, J = 17.6, 11.0 Hz, 1H), 5.75–5.88 (m, 1H), 5.93 (s, 2H), 6.74 (s, 1H), 7.21 ppm (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.1, 29.0, 33.7, 34.7, 40.9, 49.4, 50.9, 66.6, 87.8, 101.4, 109.7, 113.8, 113.9, 118.5, 136.8, 139.4, 139.8, 146.7, 148.3 ppm; IR (film): $\tilde{\nu}$ = 2920, 1501, 1474, 1245, 1040, 935, 912 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{19}H_{25}INO_2$: 426.0924 $[M+H]^+$; found: 426.0924.

1-(2-(6-Iodobenzo[*d*][1,3]dioxol-5-yl)ethyl)-1-azaspiro[4.4]non-6-ene (38): Following the general procedure D, the Grubbs generation II (2 mg, 0.0025 mmol) -catalyzed RCM of azepine hydrochloride salt **37** (23 mg, 0.05 mmol) gave, after flash column chromatography on silica gel (eluent: EtOAc/ hexane = 1:2), spiro-pyrrolidine **38** (17.5 mg, yield: 94%) as a pale-yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.58–1.67 (m, 1H), 1.75–1.98 (m, 5H), 2.30 (tt, J = 7.0, 2.2 Hz, 2H), 2.38–2.50 (m, 2H), 2.73–2.89 (m, 3H), 2.92–3.02 (m, 1H), 5.56 (dt, J = 5.6, 2.2 Hz, 1H), 5.80 (dt, J = 5.6, 2.3 Hz, 1H), 5.92 (s, 2H), 6.74 (s, 1H), 7.20 ppm (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.4, 29.7, 31.5, 38.2, 40.8, 50.0, 51.3, 77.7, 87.8, 101.4, 109.6, 118.5, 132.2, 134.7, 136.8, 146.7, 148.4 ppm; IR (film): $\tilde{\nu}$ = 2921, 2850, 1501, 1402, 1225, 1041, 935 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{17}H_{21}INO_2$: 398.0611 $[M+H]^+$; found: 398.0606.

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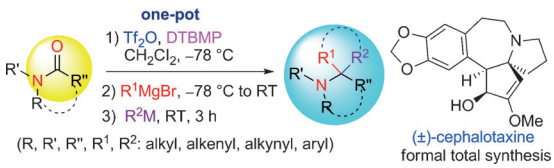

Four bonds in one pot! Cleavage of two bonds of an amide carbonyl group and replacement by two new C–C bonds can be achieved in one pot under mild conditions by using amide activation with Tf_2O. A concise formal total synthesis of racemic cephalotaxine has been accomplished by means of this methodology (see scheme; DTBMP = 2,6-di-*tert*-butyl-4-methylpyridine).

Synthetic Methods