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Role of the *gem*-Difluoro Moiety in the Tandem Ring-Closing Metathesis−Olefin Isomerization: Regioselective Preparation of Unsaturated Lactams

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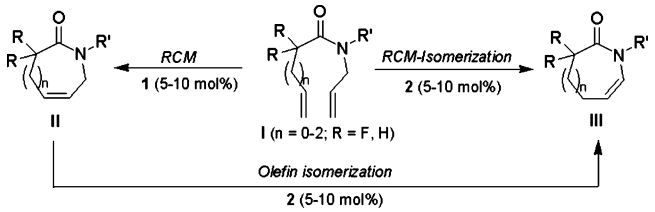

Careful selection of the metathesis catalyst, solvent, and reaction conditions allows for the efficient and regioselective synthesis of isomeric fluorinated and nonfluorinated lactam derivatives **II** and **III** from precursor amides **I** through a ring-closing metathesis (RCM) reaction or a tandem RCM−isomerization protocol, respectively. The presence of the *gem*-difluoro moiety in the starting materials exerts a pivotal effect by directing the isomerization step, making the overall tandem transformation a regioselective process. The scope, limitations, and synthetic usefulness of this protocol are also discussed.

Introduction

In the past decade, the ring-closing metathesis reaction (RCM) has emerged as a powerful synthetic tool for the creation of carbon−carbon bonds, allowing for the synthesis of medium- and large-sized unsaturated heterocyclic systems.[1] This development has been made possible mostly as a result of the discovery of new, more stable ruthenium catalysts,[2] the three most common of which are shown in Figure 1.

Although the RCM reaction is, in general, a clean process, ruthenium catalysts **1** and **2** occasionally produce what in some cases may be construed as undesired side reactions. Thus, the desired reaction products are sometimes accompanied by variable amounts of other compounds that arise as a result of isomerization of the newly created double bond.[3,4] For example, in their study of the RCM mechanism of *N*,*N*-diallyltosylamide catalyzed by several ruthenium complexes, Dixneuf and co-workers found that the reaction conditions and the nature of the catalyst had a great effect on the final mixture.[5]

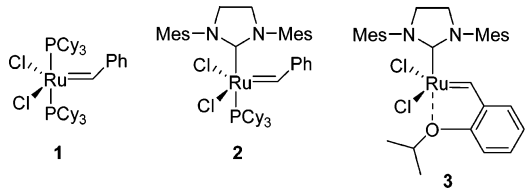

FIGURE 1. The most common metathesis catalysts.

Several reports indicate that the decomposition products of Ru-metathesis catalysts (generally Ru−hydride complexes) may be responsible for these side reactions and specifically for alkene isomerization.[6] In addition, Grubbs et al. recently demonstrated

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(1) (a) Philips, A. J.; Abell, A. D. *Aldrichimica Acta* **1999**, *32*, 75−89. (b) Schultz-Fademrecht, C.; Deshmukh, P. H.; Malagu, K.; Procopiou, P. A.; Barrett, A. G. *Tetrahedron* **2004**, *60*, 7515−7524. (c) Deiters, A.; Martin, S. F. *Chem. Rev.* **2004**, *104*, 2199−2238.

(2) Grubbs, R. H. In *Handbook of Metathesis*; Wiley-VCH Verlag Gmbh and Co. KGaA: Weinheim, 2003; Vols. 1−3.

(3) Review: Schmidt, B. *Eur. J. Org. Chem.* **2004**, 1865−1880 and references therein.

(4) During the preparation of this manuscript Grubbs and co-workers published a paper that describes a method for the suppression of undesired isomerization side reactions that are sometimes associated with olefin metathesis: Hong, S. H.; Sanders, D. P.; Lee, C. W.; Grubbs, R. H. *J. Am. Chem. Soc.* **2005**, *127*, 17160−17161.

(5) Bassetti, M.; Centola, F.; Sémeril, D.; Bruneau, C.; Dixneuf, P. H. *Organometallics* **2003**, *22*, 4459−4466.

(6) Fürstner, A.; Ackermann, L.; Gabor, B.; Goddard, R.; Lehmann, C.; Mynott, R.; Stelzer, F.; Thiel, D. *Chem. Eur. J.* **2001**, *7*, 3236−3253.

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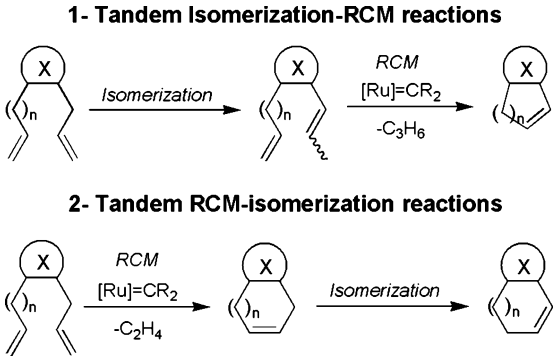
SCHEME 1. Tandem "Isomerization−RCM" and Tandem "RCM−Isomerization" Reactions



that the second generation ruthenium catalyst **2** evolves into a ruthenium hydride when heated in benzene.[7] Despite the widespread perception that these side reactions constitute a general problem, it is also true that they have been used advantageously by several authors in specific synthetic strategies. Thus, a growing number of newly discovered catalytic processes mediated by Ru catalysts **1**−**3** that do not involve olefin metathesis and therefore possess even greater synthetic versatility have appeared in the literature.[8,9]

From a synthetic point of view, the tandem "isomerization−RCM" and the tandem "RCM−isomerization" reactions might constitute the most useful and selective nonmetathetic transformations mediated by these ruthenium catalysts. The combination of these two strategies allows for the preparation of different types of carbo- and heterocyclic systems in a very efficient and simple manner (Scheme 1).

Whereas several examples of the application of the first protocol are already known,[10] the alternative RCM−isomerization is much less common. Two recent examples of this approach have been Snapper's and Schmidt's independent use of tandem RCM−isomerization reactions for the synthesis of cyclic enol ethers,[11] which would otherwise be far more difficult to obtain. It is important to point out, however, that in both cases the applied protocols require the presence of an additive to promote the transformation of the Ru-carbene into an Ru-hydride complex, which is ultimately responsible for the isomerization processes. It is also worth noting that apart from these two preparations of enol ethers, there are no other examples of the application of the tandem RCM−isomerization protocol to date.[12]

Concurrently, the development of new synthetic methodologies for the preparation of nitrogen heterocyclic compounds is of great importance in organic synthesis, as these substances constitute the basic structural elements of many potentially bioactive compounds. Among nitrogen heterocycles, lactams have attracted considerable interest, mostly because of their usefulness in drug discovery. One approach that has been applied successfully to the design of biologically active compounds is the inclusion of such compounds in peptidic chains. Thus, for instance, Freidinger lactams have been used extensively for the preparation of conformationally restricted peptidomimetics.[13] In addition, lactams are present in the backbone of several natural products, including bengamides, which have shown important cytotoxic properties.[14]

Unsaturated lactams constitute especially versatile building blocks because the presence of the double bond allows for further functionalization, including but not limited to epoxidation and dihydroxylation. Strategies involving RCM reactions have already been applied successfully to the synthesis of several unsaturated lactam derivatives.[15] The incorporation of fluorine atoms in these compounds would constitute an interesting structural variation, as their introduction is known to impart unique biological properties to the parent molecule.[16] Several methodologies specifically regarding the preparation of fluorinated lactams have been described in the literature,[17] but to the best of our knowledge only one example of their preparation through an RCM reaction has been described thus far.[18]

In this paper, we report on new examples of the tandem RCM−isomerization reaction that allow for the efficient preparation of fluorinated as well as nonfluorinated, unsaturated lactam derivatives. The pivotal role of the *gem*-difluoro moiety in directing the isomerization step is also discussed. The novelty here is that, in contrast with previously reported methods,[11] our protocol for the tandem sequence RCM−isomerization does not require the use of any additives to generate the ruthenium hydride species, which are believed to be responsible of the regioselective isomerization reaction. We also discuss the scope, limitations, and synthetic usefulness of this new protocol.

(7) Hong, S. H.; Day, M. W.; Grubbs, R. H. *J. Am. Chem. Soc.* **2004**, *126*, 7414−7415.

(8) For a recent revision of nonmetathetic reactions mediated by Grubbs' catalysts, see: Alcaide, B.; Almendros, P. *Chem. Eur. J.* **2003**, *9*, 1258−1262.

(9) For the deprotection of allylic amines through isomerization reactions with Grubbs' catalysts, see: (a) Alcaide, B.; Almendros, P.; Alonso, J. M.; Aly, M. F. *Org. Lett.* **2001**, *3*, 3781−3785. (b) Alcaide, B.; Benito, P.; Alonso, J. M.; Luna, A. *Synthesis* **2005**, 668−672. For the Kharasch addition of chloroform across olefins mediated by ruthenium catalysts, see: (c) Tallarico, J. A.; Malnick, L. M.; Snapper, M. L. *J. Org. Chem.* **1999**, *64*, 344−345.

(10) For representative examples, see: (a) Fürstner, A.; Thiel, O. R.; Ackermann. L.; Schanz, H.-J.; Nolan, S. P. *J. Org. Chem.* **2000**, *65*, 2204−2207. (b) Kinderman, S. S.; van Maarseveen, J. A.; Schoemaker, H. E.; Hiemstra, H.; Rutjes, F. P. J. T. *Org. Lett.* **2001**, *3*, 2045−2048. (c) Arisawa, M.; Terada, Y.; Nakagawa, M.; Nishida, A. *Angew. Chem., Int. Ed.* **2002**, *41*, 4732−4734. (d) Huang, J.; Xiong, H.; Hsung, R. P.; Rameshkumar, C.; Mulder, J. A.; Grebe, T. P. *Org. Lett.* **2002**, *4*, 2417−2420.

(11) (a) Sutton, A. E.; Seigal, B. A.; Finnegan, D. F.; Snapper, M. L. *J. Am. Chem. Soc.* **2002**, *124*, 13390−13391. (b) Schmidt, B. *J. Org. Chem.* **2004**, *69*, 7672−7687. For a recent example of the application of the RCM−isomerization protocol, see: Bressy, C.; Menant, C.; Piva, O. *Synlett* **2005**, 577−582.

(12) Snapper and co-workers described one example of the preparation of a tosyl enamide by means of his RCM−isomerization protocol (see ref 11a).

(13) (a) Freidinger, R. M.; Veber, D. F.; Perlow, D. S.; Brooks, J. R.; Saperstein, R. *Science* **1980**, 656−658. (b) Freidinger, R. M.; Perlow, D. S.; Veber, D. F. *J. Org. Chem.* **1982**, *47*, 104−109. (c) For a review, see: Cluzeau, J.; Lubell, W. D. *Biopolymers (Peptide Sci.)* **2005**, *80*, 98−150.

(14) See, for example: (a) Adamczeski, M.; Quiñoà, E.; Crews, P. *J. Org. Chem.* **1990**, *55*, 240−242. (b) Fernandez, R.; Dherbomez, M.; Letourneux, Y.; Nabil, M.; Verbist, J. F.; Biard, J. F. *J. Nat. Prod.* **1999**, *62*, 678−680. (c) Thale, Z.; Kinder, F. R.; Bair, K. W.; Bontempo, J.; Czuchta, A. M.; Versace, R. W.; Phillips, P. E.; Sanders, M. L.; Wattanasin, S.; Crews, P. *J. Org. Chem.* **2001**, *66*, 1733−1741.

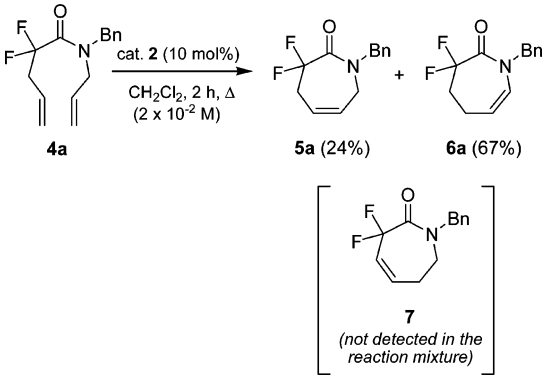
(15) (a) Fu, G. C.; Grubbs, R. H. *J. Am. Chem. Soc.* **1992**, *114*, 7324−7325. (b) Fu, G. C.; Nguyen, S. T.; Grubbs, R. H. *J. Am. Chem. Soc.* **1993**, *115*, 9856−9857. (c) Huwe, C. M.; Kiehl, O. C.; Blechert, S. *Synlett* **1996**, 65−66. (d) Rutjes, F. P.; Schoemaker, H. E. *Tetrahedron Lett.* **1997**, *38*, 677−680. (e) Miller, S. J.; Blackwell, H. E.; Grubbs, R. H. *J. Am. Chem. Soc.* **1996**, *118*, 9606−9614.

(16) Baasner, B.; Hagemann, H.; Tatlow, J. C. *Houben-Weyl Methods in Organic Chemistry*, Georg Thieme Verlag: Sttutgart, 1999; Vol. E10a, Organo-Fluorine Compounds.

(17) (a) Uneyama, K.; Yanagiguchi, T.; Asai, H. *Tetrahedron Lett.* **1997**, *38*, 7763−7764. (b) Nagashima, H.; Isono, Y.; Iwamatsu, S. *J. Org. Chem.* **2001**, *66*, 315−319. (c) Weber, K.; Gmeiner, P. *Synlett* **1998**, 885−887.

(18) Marhold, M.; Buer, A., Hiemstra, H.; van Maarseveen, J. H.; Haufe, G. *Tetrahedron Lett.* **2004**, *45*, 57−60.

SCHEME 2. Initial Formation of Seven-Membered Lactams 5a and 6a



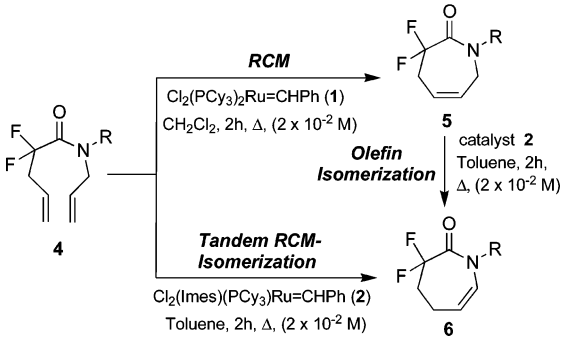
Results and Discussion

As part of our ongoing project directed toward the preparation of fluorinated nitrogen heterocycles,[19] we planned to use a ring-closing metathesis reaction as the key step in the preparation of new fluorinated lactams. Our initial approach for the preparation of seven-membered fluorinated lactams **5** was quite simple: as starting materials for the RCM reaction we synthesized several diolefinic tertiary amides **4** (Scheme 2), which were easily prepared either through *N*-allylation of the corresponding secondary fluorinated amides or reaction of 2,2-difluoro-4-pentenoic acid with secondary allylic amines.[20]

We expected amides **4** to afford ϵ-lactams **5** as major reaction products under standard RCM conditions, and indeed, in an initial assay, the RCM of **4a** took place easily in 2 h with catalyst **2** in refluxing dichloromethane. However, to our surprise, the expected reaction product **5a** was only a minor constituent of the crude reaction mixture, appearing together with an isomer in a 1:3 ratio. Fortunately, these two products were easily separated with standard chromatographic techniques, and the major isomer was subsequently identified as the enamide **6a** (Scheme 2). Interestingly, the unsaturated lactam **7**, resulting from a double bond isomerization toward the opposite side of the bond, was not observed at all, which seemed to reveal an intriguing influence of the CF_2 group in the regioselectivity of the process.

The formation of lactam **6a**, which arises from an isomerization reaction following the RCM, prompted us to optimize the reaction conditions in order to achieve the regioselective formation of either amides **5** or **6**. We first studied the influence of the solvent, carrying out the reaction at room temperature in the presence of catalyst **2** (10 mol %). In solvents such as dichloromethane, tetrahydrofuran, and chloroform the reaction was very fast. In fact, it was completed in only 10 min at room temperature, with the expected RCM product **5** as the only identified (with the aid of GC−MS) and isolated reaction product. Similar results were obtained with carbon tetrachloride and trifluorotoluene. In these cases, however, longer reaction times of up to 2 h were required to reach complete conversion. Interestingly, a different situation occurred when toluene was used as solvent; after 2 h, a nearly 1:1 mixture of both the metathesis and the isomerized products was obtained.[21]

TABLE 1. Regioselective Preparation of Fluorinated Lactams 5 and 6



entry	4	method[a]	R	yield (%) (5)	yield (%) (6)
1	**4a**	A	CH_2Ph	95 (**5a**)	
2	**4b**	A	*p*−$MeOC_6H_4$	89 (**5b**)	
3	**4c**	A	CH_2CO_2Et	70 (**5c**)	
4	**4d**	A	*c*-C_6H_{11}	82 (**5d**)	
5	**4a**	B	CH_2Ph		73 (**6a**)
6	**4b**	B	*p*-$MeOC_6H_4$		93 (**6b**)
7	**4c**	B	CH_2CO_2Et		72 (**6c**)
8	**4d**	B	*c*-C_6H_{11}		95 (**6d**)
9	**4e**	B	*p*-FC_6H_4		70 (**6e**)
10	**4f**	B	*o*-$MeOC_6H_4$		91 (**6f**)

[a] Method A: refluxing dichloromethane (2×10^{-2} M); **1** (5−10 mol %); 5−6 h. Method B: refluxing toluene (2×10^{-2} M); **2** (5−10 mol %), 1−2 h.

We next turned our attention to the combined influence of temperature and catalyst. After testing several combinations of temperatures, catalysts, and solvents, we found that when the reaction was carried out in the presence of Grubbs' catalyst **1** (5−10 mol %)[20] in refluxing dichloromethane, ϵ-lactams **5** were formed exclusively as a result of a direct RCM reaction with no significant concurrent isomerization (Table 1, Method A, entries 1−4). In sharp contrast, when catalyst **2** (5−10 mol %)[20] was used in refluxing toluene, amides **4a**−**f** underwent the tandem RCM−isomerization sequence to furnish the corresponding seven-membered enamides **6a**−**f** as the exclusive reaction products in good to excellent yields (Table 1, Method B, entries 5−10). We also found that the overall process could be carried out in two steps. For example, when lactam **5a**, prepared with Method A, was heated in toluene with catalyst **2**, an isomerization reaction took place smoothly, affording lactam **6a** in 95% yield, with no need for any additives to promote the isomerization. Moreover, in the case of these seven-membered rings the RCM proceeds much faster than the isomerization reaction, thus preventing the formation of ring-contracted products that would arise if the RCM reaction took place on the isomerized olefin.[22,23]

(19) (a) Fustero, S.; Piera, J.; Sanz-Cervera, J. F.; Catalán, S.; Ramírez de Arellano, C. *Org. Lett.* **2004**, *6*, 1417−1420. (b) Fustero, S.; Bartolomé, A.; Sanz-Cervera, J. F.; Sánchez-Roselló, M.; Soler, J. G.; Ramírez de Arellano, C.; Simón-Fuentes, A. *Org. Lett.* **2003**, *5*, 2523−2526. (c) Fustero, S.; Salavert, E.; Sanz-Cervera, J. F.; Piera, J.; Asensio, A. *Chem. Commun.* **2003**, 844−845.

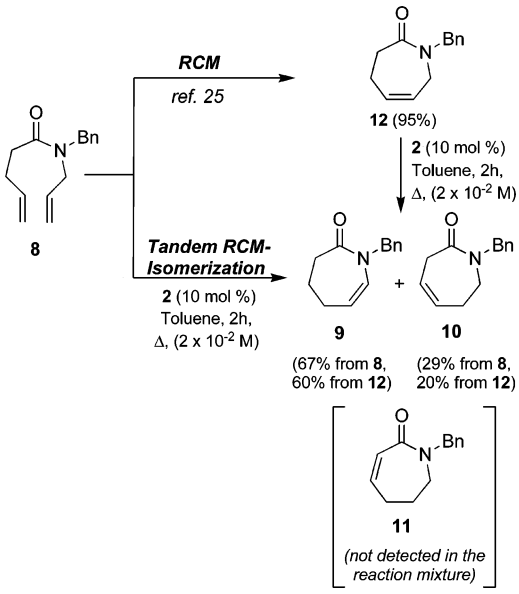
(20) See Supporting Information for experimental details.

(21) The different behavior of toluene as solvent had already been observed by Fürstner in some RCM processes. He hypothesized that competing interactions between the mesityl group and aromatic solvents might reduce the stabilizing effect of the intramolecular $\pi-\pi$ stacking with the benzylidene substituent; as a result, the catalyst would have more conformational freedom and therefore could display a different reactivity. See ref 6.

(22) Double bond isomerization prior to the RCM has been observed in several reports. See ref 10.

(23) The preparation of nonfluorinated analogues to **6** has been described through a tandem isomerization−RCM of enynes, the inverse process of that described here. See ref 10d.

SCHEME 3. Preparation of Seven-Membered Lactams 9, 10, and 12



We next turned our attention to the preparation of the corresponding nonfluorinated lactam derivatives not only to extend the scope of this RCM−isomerization protocol[24] but also to compare their behavior with that of their fluorinated counterparts under similar reaction conditions. Thus, when we applied our strategy (Method B) to the nonfluorinated amide **8**, we observed the formation of the expected lactam **9** in 67% yield along with another isomeric lactam **10** (29%), which was easily separated by means of flash chromatography. This latter compound arises from the double bond isomerization toward the opposite side (Scheme 3). It is also interesting to note that the more stable α,β-unsaturated lactam **11** was not detected in the crude mixture. As we had done with their fluorinated counterparts, we also performed this synthesis using a two-step sequence to check the results of the olefin isomerization under the conditions set out by us. Thus, the nonisomerized RCM product **12** was easily prepared as described by Guibé and coworkers.[25] Treatment of lactam **12** with catalyst **2** in refluxing toluene afforded a mixture of lactams **9** and **10** in a 2:1 ratio with a yield of 79%. Similar results were also obtained with lactam **12** when the ruthenium hydride complex **[**RuHCl(CO)-$(PPh_3)_3$], a typical isomerization catalyst, was used instead of the second generation catalyst **2**, giving in this case lactams **9** and **10** in a 3:1 ratio with 80% yield. This result seems to support our hypothesis that an Ru hydride species resulting from the heating of catalyst **2** causes the isomerization process, as discussed above.

These results led us to pose three questions concerning the overall process, namely, (i) what the possible mechanism of the tandem protocol is, (ii) what role the *gem*-difluoro moiety plays in the observed regioselectivity of the isomerization process, and (iii) how the isomeric lactams are formed. In answering these questions, we considered that the relatively high temperature used in the process might have led to the generation of a ruthenium hydride species from catalyst **2**, thereby causing the formation of Ru hydride, which could in turn be responsible of the observed isomerization.[26] We thus proposed the mechanism shown in Scheme 4 as a plausible explanation for our results.

To test this hypothesis and also to answer our other two questions, we performed a monitored experiment and found that when amide **4a** was heated in an NMR tube in deuterated toluene in the presence of catalyst **2**, after 10 min at 80 °C a 1:1 mixture of amides **5a** and **6a** were the only products observed in the ^{1}H NMR spectrum. Since compound **6a** is the only product that was isolated after 2 h of heating under these conditions (Table 2, entry 5), this indicates that the cyclization of dienic amides **4** occurs rapidly, with lactam **5** being formed first. The ruthenium hydride generated in the reaction conditions could then add to the olefinic moiety of lactam **5**, giving rise to the isomeric intermediates **A** and **B** (Scheme 4). β-Elimination of the appropriate hydride would lead to the final isomerized amides. Intermediates **A** and **B** each contain two different kinds of suitable hydrogen atoms that can undergo the elimination process (H^2 and H^4 for **A**; H^1 and H^3 for **B**). The elimination of hydrogen H^2 or H^3 on intermediates **A** and **B** would cause the formation of transition states (TSs) **E** and **F**, respectively, which in turn would again revert to the starting lactam **5** (Scheme 4). In contrast, the elimination of hydrogen H^4 on intermediate **A** would lead to TS **C**, the formation of which is favored as a result of the stabilization of the positive partial charge in the α carbon to the nitrogen, which in turn is caused by the lone nitrogen electron pair. Finally, the elimination of hydrogen H^1 on intermediate **B** would cause the formation of TS **D**, which would be destabilized due to the fact that the partial positive charge on the C atom contiguous to the *gem*-difluoro moiety should be destabilized by its electron withdrawing effect. Thus, the formation of TS **D** would be disfavored in comparison to that of TS **C**. Since TSs **C** and **D** would lead to the formation of lactams **6** and **7**, respectively, this mechanism, which takes into account the destabilizing influence of the *gem*-difluoro group on TS **D** as compared to the stabilizing effect of the N atom on TS **C**, would explain why lactams **7** are not observed as reaction products. Finally, the amide **5** formed from TSs **E** and **F** would once again be subjected to the catalytic cycle, forming at the end of the process the most thermodynamically stable product **6**. The formation of this compound is therefore favored by the high temperature used in the reaction. At this point we decided to carry out ab initio optimization of the conformers of compounds **5a**, **6a**, and **7** at HF/6-31G* level of theory. Our results showed that compound **6a** is 1.8 kcal·mol^{-1} more stable than **5a**, which at first glance seems to point to a thermodinamic control of the reaction product. However, our calculations also showed that compound **7** has a very similar energy compared to compound **5a** (**7** is 1.7 kcal·mol^{-1} less stable than **6a** and 0.1 kcal·mol^{-1} more stable than its isomer **5a**). Despite this similarity in energy content, however, **7** was never detected in our reactions, even though we carefully monitored their evolution by means of GC−MS and NMR techniques. This fact seems to point out that the absence of **7**

(24) The synthesis of nonfluorinated cyclic enamides via copper-catalyzed intramolecular vinylation of amides was described very recently. However, this method does not afford rings with more than seven members, and it is greatly affected by the basicity of the substituent on the nitrogen atom. Our method thus circumvents the problems of this approach. See: Hu, T.; Li, C. *Org. Lett.* **2005**, *7*, 2035−2038.

(25) Vo-Thanh, G.; Voucard, V.; Sauriat-Dorizon, H.; Guibé, G. *Synlett* **2001**, 37−40.

(26) Ru-hydride species are known to catalyze olefin isomerization: (a) Wakamatsu, H.; Nishida, M.; Adachi, N.; Mori, M. *J. Org. Chem* **2000**, *65*, 3966−3970 and references therein. (b) Krompiec, S.; Pigulla, M.; Szczepankiewicz, W, Bieg, T.; Kudnik, N.; Leszczynska-Sejda, K., Kubicki, M.; Borowiak, T. *Tetrahedron Lett.* **2001**, 7095−7098.

SCHEME 4. Possible Mechanism for Formation of Isomerized Lactams

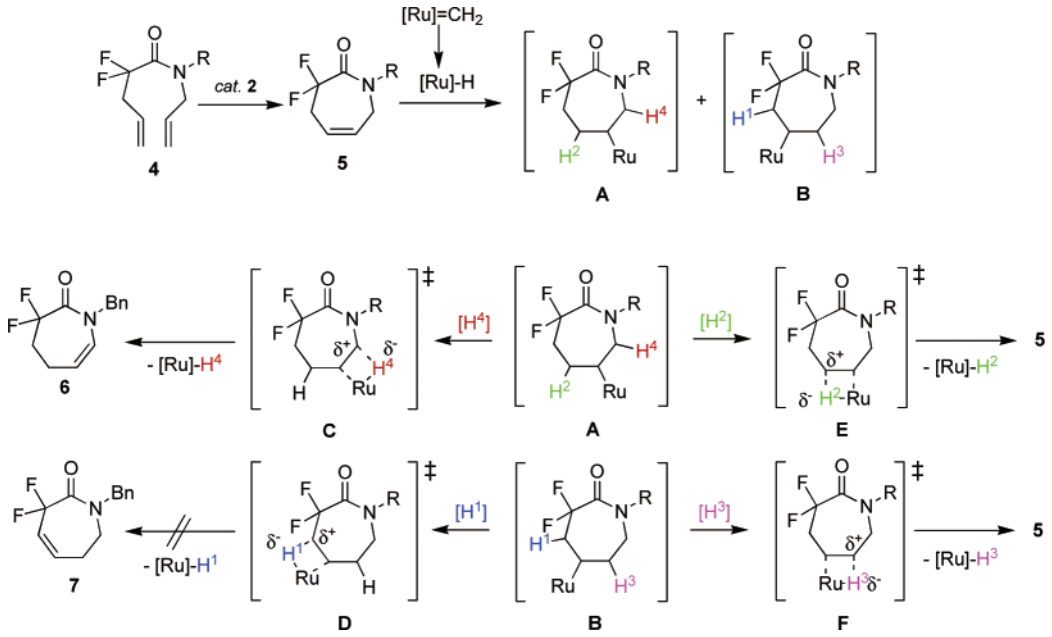
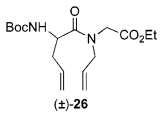
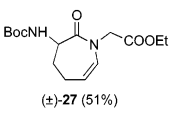
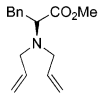
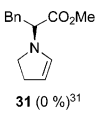
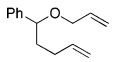
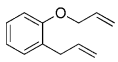
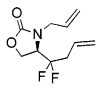
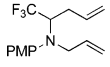


TABLE 2. Further Tandem RCM-olefin Isomerization Results

entry	starting material	isomerized, cyclized product[a]
1	 (±)-**26**	 (±)-**27** (51%)
2	 **28**	 **29** (65%)
3	 **30**	 **31** (0 %)[31]
4	 (±)-**32**	 (±)-**33** (60%)
5	 **34**	 **35** (46%) +  **36** (23%)
6	 (*R*)-**37**	 (*R*)-**38** (85%)
7	 (±)-**39**	 (±)-**40** (75%)

[a] Yields are given in parentheses.

might be due to an electronic effect caused by the presence of the CF_2 group, and hence the lack of formation of **7** must be caused by kinetic control, even though the isomerization product **6a** is also the most stable of the three possible isomers. This result would thus agree with our proposed mechanism for the observed selectivity in the formation of **6a**.[27]

This proposed mechanism would also explain why nonfluorinated amides **8** afford a mixture of isomerized lactams **9** and **10** when treated with catalyst **2** in hot toluene. Thus, amides **8** would first cyclize to lactam **12**, the reaction of which with a ruthenium hydride gives rise to the corresponding intermediates to **A** and **B**. In this case, the absence of the *gem*-difluoro moiety would cause TS **D** not to be destabilized; the result would thus be the observed mixture of lactams **9** and **10**. Since the presence of the nitrogen atom still favors TS **C** over **D**, this could explain why amide **9** is the major reaction product, as it arises from the former TS. This mechanism also offers a possible explanation of why the α,β-unsaturated amides **11** are never formed, as the electron-withdrawing effect of the carbonyl group would disfavor the corresponding transition state with a partial positive charge on the contiguous carbon atom (Scheme 4).

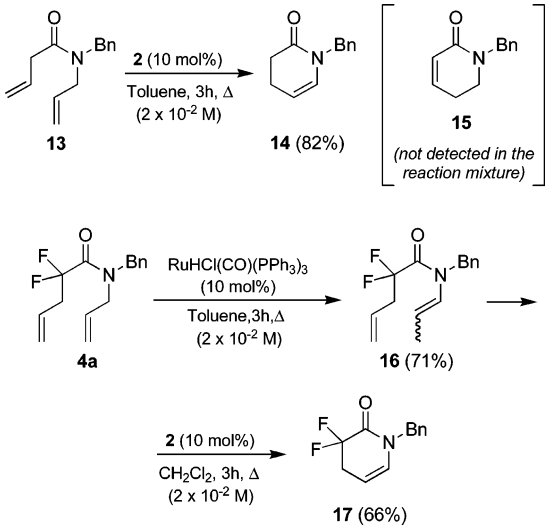
In summary, and remembering that the isomeric lactams **7** (Scheme 2) and **11** (Scheme 3) were never detected in our reactions, we can conclude that both the CF_2 group and the carbonyl exert a decisive influence on the regioselectivity of the process. In this case, the CF_2 group seems to behave like a protected carbonyl group, thus hindering the formation of **7** in a manner similar to that in which the formation of nonfluorinated derivatives such as **11** are also hindered.[28]

We then extended our study to the preparation and isomerization of lactams with different ring sizes. Thus, when amide **13** was subjected to the tandem sequence (Method B), it afforded the isomerized δ-lactam **14** exclusively and in good yield (Scheme 5). Once again, no α,β-unsaturated δ-lactam **15** was detected, probably because of the electron withdrawing effect of the carbonyl group.

We decided to prepare the corresponding difluorinated analogue **17** by means of a strategy different from that used for the ϵ-lactams **5a** and **6a** because of the ease with which

(27) A theoretical study of the mechanism of these reactions is currently underway in our laboratory and will be published in due course.

SCHEME 5. Preparation of Six-Membered Lactams 14 and 17

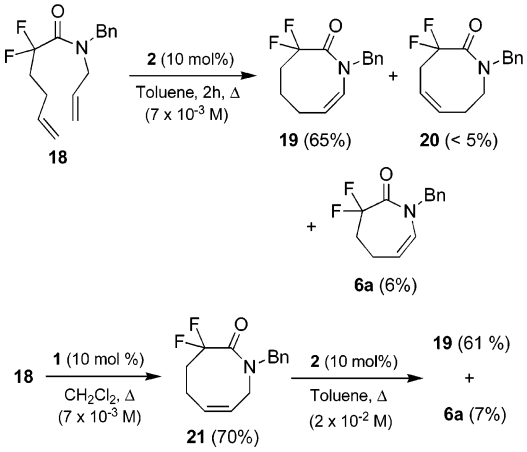


precursor **4a** can be obtained. Thus, treatment of amide **4a** with the ruthenium hydride catalyst [RuHCl(CO)(PPh_3)$_3$] regioselectively afforded, as expected, its enamidic isomer **16** in 71% yield, which was then cyclized under standard RCM conditions to yield exclusively the desired δ-lactam **17** in 66% yield (Scheme 5).

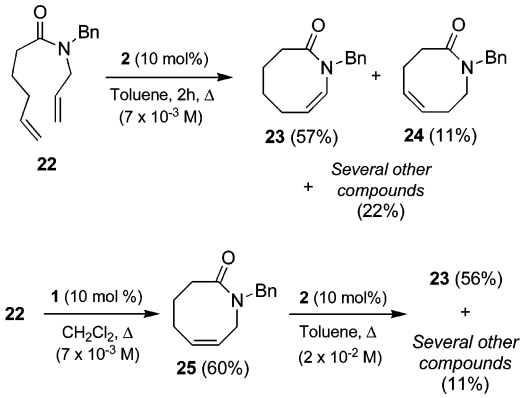
We also tested our tandem protocol on the preparation of eight- and nine-membered cyclic enamides (Schemes 6 and 7). Although the RCM−isomerization sequence was efficient in the preparation of the eight-membered lactams **19** (65%) and **23** (57%), the yields were somewhat lower than those of the previously obtained lactams. Additionally, in contrast with the formation of the six- and seven-membered rings described above, we also detected the formation of variable amounts of other lactam derivatives in these cases by means of GC−MS analysis. In the case of the eight-membered fluorinated lactams, the main product **19** was accompanied by small amounts of two other compounds, namely, the isomeric ς-lactam **20** (<5%) and the seven-membered lactam **6a** (6%) (Scheme 6). Compound **6a**, which was separated easily by means of flash chromatography, results from a competitive tandem isomerization-RCM sequence.

Although the yield of the fluorinated lactam **19** is still synthetically useful, the results obtained for its nonfluorinated counterpart were less satisfactory. Thus, when our RCM−isomerization protocol was applied to compound **22**, GC−MS analysis indicated that besides the cyclic enamide **23**, significant

SCHEME 6. Preparation of Eight-Membered Fluorinated Lactams 19 and 21



SCHEME 7. Preparation of Eight-Membered Lactams 23, 24, and 25

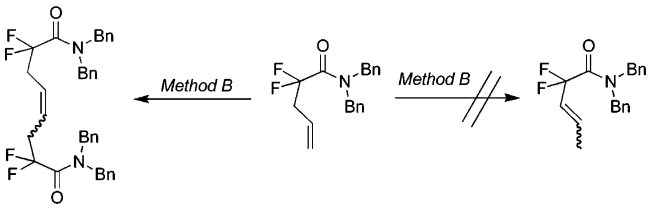


amounts of other products identified as isomeric eight- (**24**, 11%), seven- (**9** + **10**, 22%), and six-membered lactams (**14**, 4%)[29] were also formed (Scheme 6). In this sense, the two-step sequence constitutes a useful alternative for the preparation of amides **19** and **23**. Thus, when difluorinated amide **18** was treated with catalyst **1** (10 mol %) (Method A), lactam **21** was isolated as the only reaction product. When, in turn, compound **21** was heated in toluene in the presence of catalyst **2**, it afforded a 9:1 mixture of lactams **19** and **6a**, respectively, in 68% overall yield. However, the best results for the preparation of lactam **19** from its isomer **21** were obtained when the ruthenium hydride catalyst **[**RuHCl(CO)(PPh_3)$_3$ (10 mol %)] was used, with lactam **19** as the only reaction product being formed in 80% yield (Scheme 6).

In the same way, lactam **25** was obtained through treatment of amide **22** with first generation Grubbs' catalyst **1** in 60% yield (Method A). When compound **25** was heated in toluene with catalyst **2**, the desired isomeric lactam **23** was isolated in 56% yield, together with a mixture of other amides, which were easily separated by means of flash column chromatography (Scheme 7).

Much less interesting from a synthetic point of view were the results obtained in the synthesis of nine-membered lactams.

(28) To confirm this hypothesis, we decided to study the isomerization process on the tertiary amide *N*,*N*-dibenzyl-2,2-difluoro-4-pentenamide. We found that when this compound was treated with catalyst **2** in conditions similar to those in Method B, only the corresponding homodimer resulting from a cross metathesis was observed. Moreover, when hydride catalyst RuHCl(CO)(PPh_3)$_3$ was used, the starting amide was recovered unchanged, without a trace of double bond isomerization, which illustrates the reluctance of the CF_2-allyl grouping to undergo isomerization processes:



(29) In this case, δ-lactam **14** would arise from the result of a double isomerization in the nonfluorinated precursor **22**. In contrast, no six-membered lactam was detected in the case of fluorinated derivatives, which indicates that the double bond isomerization catalyzed by ruthenium catalyst **2** does not take place on the difluoroolefinic chain.

In this case, regardless of whether the starting amides contained the *gem*-difluoro moiety or not, complex mixtures of nine-, eight-, seven-, and six-membered lactams were obtained (15%, 36%, 16%, and 3% and 0%, 26%, 23%, and 19% yields for fluorinated and nonfluorinated derivatives, respectively, as determined through GC−MS). Evidently, and in contrast with smaller rings, the formation of the nine-membered ring is disfavored, a circumstance that facilitates double bond isomerizations prior to the RCM, which in turn promotes the formation of complex mixtures of lactams with smaller ring sizes.

Finally, to extend the scope of this method, we decided to apply our tandem RCM−isomerization protocol (Method B) to some compounds that had previously been obtained by other authors through standard RCM methods (Table 2). Thus, the tandem protocol was tested first on amide (±)-**26** (entry 1),[30] which led to the isolation of the protected Freidinger lactam (±)-**27** in a regioselective fashion, albeit in moderate yield (51%).

The next two examples (entries 2 and 3) illustrate the different behavior of two *N*,*N*-diallylamines. Thus, while diallyltosylamide **28** provided the expected isomeric *N*-tosyl-2,3-dihydropyrrole **29**[10b] in good yield when subjected to Method B, the phenylalanine methyl ester derivative **30** did not afford the expected derivative **31**.[31]

The following two entries in Table 2 (entries 4 and 5) show the results for the application of our metathesis−isomerization sequence to the synthesis of seven-membered cyclic enol ethers from acyclic allyl ethers. Cyclic enol ether (±)-**33** had already been synthesized by Snapper and co-workers in 54% yield using their tandem RCM−isomerization protocol with catalyst **2** in refluxing CH_2Cl_2 under a 95:5 N_2/H_2 atmosphere.[11a] With our protocol, the same compound (±)-**33** was obtained in 60% yield from (±)-**32** simply by reacting it with ruthenium catalyst **2** in refluxing toluene. Once again, the reaction conditions of our Method B probably cause the generation of a ruthenium hydride from catalyst **2**, thus allowing the tandem RCM−isomerization reactions to be performed conveniently and in the absence of additives.[32]

When our RCM−isomerization protocol was applied to the dienic system **34** (entry 5), a mixture of two isomerization products **35** and **36** resulted. The fact that the enol ether **35** is the major product proves once again the decisive influence of the heteroatom on the isomerization step.

The last two examples involve the synthesis of fluorinated compounds (*R*)-**38** and **40**. Our group had previously reported on the use of substrate (*R*)-**37** (entry 6) as starting material for the preparation of bicyclic difluorinated oxazolidinones by means of RCM with catalyst **1**.[33] Here, in contrast, when we refluxed a toluene solution of (*R*)-**37** in the presence of catalyst **2**, a regioselective double bond isomerization took place after the RCM, thus affording compound (*R*)-**38** in excellent yield (85%).

Finally, we studied the application of our protocol to the preparation of CF_3-substituted piperidines. In this context, Bonnet-Delpon and co-workers very recently published a straightforward route to this class of compounds through metathesis cyclization of unsaturated trifluoromethylamines with the first generation catalyst **1**.[34] As in previous examples, both the metathesis product (arising from the regular RCM reaction with catalyst **1**) and the acyclic diene **39** were easily transformed into the final isomerized tetrahydropiperidines **40** in good yield through treatment with catalyst **2** in refluxing toluene[35] (Table 2, entry 7).

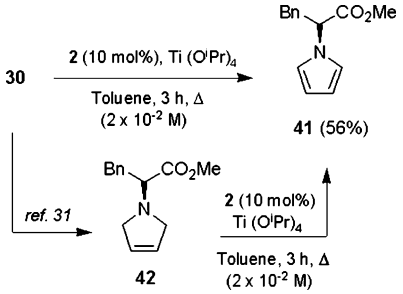
The outcome of all of the reactions depicted in Table 2 can be easily explained, since the result of the isomerization process is conditioned either by the presence of the *gem*-difluoro moiety, in which case the product of the isomerization toward the opposite side of the double bond is formed exclusively, or by the heteroatom, which favors the isomerization toward the heteroatom itself. When both structural features are present simultaneously, they influence the isomerization reaction in the same direction, thus making these processes highly regioselective.

Conclusion

In conclusion, we have developed several new examples of our tandem RCM−isomerization protocol that prove its usefulness in the synthesis of isomerized lactams of various ring sizes. The process is efficient in the preparation of five- to eight-membered rings, in which the RCM step is very fast because of the favorable ring size formation and thus occurs well before the isomerization. The only limitation to the method involves the formation of nine-membered rings. In this case, the less favored RCM step occurs more slowly, allowing the isomerization processes to take place first, which leads to the formation of mixtures of products with several ring sizes. Still, our results lead us to the conclusion that the second-generation Grubbs' catalyst **2** in refluxing toluene is likely to generate a ruthenium hydride species in situ, without the need for additives, which

(30) Hoffmann, T.; Waibel, R.; Gmeiner, P. *J. Org. Chem.* **2003**, *68*, 62−69.

(31) In this case, when substrate **30** was subjected to the tandem protocol conditions [$Ti(O^iPr)_4$ must be used as additive in this case because of the presence of a free amine group], pyrrol **41** was the only product isolated, arising from the aromatization of the isomerized product in the workup procedure. The same results were obtained when we started from the 2,5-dihydropyrrol **42** previously synthesized by RCM in a two-step sequence as described by Yang et al. See: Yang, Q.; Xiao, W.-J.; Yu, Z. *Org. Lett.* **2005**, *7*, 871−874. It is assumed that the basicity of the nitrogen atom plays an important role in the nature of the final product. The presence of an electron-withdrawing group in the nitrogen atom prevents the dehydrogenation step towards the corresponding pyrrole.

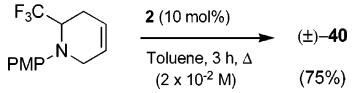


(32) In contrast, when we treated difluorinated compound **4a** in refluxing toluene as in Schmidt's protocol (NaOH/*i*-PrOH),[11b] only 30% of the isomerization product **6a** was observed even after continuous heating of the reaction flask for 1 week.

(33) Fustero, S.; Navarro, A.; Pina, B.; García Soler, J.; Bartolomé, A.; Asensio, A.; Simón, A.; Bravo, P.; Fronza, G.; Volonterio, A.; Zanda, M. *Org. Lett.* **2001**, *3*, 2621−2624.

(34) Magueur, G.; Legros, J.; Meyer, F.; Ourévitch, M.; Crousse, B.; Bonnet-Delpon, D. *Eur. J. Org. Chem.* **2005**, 1258−1265.

(35) Similar results were also obtained in a two-step sequence in which the initially formed, nonisomerized metathesis product was treated with catalyst **2** in refluxing toluene:



may, in turn, be responsible for the isomerization reaction. We have also demonstrated the crucial influence exerted by the *gem*-difluoro moiety in directing the isomerization step, making the tandem RCM−isomerization a regioselective and hence synthetically useful process.

Experimental Section

General Procedure for Preparation of Amides 4. A catalytic amount of dimethylformamide (DMF) (0.1 mL) was added to a solution of 2,2-difluoro-4-pentenoic acid (5.15 mmol) in dry dichloromethane (17 mL). The solution was cooled with an ice bath, after which oxalyl chloride (2.0 M in DCM, 5.15 mmol) was added dropwise. The resulting brown solution was stirred for 1 h at room temperature. The reaction was then cooled again to 0 °C, after which Et_3N (10.3 mmol), the corresponding primary amine (5.7 mmol), and a catalytic amount of DMAP were added simultaneously. Upon completion of the addition, the ice bath was removed and the reaction mixture was stirred for 5−6 h at room temperature. The crude mixture was then diluted with dichloromethane (20 mL) and washed with saturated ammonium chloride (3 × 15 mL). The organic layer was dried over anhydrous sodium sulfate and filtered, and the solvents were removed under reduced pressure. The resulting brown oil was purified by means of flash chromatography to afford the corresponding secondary amide. A solution of the secondary amide in dry DMF (13 mL) was then added to a suspension of NaH (3.73 mmol) in dry DMF (4 mL) at 0 °C. After the resulting solution stirred for 15 min, allyl bromide (9.3 mmol) was added dropwise. The ice bath was then removed, and the reaction mixture was stirred at room temperature until TLC analysis indicated that the starting material was no longer present (3−4 h). The DMF was removed under reduced pressure, and the resulting yellow residue was treated with water (20 mL) and extracted with ethyl acetate (3 × 20 mL). The organic layer was dried over anhydrous sodium sulfate and filtered, and the solvents were removed under reduced pressure. After purification of the residue by means of flash chromatography, amides **4** were obtained.

***N*-Allyl-*N*-benzyl-2,2-difluoro-4-pentenamide (4a).** Flash chromatography [*n*-hexanes−EtOAc (10:1)] (R_f = 0.40) afforded **4a** as a pale yellow oil (60% overall yield). ^{1}H, ^{13}C, and ^{19}F NMR showed the presence of two rotamers around the amide bond in a 1.4:1 ratio. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.84−2.98 (m, 2H), 3.80 (d, J = 5.8 Hz, 1H, minor rotamer), 3.95 (d, J = 5.8 Hz, 1H, major rotamer), 4.51 (s, 1H, major rotamer), 4.65 (s, 1H, minor rotamer), 4.99−5.24 (m, 4H), 5.60−5.86 (m, 2H), 7.13−7.28 (m, 5H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 39.5 (t, $^2J_{CF}$ = 23.9 Hz), 47.9 (t), 48.2 (t), 48.9 (t, $^4J_{CF}$ = 6.3 Hz), 49.7 (t, $^4J_{CF}$ = 6.3 Hz), 118.1 (t), 118.5 (t, $^1J_{CF}$ = 255.9 Hz), 118.7 (t), 121.1 (t); 127.4 (d), 127.6 (d), 127.7 (d), 128.0 (d), 128.3 (t, $^3J_{CF}$ = 5.2 Hz), 128.7 (d), 131.3 (d), 132.8 (d), 135.9 (s), 136.13 (s), 163.2 (t, $^2J_{CF}$ = 29.0 Hz), 163.4 (t, $^2J_{CF}$ = 29.3 Hz); ^{19}F NMR ($CDCl_3$, 282.4 MHz) δ −98.1 (t, J_{FH} = 18.0 Hz, 2F, minor rotamer), −99.1 (t, J_{FH} = 18.0 Hz, 2F, major rotamer); HRMS (EI$^+$) calcd for $C_{15}H_{17}F_2NO$ (M^+) 265.1278, found 265.1286.

General Procedure for Preparation of ϵ-Lactams 5. Method A. A solution of ruthenium catalyst **1** (5 mol % for **5a**−**c**; 10 mol % for **5d**) in dry dichloromethane was added via cannula to a solution of amides **4** (0.8 mmol) in dichloromethane (2×10^{-2} M). The resulting dark brown solution was heated at reflux until TLC indicated that the starting material was no longer present (usually after 5−6 h). The solvents were removed under reduced pressure, and the residue was purified by means of flash chromatography.

1-Benzyl-3,3-difluoro-1,3,4,7-tetrahydro-2*H*-2-azepinone (5a). Flash chromatography [*n*-hexanes−EtOAc (7:1)] (R_f = 0.10) afforded **5a** as a pale brown oil (95% yield). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.80 (tq, J = 16.1, 2.1 Hz, 2H), 3.82−3.84 (m, 2H), 4.63 (s, 2H), 5.53−5.58 (m, 1H), 5.62−5.68 (m, 1H), 7.15−7.27 (m, 5H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 34.7 (t, $^2J_{CF}$ = 26.5 Hz), 45.5 (t, $^4J_{CF}$ = 4.9 Hz), 52.5 (t), 116.5 (t, $^1J_{CF}$ = 247.8 Hz), 124.1 (t, $^3J_{CF}$ = 6.0 Hz), 125.2 (d), 127.8 (d), 127.8 (d), 128.7 (d), 136.0 (s), 164.4 (t, $^2J_{CF}$ = 28.8 Hz); ^{19}F NMR ($CDCl_3$, 282.4 MHz) δ −101.3 (t, J_{FH} = 16.0 Hz, 2F); HRMS (EI$^+$) calcd for $C_{13}H_{13}F_2NO$ (M^+) 237.0965, found 237.0956. Anal. Calcd for $C_{13}H_{13}F_2NO$: C, 65.81; H, 5.52; N, 5.90. Found: C, 65.83; H, 5.52; N, 5.80.

General Procedure for Preparation of Cyclic Enamides 6. Method B. This method is analogous to Method A, except that here catalyst **2** is used and the solvent is toluene under reflux. With this catalyst (5 mol % for **6a**−**c**; 10% mol for **6d**−**f**), the reactions took 2−3 h to complete.

1-Benzyl-3,3-difluoro-1,3,4,5-tetrahydro-2*H*-2-azepinone (6a). Flash chromatography [*n*-hexanes−EtOAc (7:1)] (R_f = 0.20) afforded **6a** as a brown oil (73% yield). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.13−2.20 (m, 2H), 2.39−2.54 (m, 2H), 4.64 (s, 2H), 5.38 (dt, J = 8.6, 6.2 Hz, 1H), 5.85 (dt, J = 8.9, 1.2 Hz, 1H), 7.21−7.23 (m, 5H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 20.3 (t, $^3J_{CF}$ = 5.6 Hz), 38.4 (t, $^2J_{CF}$ = 24.2 Hz), 51.5 (t), 116.7 (t, $^1J_{CF}$ = 249.3 Hz), 117.5 (d), 127.8 (d), 128.0 (d), 128.7 (d), 128.9 (d), 136.0 (s), 164.4 (t, $^2J_{CF}$ = 29.6 Hz); ^{19}F NMR ($CDCl_3$, 282.4 MHz) δ −96.9 (t, J_{FH} = 15.5 Hz, 2F); HRMS (EI$^+$) calcd for $C_{13}H_{13}F_2NO$ (M^+) 237.0965, found 237.0962. Anal. Calcd for $C_{13}H_{13}F_2NO$: C, 65.81; H, 5.52; N, 5.90. Found: C, 65.72; H, 5.60; N, 5.99.

Synthesis of Seven-Membered, Nonfluorinated Lactams 9 and 10. These were prepared from **8** as starting material by means of the general procedure described above for compounds **6** (Method B). Flash chromatography [*n*-hexanes−EtOAc (5:1)] afforded 1-benzyl-2,3,4,5-tetrahydro-1*H*-2-azepinone (**9**) (R_f = 0.25) (67% yield) and 1-benzyl-2,3,6,7-tetrahydro-1*H*-2-azepinone (**10**) (R_f = 0.10) (29% yield), both as brown oils. **Data for 1-benzyl-2,3,4,5-tetrahydro-1*H*-2-azepinone (9):** ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.97−2.10 (m, 4H), 2.52−2.56 (m, 2H), 4.57 (s, 2H), 5.27 (dt, J = 9.0, 5.6 Hz, 1H), 5.83 (dt, J = 9.0, 1.4 Hz, 1H), 7.17−7.24 (m, 5H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 26.1 (t), 26.5 (t), 35.9 (t), 50.4 (t), 117.8 (d), 127.3 (d), 127.8 (d), 128.5 (d), 129.6 (d), 137.6 (s), 174.1 (s); HRMS (EI$^+$) calcd for $C_{13}H_{15}NO$ (M^+) 201.1154, found 201.1127. **Data for 1-benzyl-2,3,6,7-tetrahydro-1*H*-2-azepinone (10):** ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.03−2.07 (m, 2H), 3.25−3.26 (m, 2H), 3.42−3.47 (m, 2H), 4.56 (s, 2H), 5.55−5.56 (m, 2H), 7.19−7.27 (m, 5H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 28.4 (t), 35.9 (t), 45.3 (t), 49.7 (t), 120.9 (d), 128.4 (d), 128.0 (d), 128.6 (d), 129.0 (d), 137.8 (s), 173.6 (s); HRMS (EI$^+$) calcd for $C_{13}H_{15}NO$ (M^+) 201.1154, found 201.1129.

Synthesis of Six-Membered Nonfluorinated and Fluorinated Lactams 14 and 17. 1-Benzyl-1,2,3,4-tetrahydro-2-pyridinone (14). Prepared from **13** with the general procedure described above for compounds **6** (Method B). Flash chromatography [*n*-hexanes−EtOAc (2:1)] (R_f = 0.15) afforded **14** as a brown oil (82% yield). Its spectroscopic data matched those previously reported.[36]

***N*-Benzyl-2,2-difluoro-*N*-[(*E*/*Z*)-1-propenyl]-4-pentenamide (16).** A solution of ruthenium hydride catalyst [RuHCl(CO)(PPh_3)$_3$] (10 mol %) in dry toluene was added via cannula to a solution of **4a** (0.3 mmol) in toluene (10 mL). The resulting dark brown solution was heated at reflux for 3 h. The solvents were removed under reduced pressure, and the residue was purified by means of flash chromatography [*n*-hexanes−EtOAc (10:1)] (R_f = 0.40), affording amide **16** as a complex mixture of amide rotamers and *E*/*Z* isomers (71% yield). The compound **16** thus obtained was used immediately in the subsequent cyclization step.

1-Benzyl-3,3-difluoro-1,2,3,4-tetrahydro-2-pyridinone (17). Prepared from **16** with the general procedure described above for compounds **6** (Method B) except that here catalyst **2** was used in refluxing dichloromethane. Flash chromatography [*n*-hexanes−EtOAc (5:1)] (R_f = 0.20) afforded **17** as a white solid (66% yield).

(36) Ojima, I.; Korda, A.; Shay, W. R. *J. Org. Chem.* **1991**, *56*, 2024−2030.

Mp 72−74 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.82 (tq, J = 17.1, 2.0 Hz, 2H), 4.69 (s, 2H), 5.03−5.09 (m, 1H), 5.99 (dt, J = 7.9, 1.7 Hz, 1H), 7.18−7.29 (m, 5H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 31.8 (t, $^2J_{CF}$ = 25.3 Hz), 49.6 (t), 101.8 (t, $^3J_{CF}$ = 5.2 Hz), 112.1 (t, $^1J_{CF}$ = 246.7 Hz), 127.8 (d), 128.1 (d), 128.3 (d), 128.9 (d), 135.5 (s), 160.2 (t, $^2J_{CF}$ = 29.9 Hz); ^{19}F NMR ($CDCl_3$, 282.4 MHz) δ −105.1 (dt, J_{FH} = 17.2, 2.6 Hz, 2F); HRMS (EI$^+$) calcd for $C_{12}H_{11}F_2NO$ (M^+) 223.0809, found 223.1077. Anal. Calcd for $C_{12}H_{11}F_2NO$: C, 64.57; H, 4.97; N, 6.27. Found: C, 64.44; H, 4.79; N, 6.06.

2,2-Difluoro-5-hexenoic Acid. A 1 M solution of the Grignard derivative from either 4-bromo-1-butene in THF (13 mmol) was added to a solution of diethyl oxalate (11.8 mmol) in THF (8 mL) at −78 °C. After stirring for 1 h, the reaction mixture was quenched with saturated aqueous NH_4Cl, and the aqueous layer was extracted with ethyl acetate (3 × 20 mL). The combined organic layers were washed with saturated aqueous NaCl (3 × 20 mL) and dried over anhydrous Na_2SO_4. Filtration and evaporation of solvents gave the corresponding crude α-keto ester, which was purified by means of flash chromatography.

Next, Deoxofluor (10.2 mmol) and ethanol as catalyst (1.2 mmol) were added to a solution of the α-keto ester (6 mmol) in dry dichloromethane (19 mL) at 0 °C. The reaction mixture was stirred for 14 h and then quenched with saturated aqueous $NaHCO_3$ and extracted with dichloromethane (3 × 20 mL). The combined organic layers were washed with aqueous HCl (3 × 15 mL) and brine (3 × 15 mL), dried over anhydrous sodium sulfate, and filtered, after which the volatiles were removed under reduced pressure to afford the intermediate difluorinated ester. This was, in turn, dissolved in dry THF (18 mL) and treated with water (5 mL) and $LiOH\cdot H_2O$ (18 mmol) in an ice bath. After stirring for 5 h, the reaction mixture was acidified with an aqueous solution of HCl and extracted with ethyl acetate (3 × 20 mL). The organic layers were washed with brine (3 × 20 mL), dried over anhydrous Na_2SO_4, and filtered, after which the filtrate was distilled under reduced pressure to afford the pure carboxylic acid in 85% yield. Bp 30−33 °C (10^{-2} Torr); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.08−2.24 (m, 4H), 4.96−5.06 (m, 2H), 5.69−5.78 (m, 1H), 10.22 (br s, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 25.5 (t, $^3J_{CF}$ = 4.6 Hz), 33.5 (t, $^2J_{CF}$ = 23.0 Hz), 115.7 (t, $^1J_{CF}$ = 250.4 Hz), 116.2 (t), 135.5 (d), 168.7 (t, $^2J_{CF}$ = 33.6 Hz). ^{19}F NMR (282.4 MHz, $CDCl_3$) δ −107.9 (t, J_{FH} = 16.0 Hz, 2F). HRMS (EI$^+$) calcd for $C_6H_8F_2O_2$ (M^+) 150.0942, found 150.0452.

General Procedure for Preparation of Difluorinated Amides 18 and 22. A catalytic amount of dimethylformamide (DMF) (0.1 mL) was added to a solution of the corresponding α,α-difluoro-ω-alkenoic acid (5.15 mmol) in dry dichloromethane (17 mL). The solution was cooled to 0 °C with an ice bath, after which oxalyl chloride (2.0 M in DCM, 5.15 mmol) was added dropwise. The resulting brown solution was stirred for 1 h at room temperature. The reaction was then cooled a second time to 0 °C, and then Et_3N (10.3 mmol), allyl benzylamine (5.7 mmol), and a catalytic amount of DMAP were added simultaneously. After the addition was completed, the ice bath was removed, and the reaction mixture was stirred for 5−6 h at room temperature. The crude mixture was then diluted with DCM (20 mL) and washed three times with saturated ammonium chloride (2 × 15 mL). The organic layer was dried over anhydrous sodium sulfate and filtered; the solvents were then removed under reduced pressure. The resulting brown oil was purified by means of flash chromatography to afford the corresponding tertiary amides **18** and **22**.

***N*-Allyl-*N*-benzyl-2,2-difluoro-5-hexenamide (18).** Flash chromatography [*n*-hexanes−EtOAc (15:1)] (R_f = 0.30) afforded **18** as a colorless oil (60% yield). ^{1}H, ^{13}C, and ^{19}F NMR showed the presence of two rotamers around the amide bond in a 1.4:1 ratio. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.24−2.28 (m, 4H), 3.81 (d, J = 6.0 Hz, 2H, minor rotamer), 3.97 (d, J = 6.0 Hz, 2H, major rotamer), 4.52 (s, 2H, major rotamer), 4.66 (s, 2H, minor rotamer), 4.93−5.21 (m, 4H), 5.61−5.83 (m, 2H), 7.13−7.29 (m, 5H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 25.8 (t, $^3J_{CF}$ = 4.9 Hz), 34.1 (t, $^2J_{CF}$ = 23.3 Hz), 48.0 (t), 48.2 (t), 49.0 (t, $^4J_{CF}$ = 6.3 Hz), 49.8 (t, $^4J_{CF}$ = 6.3 Hz), 115.4 (t), 118.1 (t), 118.7 (t), 119.5 (t, $^1J_{CF}$ = 255.0 Hz), 127.4 (t), 127.6 (d), 127.7 (d), 128.0 (d), 128.7 (d), 128.7 (d), 131.4 (d), 133.0 (d), 136.0 (s), 136.2 (s), 136.7 (d), 163.4 (t, $^2J_{CF}$ = 29.3 Hz), 163.6 (t, $^2J_{CF}$ = 29.3 Hz); ^{19}F NMR ($CDCl_3$, 282.4 MHz) δ −109.1 (t, J_{FH} = 17.3 Hz, 2F, minor rotamer), −110.0 (t, J_{FH} = 17.3 Hz, 2F, major rotamer); HRMS (EI$^+$) calcd for $C_{16}H_{19}F_2NO$ (M^+) 279.1435, found 279.1467.

Synthesis of Eight-Membered Fluorinated and Nonfluorinated Lactams 19, 21, and 23. 1-Benzyl-3,3-difluoro-1,2,3,4,5,6-hexahydro-2-azocinone (19). Prepared from **18** with the general procedure described above for compounds **6** (Method B). GC−MS analysis showed a mixture of compounds **19**, **20**, and **6a** in a 13:1:1.2 ratio. Flash chromatography [*n*-hexanes−EtOAc (5:1)] (R_f = 0.30) afforded **19** as a yellow oil (65% yield). In the ^{1}H NMR spectrum some signals appear broadened because of conformational equilibrium. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.19−2.03 (br m, 6H), 4.35 (br s, 1H), 4.78 (br s, 1H), 5.35 (q, J = 8.2 Hz, 1H), 5.89 (d, J = 7.5 Hz, 1H), 7.22−7.27 (m, 5H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 20.7 (t, $^3J_{CF}$ = 4.6 Hz), 23.6 (t), 33.0 (t, $^2J_{CF}$ = 25.3 Hz), 51.7 (t), 119.6 (t, $^1J_{CF}$ = 251.7 Hz), 125.5 (t, $^4J_{CF}$ = 2.0 Hz), 126.7 (d), 127.8 (d), 128.5 (d), 128.9 (d), 135.5 (s), 164.6 (t, $^2J_{CF}$ = 27.9 Hz); ^{19}F NMR ($CDCl_3$, 282.4 MHz) δ −112.2 (dd, J_{FF}= 245.7 Hz, J_{HF} = 13.8 Hz, 1F), −99.6 (d, J_{FF} = 240.5 Hz, 1F); HRMS (EI$^+$) calcd for $C_{14}H_{15}F_2NO$ (M^+) 251.1122, found 251.1129.

1-Benzyl-3,3-difluoro-1,2,3,4,5,8-hexahydro-2-azocinone (21). Prepared from **18** with the general procedure described above for compounds **5** (Method A). Flash chromatography [*n*-hexanes−EtOAc (7:1)] (R_f = 0.15) afforded **25** as a yellow oil (70% yield). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.08−2.22 (m, 2H), 2.30−2.37 (m, 2H), 3.83 (d, J = 7.2 Hz, 2H), 4.57 (s, 2H), 5.69−5.83 (m, 2H), 7.19−7.28 (m, 5H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 19.9 (t, $^3J_{CF}$ = 6.3 Hz), 35.0 (t, $^2J_{CF}$ = 25.3 Hz), 42.5 (t, $^4J_{CF}$ = 5.5 Hz), 51.0 (t), 118.4 (t, $^1J_{CF}$ = 249.5 Hz), 127.8 (d), 128.4 (d), 128.7 (d), 129.4 (d), 132.8 (d), 136.3 (s), 165.5 (t, $^2J_{CF}$ = 28.8 Hz); ^{19}F NMR ($CDCl_3$, 282.4 MHz) δ −104.3 (br s, 2F); HRMS (EI$^+$) calcd for $C_{14}H_{15}F_2NO$ (M^+) 251.1122, found 251.1109. Anal. Calcd for $C_{14}H_{15}F_2NO$: C, 66.92; H, 6.02; N, 5.57. Found: C, 66.74; H, 6.15; N, 5.42.

1-Benzyl-1,2,3,4,5,6-hexahydro-2-azocinone (23). Prepared from **22** with the general procedure described above for compounds **6** (Method B). GC−MS analysis showed the presence of compounds **23**, **24**, **9**, **10**, and **14** in a 14:3:3:2:1 ratio. Flash chromatography [*n*-hexanes−EtOAc (4:1)] (R_f = 0.20) afforded pure **23** as a brown oil (57% yield). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.40 (br s, 2H), 1.61−1.77 (m, 4H), 2.43−2.47 (m, 2H), 4.57 (s, 2H), 5.34 (q, J = 8.0 Hz, 1H), 5.87 (d, J = 7.9 Hz, 1H), 7.19−7.24 (m, 5H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 23.1 (t), 23.7 (t), 24.6 (t), 30.0 (t), 49.0 (t), 125.9 (d), 127.3 (d), 128.3 (d), 128.4 (d), 128.6 (d), 137.1 (s), 173.7 (s); HRMS (EI$^+$) calcd for $C_{14}H_{17}NO$ (M^+) 215.1310, found 215.1304.

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Supporting Information Available: Experimental procedures and characterization data for compounds **5c**−**g** and **6b**−**e**, their precursors, and compounds **26**−**42**, as well as the results for ab initio energy calculations of compounds **5a**, **6a**, and **7**. This material is available free of charge via the Internet at http://pubs.acs.org.

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