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Sequential *N*-Acylamide Methylenation−Enamide Ring-Closing Metathesis: Construction of Benzo-Fused Nitrogen Heterocycles

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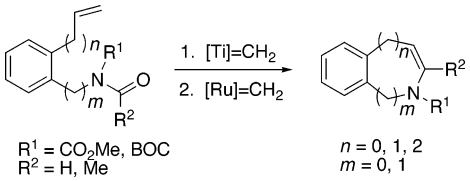

The dimethyltitanocene methylenation of *N*-acylamides derived from *ortho*-vinylanilines, *ortho*-allylaniline, and *ortho*-vinylbenzylamine provides the corresponding enamides, which upon exposure to the second generation Grubbs ruthenium catalyst give access to indoles, 1,4-dihydroquinolines, and 1,2-dihydroisoquinolines, respectively. This sequential protocol also allows the synthesis of dihydrobenzoazepines, although the ring-closing metathesis (RCM) step is complicated by the alkene isomerization processes. From certain substrates, the direct annulation is observed in the titanium-mediated step, which is likely to occur through an olefin metathesis−intramolecular olefination sequence.

Introduction

Ruthenium-catalyzed ring-closing metathesis (RCM)[1] has emerged as a powerful methodology for the construction of a great variety of nitrogen heterocycles from azadiene substrates.[2] In this context, cyclizations involving alkenyl enamides,[3] such as azadienes in which the nitrogen atom is directly connected to one of the double bonds, are particularly interesting since the resulting cyclic enamides constitute versatile moieties amenable to further functionalization.[4,5] Our interest in the development of heterocyclic annulation methodologies led us to consider the synthesis of a variety of enamide-containing benzo-fused heterocycles (indoles, 1,4-dihydroquinolines, 1,2-dihydroisoquinolines, and dihydrobenzoazepines) by RCM reactions of appropriate linear enamides. These substrates would be prepared[6] by taking advantage of olefination protocols, which, in combination with the subsequent RCM step, would make our heterocyclic targets conveniently available from alkenyl amides (Scheme 1).

Titanium-based complexes are distinctive reagents in organic synthesis due to their ability to olefinate carboxylic acid derivatives.[7] Among them, the Tebbe,[8] Takai−Utimoto,[9] Petasis (dimethyltitanocene, Cp_2TiMe_2)[10] and, more recently, Takeda[11]

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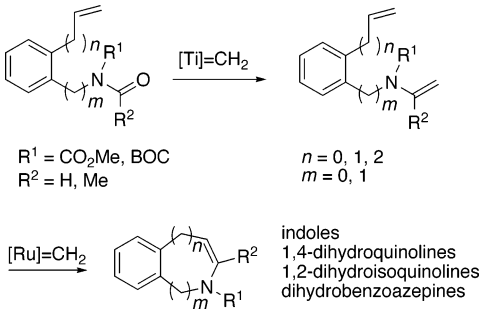
SCHEME 1. Synthetic Strategy



reagents have proven to be very effective for the olefination of esters.[12] The above olefination step has been combined with the subsequent ruthenium (or molybdene)-catalyzed RCM of the resulting enol ethers, which constitutes the key step of several brilliant approaches to cyclic enol ethers.[13] In the same context, Nicolaou[14] has reported the direct conversion of alkenyl esters to cyclic enol ethers through tandem olefination−RCM sequences promoted by both the Tebbe and Petasis reagents. Interestingly, under the Tebbe[15] or Takai−Utimoto[16] protocols, other authors have observed similar cyclizations, which are better explained by the alternative olefin metathesis−intramolecular olefination sequences.[17,18] In contrast with this intense activity, the olefination of amides has received much less attention,[7,19] with dimethyltitanocene[20] appearing to be the reagent of choice, in particular, for the methylenation of N-protected lactams.[21] To our knowledge, the possibility of combined olefination−metathesis processes leading to cyclic enamides has not been investigated so far.

Results and Discussion

We set out to explore the feasibility of the proposed amide methylenation−enamide RCM two-step sequence starting from amides derived from anilines **1**, which bear vinyl groups with different degrees of substitution at the *ortho* position. In this case, the annulation step would result in the direct formation of an aromatic indole system,[22] a process that has been previously explored by Nishida[23] on related enamide substrates coming from different precursors.

Thus, *N*-alkoxycarbonyl (methoxycarbonyl or Boc)-protected amides **1a**−**g** were subjected to the methylenation protocol we had previously established with model systems (1.5 molar equiv of dimethyltitanocene, toluene/pyridine 4:1, reflux, 4 h).[24] The results are summarized in Table 1. In the isopropenyl series (entries 1−3), acetamide **1a** gave the expected enamide **2a** along with minor amounts of the deacylated product **6**.[25] More satisfactorily, from acetamide **1b** and formamide **1c**, the reaction took place chemoselectively at the amide carbonyl group to give the corresponding enamides **2b**,**c** in high conversion yields (^{1}H NMR). Due to the sensitive enamide functionality, the isolated yields after column chromatography were only moderate (60−65%). Similar results were obtained from amides **1d**,**e**, carrying a 1-propenyl substituent, which led to the unstable enamides **2d**,**e** in 50% yield (entries 4 and 5).

Considering the precedents of RCM reactions involving electron-rich alkenes,[3] the enamide cyclization step was performed using the commercially available second generation Grubbs catalyst in toluene either at 80 °C or at reflux. Probably owing to steric effects, the formation of a 2,3-disubstituted indole by RCM of enamides **2a**,**b** was not observed in any of the conditions tried. However, cyclization did take place from **2c**−**e** giving access to indoles **3**−**5**.

Interestingly, the unsubstituted vinyl derivative **1f** or **1g** upon treatment with dimethyltitanocene gave the expected enamide **2f** or **2g** along with minor amounts of indoles **4** or **5** (entries 6 and 7). We were unable to find conditions (modifying the amount of reagent, temperature, or reaction time) to drive the reaction to the complete formation of indoles. From the synthetic standpoint, this was of little consequence as the heterocycles could be obtained in acceptable overall yields (40−50%) by subjecting the crude olefination mixtures to the ruthenium catalyst.

The competitive formation of indoles under the olefination protocol could be attributed to a tandem sequence involving a methylenation−enamide RCM (similar to Nicolaou's reports[14]) or, alternatively, an olefin metathesis−intramolecular olefination (similar to Hirama's[15] or Rainier's[16] reports). To ascertain the operative mechanism, the enamide **2f** was independently treated

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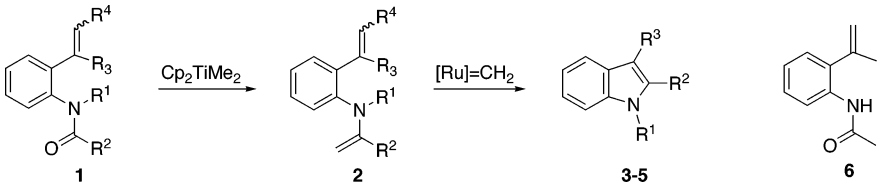
(25) The loss of the alkoxycarbonyl group was the only observed process when amides **1a**−**c** were subjected to the Takai−Utimoto methylenation protocol.[9,16]

TABLE 1. Synthesis of Indoles 3−5 from Amides 1



entry	R^1	R^2	R^3	R^4 (for **1**, **2**)	amide	olefination products[a]	enamide (yield, %)[b]	indole (yield, %)[b]
1	CO_2Me	Me	Me	H	**1a**	**2a** + **6** (6:1)	45	
2	Boc	Me	Me	H	**1b**	**2b**	65	
3	CO_2Me	H	Me	H	**1c**	**2c**	61	**3** (90)[c]
4	CO_2Me	Me	H	Me	**1d**	**2d**	50	**4** (85)[d]
5	CO_2Me	H	H	Me	**1e**	**2e**	50	**5** (90)[c]
6	CO_2Me	Me	H	H	**1f**	**2f** + **4** (2:1)	25	**4** (40)[d,e]
7	CO_2Me	H	H	H	**1g**	**2g** + **5** (6:1)		**5** (50)[c,e]

[a] General olefination conditions: Cp_2TiMe_2, 1.5 molar equiv, 100:1 toluene/pyridine, reflux, 4 h. [b] Isolated yield after flash chromatography. [c] Second generation Grubbs catalyst (6 mol %), toluene 80 °C, 4 h. [d] Second generation Grubbs catalyst (6 mol %), toluene reflux, 4 h. [e] Overall yield from amides **1f**,**g**.

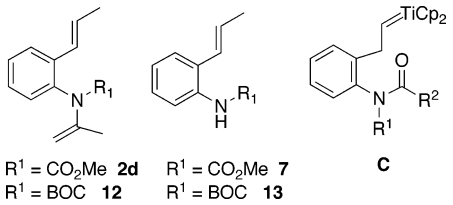


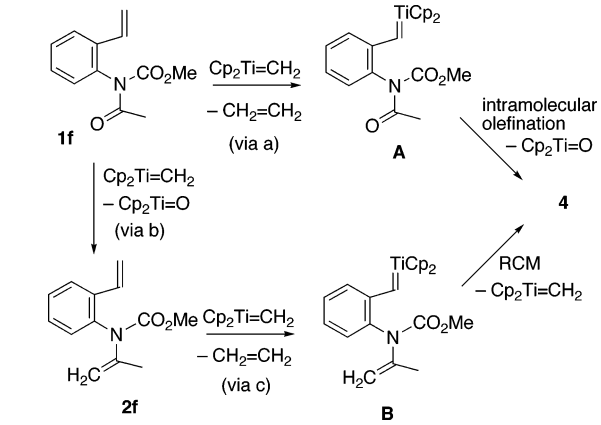
FIGURE 1.

with dimethyltitanocene. After 8 h at reflux, NMR analysis indicated the presence of unaffected **2f** along with open-chain carbamate **7** (Figure 1), incorporating an additional methyl group at the alkenyl moiety, and only very minor amounts of indole **4** (ratio 3:2:0.5). The formation of compound **7** was striking, being produced by a nonmetathetic interaction of the vinyl substituent of **2f** with dimethyltitanocene,[26] followed by hydrolysis of the enamide function.

Since the acyclic enamide was not a clear precursor of the indole, we believe that the cyclization was mainly the result of a metathesis−intramolecular olefination process that would take place through titanium alkylidene **A**, as indicated in Scheme 2 (via a). This process would be competitive with the usual methylenation leading to enamide **2f** (via b), and it would not have been observed in the above isopropenyl or 1-propenyl series due to the higher substitution of the carbon−carbon double bond hampering the initial interaction with the titanium methylene $Cp_2Ti{=}CH_2$. Accordingly, the extent of cyclization is affected by the steric environment around the amide carbonyl group[16b,c] as evidenced by the different product ratio obtained from acetamide **1f** (2:1) or formamide **1g** (6:1). Further results obtained in the quinoline and isoquinoline series (see below) support this mechanistic hypothesis.

Attention was next focused on the construction of the 1,4-dihydroquinoline system starting from N-protected amides derived from *ortho*-allylaniline (Table 2).[27] This approach would

SCHEME 2



complement existing RCM-based syntheses of 1,2-dihydroquinolines from *N*-allyl derivatives of *ortho*-vinylaniline.[28]

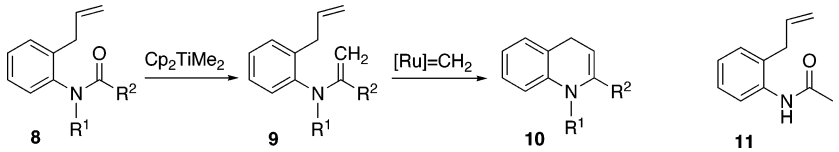
The dimethyltitanocene methylenation was first performed with acetamides **8a** and **8b** to give the expected enamides **9a** and **9b** in consistent reproducible 51 and 55% yields, respectively (entries 1 and 2). Significant amounts of the deacylated product **11** were also obtained from the *N*-(methoxycarbonyl) substrate, reflecting again an incomplete discrimination between the amide and carbamate carbonyl group. However, contrary to that observed in the analogous monosubstituted vinyl substrate **1f**, no trace of cyclized products (1,4-dihydroquinolines) was detected in the reaction mixtures. We can consider that the formation of the titanium alkylidene required for the intramolecular olefination step (**C**, Figure 1) was now less favored, probably because of the absence of conjugation with the aromatic ring (compare with **A**, Scheme 2). On the other hand, it should be noted that treatment of enamides **9a**,**b** with excess dimethyltitanocene (2−4 molar equiv) resulted in the formation of complex reaction mixtures, from which only open-chain isomerized 1-propenyl products, such as enamides **2d** or **12** or carbamates **7** (identical to that obtained from enamide **2f**) or **13**, could be isolated in variable yields.

(26) As far as we know, this alkylation is unprecedented. In fact, we have observed that styrene can be converted into 1-propenylbenzene by treatment with dimethyltitanocene (2 molar equiv) in toluene at reflux for 8 h. We appreciate the suggestion of one of the reviewers pointing out a plausible mechanism for this transformation: a [2 + 2] cycloaddition between the titanium carbene and the alkene followed by β-hydride abstraction would give an allyl titanium hydride, which would undergo reductive elimination.

(27) For a preliminary communication of this part of the work, see ref 24.

(28) (a) Theeraladanon, C.; Arisawa, M.; Nishida, A.; Nakagawa, M. *Tetrahedron* **2004**, *60*, 3017−3035. (b) See also ref 3d.

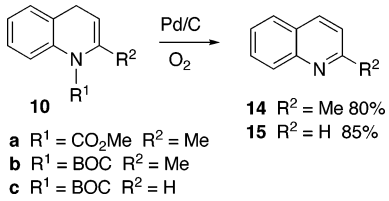
TABLE 2. Synthesis of 1,4-Dihydroquinolines 10 from Amides 8



entry	R^1	R^2	amide	olefination conditions[a]	olefination products	enamide (yield, %)[b]	1,4-dihydroquinoline (yield, %)[b,c]
1	CO_2Me	Me	**8a**	A	**9a** + **11** (3:1)	51	**10a** (80)
2	Boc	Me	**8b**	A	**9b**	55	**10b** (80)
3	Boc	H	**8c**	A	**9c**		**10c** (45)[d]
4	Boc	Et	**8d**	B	**9d** + **10d** (3:2)		**10d** (40)[d]

[a] Conditions A: Cp_2TiMe_2, 1.5 molar equiv, 100:1 toluene/pyridine, reflux, 4 h. Conditions B: Cp_2TiMe_2, 4 molar equiv, 100:1 toluene/pyridine, reflux, 16 h. [b] Isolated yield after column chromatography. [c] Second generation Grubbs catalyst (6 mol %), toluene 80 °C, 4 h. [d] Overall isolated yield from **9c**,**d**.

SCHEME 3



As expected, the subsequent ruthenium-catalyzed RCM of isolated enamides **9a**,**b** in toluene at 80 °C led to 1,4-dihydroquinolines **10a**,**b** in good yields (80%). Similarly, the titanium-mediated methylenation−ruthenium-catalyzed RCM two-step sequence was carried out from formamide **8c** (entry 3) to give 1,4-dihydroquinoline **10c** in 45% overall yield through enamide **9c** (the only product in the reaction mixture, not isolated). Finally, the sensitive 1,4-dihydroquinolines **10a**−**c** could be oxidized to the corresponding fully aromatic derivatives **14** and **15** by treatment with oxygen in the presence of 5% Pd/C (Scheme 3).

Significantly, the methylenation of the more hindered amide carbonyl group of propionamide **8d** (entry 4) was clearly slower, thus allowing the competitive olefin metathesis−intramolecular olefination through titanium alkylidene **C** (R^1 = Boc, R^2 = Et). The reaction required stronger conditions (conditions B, Table 2) to reach completion, leading to a 3:2 mixture of the expected enamide **9d** and 1,4-dihydroquinoline **10d**. As in the above indole series, we were not able to drive the reaction to the exclusive formation of **10d**. However, this product was obtained in 40% overall yield from **8d** upon exposure of the olefination mixture to the ruthenium catalyst.

The isoquinoline annulation[29] based on the same concepts required the chemistry outlined above to be extended to amide precursors derived from *ortho*-vinylbenzylamine. To this end, we undertook the methylenation of amides **16a**−**c** (Table 3), assuming that reaction of the titanium carbene at the monosubstituted conjugated carbon−carbon double bond ultimately leading to the cyclic enamide (1,2-dihydroisoquinoline) would interfere to some extent with the usual reaction at the carbonyl group. Indeed, treatment of acetamide **16a** with dimethyltitanocene under the usual conditions (conditions A, entry 1) led to a 3:1 mixture of the unstable enamide **17a** and 1,2-dihydroisoquinoline **18a**, which were not isolated. Satisfactorily, upon exposure of the mixture to the ruthenium catalyst, complete conversion to **18a** was accomplished in 55% overall yield. Methylenation of acetamide **16b** was a little slower and required the use of 3 molar equiv of the reagent (conditions B, entry 2) to give a mixture of acyclic and cyclic enamides **17b** and **18b**, along with significant amounts of 1-propenyl enamide **19** produced by reaction of **17b** with dimethyltitanocene.[26] From the synthetic standpoint, both enamides **17b** and **19** were suitable substrates for the isoquinoline synthesis since treatment of the olefination mixture with the ruthenium catalyst gave **18b** in 50% overall yield. Finally, methylenation of the less hindered formamide **16c** smoothly gave the enamide **17c** (entry 3), which was directly converted into 1,2-dihydroisoquinoline **18c** in 60% overall yield.

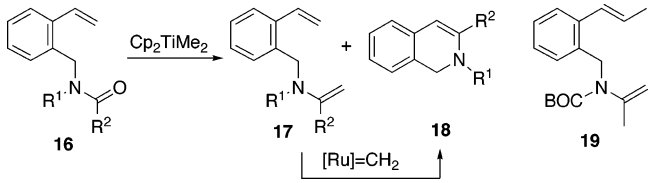
We also considered extending the above isoquinoline annulation to analogous indole substrates for the carboline synthesis. This proposal was tested on *N*-Boc-protected formamide **20**, which was converted into the corresponding enamide **21** under the usual conditions (Scheme 4). Without isolation, **21** was subjected to ruthenium-catalyzed RCM in toluene at reflux to give a highly unstable cyclic enamide, which was converted into tetrahydro-γ-carboline **22** by catalytic hydrogenation. The overall yield of the process was 35%.

The successful preparation of indoles, 1,4-dihydroquinolines, and 1,2-dihydroisoquinolines led us to examine the methylenation−RCM sequence for the construction of benzo-fused seven-membered cyclic enamides. With this aim, we selected *N*-Boc formamides **23**, **25**, **28**, and **32** as potential precursors of 2-benzoazepine, 1-benzoazepine, 1,5-benzoxazepine, and 3-benzoazepine systems, respectively. The results of this study are summarized in Table 4.

As expected, the titanium-mediated methylenation proceeded efficiently to give the corresponding enamides as the only products in high conversion yields. However, RCM of the crude enamides was now a sluggish reaction, requiring several additions of the second generation Grubbs catalyst. Thus, enamide **24** remained unaffected after 8 h in toluene at 80 °C, and its complete consumption required heating at 110 °C for 18 h (conditions A). Significantly, the 1,2-dihydroisoquinoline **18c** rather than the expected seven-membered ring was formed, which indicated that a slow isomerization to the more stable 1-propenyl substituent had taken place, followed by ring closure of the isomerized intermediate.[30] This result was not completely unexpected as it has been reported[31] that double bond migrations can interfere with the desired metathesis reaction,[32] in particular, in slow reactions requiring high catalyst loading or high

(29) For an example of 1,2-dihydroisoquinoline synthesis by RCM, see ref 3c.

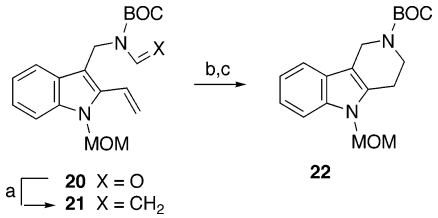
TABLE 3. Synthesis of 1,2-Dihydroisoquinolines 18 from Amides 16



entry	R^1	R^2	amide	olefination conditions[a]	olefination products	1,2-dihydroisoquinoline (yield, %)[b]
1	CO_2Me	Me	**16a**	A	**17a** + **18a** (3:1)[c]	**18a** (55)[d]
2	Boc	Me	**16b**	B	**17b** + **18b** + **19** (3:3:2)	**18b** (50)[e]
3	Boc	H	**16c**	A	**17c**[f]	**18c** (60)[d]

[a] Conditions A: Cp_2TiMe_2, 1.5 molar equiv, 100:1 toluene/pyridine, reflux, 4 h. Conditions B: Cp_2TiMe_2, 3 molar equiv, 100:1 toluene/pyridine, reflux, 8 h. [b] Overall isolated yields from amides **16**. [c] Minor amounts of recovered **16a**. [d] Second generation Grubbs catalyst (6 mol %), toluene 80 °C, 4 h. [e] Second generation Grubbs catalyst (6 mol %), toluene reflux, 4 h. [f] Trace amounts of **18c**.

SCHEME 4[a]

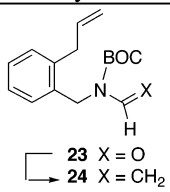
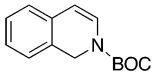
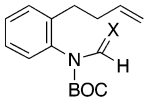
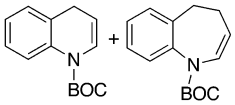
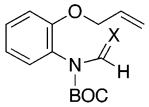
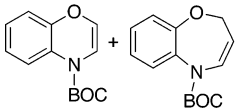
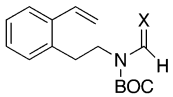
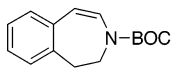


[a] Reagents and conditions: (a) Cp_2TiMe_2 (1.5 molar equiv) 4:1 toluene/pyridine, reflux, 4 h; (b) 2 × 6 mol % second generation Grubbs catalyst, toluene reflux, 10 h; (c) H_2, 5% Pd/C, MeOH, rt, 4 h.

temperatures. Ruthenium hydride species formed by decomposition of the catalyst are probably responsible for this unwanted reaction.[31]

A similar double bond isomerization to an internal position also interfered, although to a lesser extent, with the metathesis reaction of enamide **26**, which embodies a 3-butenyl chain (entry 2). Under conditions A, the reaction gave a 4:1 mixture of the 1,4-dihydroisoquinoline **10c** and the expected seven-membered ring **27**. Although the isomerization could be reduced simply by working at a lower temperature (conditions B), a more satisfactory result was obtained when, taking advantage of the recent report by Grubbs,[33] the reaction was performed in the presence of benzoquinone (conditions C). In this case, a 1:7 mixture of **10c** and **27** was obtained, from which the desired dihydro-1-benzoazepine **27** was isolated in a quite acceptable 50% overall yield from amide **25**. However, in our hands, benzoquinone was not able to prevent the isomerization of the allyloxy moiety of enamide **29** to the same extent, as the use of conditions C led to a 3:1 mixture of the oxazine **30** and the oxazepine **31** (entry 3). Finally, the nonisomerizable enamide **33** (entry 4) slowly underwent cyclization under conditions A to give the 3-benzoazepine **34** in a modest 35% overall yield from **32**.

TABLE 4. Methylenation−RCM from Amides 23, 25, 28, and 32

entry	amide methylenation[a]	RCM conditions[b,c]	products (ratio, yield, %)[d]
1		A	
	23 X = O 24 X = CH_2		**18c** (40)
2			
	25 X = O 26 X = CH_2		**10c** **27**
		A	4:1
		B	1:2
		C	1:7, **27** (50)
3		C	
	28 X = O 29 X = CH_2		**30** **31**
			3:1
4		A	
	32 X = O 33 X = CH_2		**34** (35)

[a] Cp_2TiMe_2 (1.5 molar equiv), 4:1 toluene/pyridine, reflux, 4 h. [b] All reactions were carried out in toluene in the presence of the second generation Grubbs catalyst. [c] Conditions A: 3 × 6% catalyst, 110 °C, 18 h. Conditions B: 3 × 10% catalyst, 80 °C, 58 h. Conditions C: 3 × 10% catalyst, benzoquinone (0.3 molar equiv), 80 °C, 58 h. [d] Isolated yields from the corresponding amides.

In conclusion, a novel two-step sequence involving a titanium-mediated *N*-acylamide methylenation followed by ruthenium-catalyzed RCM of the resulting enamides has been studied. The protocol allows the efficient assembling of several benzo-fused

(30) For examples of unwanted alkene isomerizations prior to the RCM step, see: (a) Fürstner, A.; Thiel, O. R.; Ackermann, L.; Schanz, H.-J.; Nolan, S. P. *J. Org. Chem.* **2000**, *65*, 2204−2207. (b) Michalak, K.; Michalak, M.; Wicha, J. *Tetrahedron Lett.* **2005**, *46*, 1149−1153. (c) See also ref 3a.

(31) For a discussion, see: Schmidt, B. *Eur. J. Org. Chem.* **2004**, 1865−1880 and references therein.

(32) For reviews of nonmetathetic activities of Grubbs ruthenium catalysts, see: (a) Alcaide, B.; Almendros, P. *Chem.—Eur. J.* **2003**, *9*, 1258−1262. (b) Schmidt, B. *Angew. Chem., Int. Ed.* **2003**, *42*, 4996−4999.

(33) Hong, S. H.; Sanders, D. P.; Lee, C. W.; Grubbs, R. H. *J. Am. Chem. Soc.* **2005**, *127*, 17160−17161.

five- or six-membered cyclic enamides (indoles, 1,4-dihydroquinolines, and 1,2-dihydroisoquinolines) from amides derived from *ortho*-alkenyl anilines or benzylamines. The extension to higher homologues is also possible, although limited by the interference of alkene isomerization processes in the slow RCM step. From some substrates, in particular, styrene derivatives, the direct annulation is observed in the titanium-mediated step, which probably occurs through an olefin metathesis−intramolecular olefination tandem process.

Experimental Section

General Procedure for the Dimethyltitanocene Methylenation. MeLi (1.6 M) in Et_2O (1.32 mL, 2.1 mmol) was slowly added in the dark under Ar to a suspension of Cp_2TiCl_2 (249 mg, 1 mmol) in anhydrous Et_2O (4 mL) cooled at 0 °C. After stirring at 0 °C for 1 h, the reaction mixture was poured into H_2O (5 mL). The organic layer was concentrated and dried to give Cp_2TiMe_2 as an orange solid. A solution of the above solid (1 mmol) in anhydrous toluene/pyridine (100:1, 6 mL) was added under Ar to a solution of the appropriate amide (0.67 mmol) in anhydrous toluene (1 mL) at room temperature, and the resulting mixture was stirred at reflux temperature in the dark for 4 h. The solvent was removed, and the resulting residue was treated with 8:2 Et_2O/CH_2Cl_2. The precipitate was filtered and the filtrate concentrated. The reaction mixture was analyzed by ^{1}H NMR. Enamides **2a**−**f** and **9a**,**b** were purified by flash chromatography. The others were directly used in the RCM step.

Methyl (1-Methylethenyl)[2-(1-methylethenyl)phenyl]carbamate (2a, Table 1, entry 1). Elution with 9:1 hexanes/AcOEt; 45% yield; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.02 (m, 3H), 2.08 (d, J = 0.6 Hz, 3H), 3.64 (s, 3H), 4.43 (s, 1H), 4.65 (q, J = 1.2 Hz, 1H), 4.95 (m, 1H), 5.14 (m, 1H), 7.14 (m, 1H), 7.25−7.30 (m, 3H); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 21.7 (CH_3), 23.3 (CH_3), 52.8 (CH_3), 106.6 (CH_2), 115.4 (CH_2), 127.3 (CH), 127.6 (CH), 129.1 (CH), 129.2 (CH), 138.8 (C), 141.6 (C), 142.8 (C), 145.3 (C), 154.5 (C); HRMS (CI) calcd for $C_{14}H_{18}NO_2$ 231.1259 (M + 1), found 231.1338.

***tert*-Butyl (1-Methylethenyl)[2-(1-methylethenyl)phenyl]carbamate (2b, Table 1, entry 2).** Elution with 9:1 hexanes/AcOEt; 65% yield; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.39 (s, 9H), 2.05 (s, 6H), 4.39 (s, 1H), 4.58 (d, J = 1 Hz, 1H), 4.99 (m, 1H), 5.13 (m, 1H), 7.05 (m, 1H), 7.25 (m, 3H); HRMS (CI) calcd for $C_{17}H_{24}NO_2$ 273.1729 (M + 1), found 273.1807.

Methyl [2-(1-Methylethenyl)phenyl]vinylcarbamate (2c, Table 1, entry 3). Elution with 98:2 hexanes/AcOEt; 61% yield; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.98 (s, 3H), 3.66 (br s, 3H), 3.84 (d, J = 15.8 Hz, 1H), 4.29 (d, J = 8.8 Hz, 1H), 4.90 (br s, 1H), 5.09 (m, 1H), 7.12 (m, 1H), 7.25−7.40 (m, 4H); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 23.4 (CH_3), 53.2 (CH_3), 94.5 (CH_2), 115.1 (CH_2), 127.9 (CH), 128.3 (CH), 129.3 (CH), 129.4 (CH), 134.3 (C), 135.0 (CH), 142.2 (C), 142.7 (C), 154.2 (C); HRMS (CI) calcd for $C_{13}H_{16}NO_2$ 217.1103 (M + 1), found 217.1181.

Methyl (2-Allylphenyl)(1-methylethenyl)carbamate (9a, Table 2, entry 1). Elution with 82:18 hexanes/AcOEt; 51% yield; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.07 (d, J = 0.8 Hz, 3H), 3.29 (d, J = 6.2 Hz, 2H), 3.65 (s, 3H), 4.52 (s, 1H), 4.68 (q, J = 1.2 Hz, 1H), 5.06 (m, 1H), 5.13 (m, 1H), 5.88 (m, 1H), 7.12 (m, 1H), 7.20−7.30 (m, 3H); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 21.8 (CH_3), 35.2 (CH_2), 52.9 (CH_3), 106.4 (CH_2), 116.4 (CH_2), 127.0 (CH), 127.7 (CH), 128.7 (CH), 130.0 (CH), 135.9 (CH), 137.7 (C), 139.8 (C), 144.1 (C), 154.6 (C); HRMS (CI) calcd for $C_{14}H_{18}NO_2$ 231.1259 (M + 1), found 231.1338.

***tert*-Butyl (2-Allylphenyl)(1-methylethenyl)carbamate (9b, Table 2, entry 2).** Elution with 95:5 hexanes/AcOEt; 55% yield; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.38 (s, 9H), 2.05 (s, 3H), 3.30 (m, 2H), 4.47 (s, 1H), 4.62 (s, 1H), 5.03 (m, 1H), 5.17 (m, 1H), 5.92 (m, 1H), 7.13 (m, 1H), 7.22 (m, 3H); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 22.0 (CH_3), 28.1 (CH_3), 35.2 (CH_2), 80.5 (C), 105.8 (CH_2), 116.8 (CH_2), 126.8 (CH), 127.3 (CH), 128.7 (CH), 129.8 (CH), 136.2 (CH), 137.5 (C), 140.7 (C), 144.3 (C), 153.2 (C); HRMS (CI) calcd for $C_{17}H_{24}NO_2$ 274.1807 (M + 1), found 274.1882.

General Procedure for the RCM Step. A solution of the appropriate enamide (1 mmol) and the second generation Grubbs catalyst (0.06 mmol) in anhydrous toluene was stirred at 80 or 110 °C under Ar and monitored by TLC to establish completion of the reaction. In some cases, a new addition of the catalyst was needed (see text). The reaction mixture was concentrated, and the resulting residue was chromatographed (flash, SiO_2).

1-(Methoxycarbonyl)-3-methylindole (3, Table 1, entry 3). Crystallized from Et_2O; 90% yield. The NMR spectra match the literature data.[34]

1-(Methoxycarbonyl)-2-methylindole (4, Table 1, entry 4). Elution with 97:3 hexanes/AcOEt; 85% yield. The NMR spectra match the literature data.[35]

1-(Methoxycarbonyl)indole (5, Table 1, entry 5). Elution with 97:3 hexanes/AcOEt; 90% yield. The NMR spectra match the literature data.[34]

1-(Methoxycarbonyl)-2-methyl-1,4-dihydroquinoline (10a, Table 2, entry 1). Elution with 9:1 hexanes/AcOEt; 80% yield; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.17 (m, 3H), 3.15 (d, J = 4.8 Hz, 2H), 3.80 (s, 3H), 5.52 (tq, J = 1, 1, 1, 4.8, 4.8 Hz, 1H), 7.10 (m, 2H), 7.20 (m, 1H), 7.57 (d, J = 7.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 20.1 (CH_3), 28.3 (CH_2), 52.9 (CH_3), 116.5 (CH), 124.3 (CH), 125.0 (CH), 125.5 (CH), 126.8 (CH), 133.0 (C), 138.1 (C), 139.2 (C), 154.0 (C); HRMS (CI) calcd for $C_{12}H_{14}NO_2$ 204.1024 (M + 1), found 204.1045.

1-(*tert*-Butoxycarbonyl)-2-methyl-1,4-dihydroquinoline (10b, Table 2, entry 2). Elution with 9:1 hexanes/AcOEt; 80% yield; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.53 (s, 9H), 2.14 (br q, J = 1.4 Hz, 3H), 3.14 (m, 2H), 5.45 (m, 1H), 7.08 (m, 1H), 7.20 (m, 2H), 7.61 (d, J = 8.2 Hz, 1H); HRMS (CI) calcd for $C_{15}H_{20}NO_2$ (M + 1) 246.3248, found 246.3259.

1-(*tert*-Butoxycarbonyl)-1,4-dihydroquinoline (10c, Table 2, entry 3). Unstable compound; elution with 1:1 hexanes/CH_2Cl_2; 45% yield; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.57 (s, 9H), 3.33 (dd, J = 1, 4 Hz, 2H), 5.26 (dt, J = 4.4, 4.4, 7.2 Hz, 1H), 6.90 (dt, J = 1.4, 1.4, 7.6 Hz, 1H), 7.05 (m, 2H), 7.19 (m, 1H), 7.90 (d, J = 8 Hz, 1H).

2-(Methoxycarbonyl)-3-methyl-1,2-dihydroisoquinoline (18a, Table 3, entry 1). Unstable compound; elution with 85:15 hexanes/AcOEt; 55% yield. The NMR spectra match the literature data.[36]

2-(*tert*-Butoxycarbonyl)-3-methyl-1,2-dihydroisoquinoline (18b, Table 3, entry 2). Unstable compound; elution with 95:5 hexanes/AcOEt; 50% overall yield from amide **16b**; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.49 (s, 9H), 2.25 (d, J = 1.2 Hz, 3H), 4.69 (s, 2H), 5.95 (q, J = 1.2 Hz, 1H), 7.01 (d, J = 7.2 Hz, 1H), 7.10−7.25 (m, 3H); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 21.6 (CH_3), 28.4 (CH_3), 47.6 (CH_2), 81.2 (C), 114.1 (CH), 123.5 (CH), 124.8 (CH), 126.3 (CH), 127.4 (CH), 130.8 (C), 132.6 (C), 138.0 (C), 152.6 (C).

2-(*tert*-Butoxycarbonyl)-1,2-dihydroisoquinoline (18c, Table 3, entry 3). Unstable compound; elution with 95:5 hexanes/AcOEt; 60% yield. The NMR spectra match the literature data.[37]

3-(*tert*-Butoxycarbonyl)-9-(methoxymethyl)-1,2,3,4-tetrahydro-γ-carboline (22). The unstable cyclic enamide obtained after the RCM step was treated at room temperature with 5% Pd/C in MeOH under a H_2 atmosphere for 4 h; elution with 9:1 hexanes/AcOEt; 35% yield from amide **20**; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.51 (s, 9H), 2.88 (m, 2H), 3.24 (s, 3H), 3.85 (m, 2H), 4.65 (s, 2H), 5.39

(34) Wenkert, E.; Alonso, M. E.; Gottlieb, H. E.; Sanchez, E. L. *J. Org. Chem.* **1977**, *42*, 3945−3949.
(35) Nagarathnam, D. *Synthesis* **1992**, 743−745.
(36) Beugelmans, R.; Chastanet, J.; Roussi, G. *Tetrahedron* **1984**, *40*, 311−314.
(37) Clarl, R. D.; Jahangir. *Heterocycles* **1991**, *32*, 1699−1703.

(s, 2H), 7.20 (m, 2H), 7.42 (m, 2H); HRMS (CI) calcd for $C_{18}H_{25}NO_3$ 303.1834 (M + 1), found 303.1832.

1-(*tert*-Butoxycarbonyl)-4,5-dihydro-1*H*-1-benzoazepine (27, Table 4, entry 2). Elution with 96:4 hexanes/AcOEt; 50% yield from amide **25**; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.49 (s, 9H), 2.31 (br s, 2H), 2.70−3.15 (br m, 2H), 4.96 (ddd, J = 3.8, 4.4, 9 Hz, 1H), 6.65 (d, J = 9 Hz, 1H), 7.15−7.20 (m, 4H); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 27.9 (CH_2), 28.3 (CH_3), 31.1 (CH_2), 81.2 (C), 115.0 (CH), 125.8 (CH), 126.7 (CH), 127.2 (CH), 127.3 (CH), 128.5 (CH), 138.0 (C), 142.4 (C), 153.2 (C); HRMS (CI) calcd for $C_{15}H_{20}NO_2$ 246.1494 (M + 1), found 246.1499.

3-(*tert*-Butoxycarbonyl)-2,3-dihydro-1*H*-3-benzoazepine (34, Table 4, entry 4). Elution with 98:2 hexanes/AcOEt; 35% yield from amide **32**; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.53 (s, 9H), 3.03 (m, 2H), 3.92 (m, 2H), 5.56 (br m, 1H), 6.95 (br m, 1H), 7.07 (m, 2H), 7.17 (m, 2H); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 28.3 (CH_3), 37.2 (CH_2), 44.4 (CH_2), 81.7 (C), 108.1 (CH), 125.7 (CH), 126.4 (CH), 126.6 (CH), 128.9 (CH), 130.2 (CH), 135.0 (C), 139.2 (C), 152.1 (C); HRMS (CI) calcd for $C_{15}H_{20}NO_2$ 246.1494 (M +1), found 246.1485.

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Supporting Information Available: General experimental protocols and detailed experimental procedures for the preparation of the amide precursors. Characterization data of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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