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RCM-Mediated Synthesis of Trifluoromethyl-Containing Nitrogen Heterocycles

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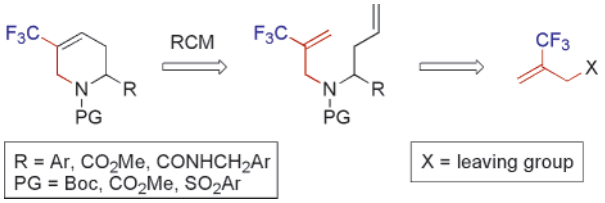


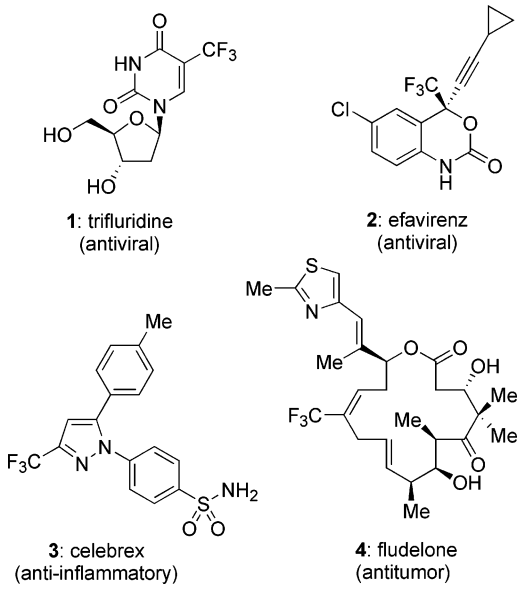
A ring-closing metathesis mediated pathway to trifluoromethyl-containing piperidines is detailed. This involves the development of a synthetic route to a new (trifluoromethyl)allylating reagent via a Diels−Alder/retro-Diels−Alder strategy, its application in the synthesis of a series of trifluormethyl-substituted diolefin precursors for ring-closing metathesis, and eventually the successful cyclization of these precursor molecules into the corresponding functionalized piperidines.

Introduction

Over the past decade or so, it has become increasingly clear that fluorine substituents often display a positive effect on the pharmacokinetics and pharmacodynamic properties of potential drugs.[1] As a result, the introduction of fluorinated substituents has become an important tool to modulate the properties of biologically active substances. Subsequently, the interest of the pharmaceutical industry in trifluoromethyl-containing compounds has grown significantly: nowadays, many trifluoromethylated products exist on the market such as analgesic, cardiovascular, respiratory, and gastrointestinal drugs.[2] Some particular examples of important trifluoromethyl-containing drugs are shown in Chart 1.

Trifluridine (**1**)[3] and efavirenz (**2**)[4] are both antiviral drugs and Celebrex (**3**)[4] is an antiinflammatory drug that are currently on the market. Another new promising candidate is the epothilone derivative fludelone (**4**), which shows an extremely high therapeutic efficacy against various carcinomas.[5]

CHART 1. Trifluoromethylated Heterocycles



Considering the general biological relevance of trifluoromethyl-containing heterocycles, combined with the difficulty

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(1) For recent reviews, see, e.g.: (a) Ismail, F. M. D. *J. Fluorine Chem.* **2002**, *118*, 27. (b) *Biomedical Frontiers of Fluorine Chemistry*; Ojima, I., McCarthy, J. R., Welch, J. T., Eds.; ACS Symposium Series 639; American Chemical Society: Washington, DC, 1996. (c) Welch, J. T.; Eswarakrishnan, S. *Fluorine in Bioorganic Chemistry*, Wiley: New York, 1991. (d) *Enantiocontrolled Synthesis of Fluoro-organic Biomedical Targets*; Soloshonok, V. A., Ed.; Wiley: New York, 1999. (e) Halpern, D. F. In *Organofluorine Compounds in Medicinal Chemistry and Biomedical Applications*; Filler, R., Kobayashi, Y., Yagupolskii, L., Eds.; Elsevier: Amsterdam, 1993; pp 101−133.

(2) For excellent overviews, see, e.g.: (a) Chambers, R. D. *Fluorine in Organic Chemistry*; Blackwell: Oxford, 2004. (b) Kirsch, P. *Modern Fluoroorganic Chemistry*; Wiley-VCH: Weinheim, 2004.

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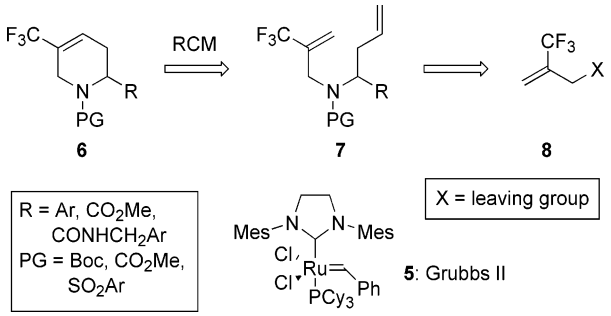
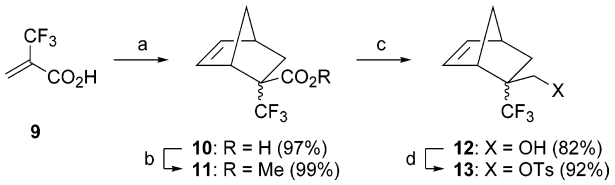
SCHEME 1. Retrosynthetic Approach



of introducing trifluoromethyl substituents in nonaromatic ring systems,[6] we started to investigate whether ring-closing metathesis (RCM) could serve as a potential approach to synthesize trifluoromethyl-substituted (hetero)cyclic building blocks.[7] Retrosynthetically, we envisaged that trifluoromethylated olefins (viz. **7**, Scheme 1) might serve as suitable precursors for the preparation of the corresponding ring systems **6** using the second generation Grubbs Ru−carbene catalyst **5**.[8] Such an approach would commence with the development of a synthetic route to an appropriate allylating reagent of type **8**.

Nowadays, owing to the emergence of relatively stable, tolerant, and versatile Ru−carbene catalysts, the applicability of RCM processes is well-established.[9] As a result, a wide range of differently substituted olefins have been successfully transformed into the corresponding (hetero)cyclic systems. Only relatively few examples of olefins with allylic fluoride substituents exist,[10,11] which are all examples of monosubstituted olefins. We were the first to report examples of disubstituted trifluoromethyl-containing olefins,[8,12] of which in this contribution a detailed account is provided, including the functionalization to heavily functionalized nitrogen heterocyclic systems.

SCHEME 2. Masking of the Acrylate[a]



[a] Reagents and conditions: (a) cyclopentadiene, CH_2Cl_2, rt, 12 h; (b) $(MeO)_2SO_2$, dry acetone, K_2CO_3, reflux, 5 h; (c) $LiAlH_4$, dry Et_2O, rt, 5 h; (d) TsCl, dry pyridine, rt, 24 h.

Results and Discussion

To have facile and straightforward access to the required trifluoromethylated olefins, a method had to be developed to incorporate the trifluoroallyl moiety in the RCM precursors **7**. In our view, *N*-alkylation with compounds of type **8** would serve this purpose, where X is a good leaving group such as chloride, bromide, or tosylate. However, these latter compounds are not commercially available nor easy to prepare from commercially available sources. In addition, the corresponding alcohol, 2-trifluoromethyl-2-propenol, is not trivial to make. For example, straightforward reduction of the corresponding carboxylic acid, 2-trifluoromethylacrylic acid, either direct via $LiAlH_4$ reduction[13] or indirect via acid chloride formation[14] followed by $LiAlH_4$ reduction[15] appeared in our hands to be either unreliable or laborious, so that we decided to develop a novel pathway for its synthesis (Scheme 2). Since the reported problems were generally associated with the reactivity of the α,β-unsaturated acrylic system, we envisaged that it would be advantageous to protect the olefin in some way. Hence, we chose to mask the double bond in a Diels−Alder reaction with cyclopentadiene, which may then be unveiled in a later stage. 2-Trifluoromethylacrylic acid (**9**) was reacted with freshly distilled cyclopentadiene to give the Diels−Alder adduct **10** as a 2:1 mixture of *endo*/*exo*-diastereoisomers in excellent yield after recrystallization.[16] This mixture was esterified ($(MeO)_2SO_2$, dry acetone, K_2CO_3, reflux, 5 h), reduced ($LiAlH_4$, dry Et_2O, rt, 5 h), and reacted with TsCl (TsCl, dry pyridine, rt, 24 h) to yield tosylate **13** in an excellent overall yield.

At this stage, the retro-Diels−Alder reaction was investigated. Initially, we chose to unmask the olefin using flash vacuum thermolysis (FVT) conditions.[8] Both T_1 (the oven where the

(3) For an entry into relevant literature, see: Carmine, A. A.; Brogden, R. N.; Heel, R. C.; Speight, T. M.; Avery, G. S. *Drugs* **1982**, *23*, 329.

(4) *The Merck Index*, 13th ed.; Merck and Co.: Whitehouse Station, NJ, 2001.

(5) Rivkin, A.; Chou, T.-C.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **2005**, *44*, 2838.

(6) Lin, P.; Jiang, J. *Tetrahedron* **2000**, *56*, 3635−3671.

(7) Previous reports from our group in RCM-mediated heterocycle synthesis: (a) Rutjes, F. P. J. T.; Schoemaker, H. E. *Tetrahedron Lett.* **1997**, *38*, 677. (b) Rutjes, F. P. J. T.; Kooistra, T. M.; Hiemstra, H.; Schoemaker, H. E. *Synlett* **1998**, 192. (c) Veerman, J. J. N.; van Maarseveen, J. H.; Visser, G. M.; Kruse, C. G.; Hiemstra, H.; Schoemaker, H. E.; Rutjes, F. P. J. T. *Eur. J. Org. Chem.* **1998**, 2583. (d) Tjen, K. C. M. F.; Kinderman, S. S.; Schoemaker, H. E.; Hiemstra, H.; Rutjes, F. P. J. T. *Chem. Commun.* **2000**, 699. (e) Doodeman, R.; Rutjes, F. P. J. T.; Hiemstra, H. *Tetrahedron Lett.* **2000**, *41*, 5979. (f) Kaptein, B.; Broxterman, Q. B.; Schoemaker, H. E.; Rutjes, F. P. J. T.; Veerman, J. J. N.; Kamphuis, J.; Peggion, C.; Formaggio, F.; Toniolo, C. *Tetrahedron* **2001**, *57*, 6567. (g) Kinderman, S. S.; van Maarseveen, J. H.; Schoemaker, H. E.; Hiemstra, H.; Rutjes, F. P. J. T. *Org. Lett.* **2001**, *3*, 2045. (h) Kinderman, S. S.; Doodeman, R.; van Beijma, J. W.; Russcher, J. C.; Tjen, K. C. M. F.; Kooistra, T. M.; Mohaselzadeh, H.; van Maarseveen, J. H.; Hiemstra, H.; Schoemaker, H. E.; Rutjes, F. P. J. T. *Adv. Synth. Catal.* **2002**, *344*, 736. (i) Hekking, K. F. W.; Van Delft, F. L.; Rutjes, F. P. J. T. *Tetrahedron* **2003**, *59*, 6751. (j) Kinderman, S. S.; de Gelder, R.; van Maarseveen, J. H.; Schoemaker, H. E.; Hiemstra, H.; Rutjes, F. P. J. T. *J. Am. Chem. Soc.* **2004**, *126*, 4100. (k) Kinderman, S. S.; van Maarseveen, J. H.; Schoemaker, H. E.; Hiemstra, H.; Rutjes, F. P. J. T. *Synthesis* **2004**, 1413. (l) Busscher, G. F.; Rutjes, F. P. J. T.; van Delft, F. L. *Tetrahedron Lett.* **2004**, *45*, 3629. (m) Kinderman, S. S.; Wekking, M. M. T.; van Maarseveen, J. H.; Schoemaker, H. E.; Hiemstra, H.; Rutjes, F. P. J. T. *J. Org. Chem.* **2005**, *70*, 5519.

(8) Part of this research has been previously published in a preliminary account: De Matteis, V.; Van Delft, F. L.; De Gelder, R.; Tiebes, J.; Rutjes, F. P. J. T. *Tetrahedron Lett.* **2004**, *45*, 959.

(9) For review articles, see: (a) Deiters, A.; Martin, S. F. *Chem. Rev.* **2004**, *104*, 2199. (b) McReynolds, M. D.; Dougherty, J. M.; Hanson, P. R. *Chem. Rev.* **2004**, *104*, 2239. (c) Fürstner, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3012. (d) Trnka, T. M.; Grubbs, R. H. *Acc. Chem. Res.* **2001**, *34*, 18.

(10) Cross-metathesis examples: (a) Imhof, S.; Randl, S.; Blechert, S. *Chem. Commun.* **2001**, 1692. (b) Chatterjee, A. K.; Morgan, J. P.; Scholl, M.; Grubbs, R. H. *J. Am. Chem. Soc.* **2000**, *122*, 3783.

(11) RCM examples: (a) Percy, J. M.; Pintat, S. *Chem. Commun.* **2000**, 607. (b) Audouard, C.; Fawcett, J.; Griffiths, G. A.; Percy, J. M.; Pintat, S.; Smith, C. A. *Org. Biomol. Chem.* **2004**, *2*, 528. (c) Masuda, T.; Shibuya, S.; Arai, M.; Yoshida, S.; Tomozawa, T.; Ohno, A.; Yamashitab, M.; Honda, T. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 669.

(12) For a similar approach to the synthesis of fluoro-substituted heterocycles, see: De Matteis, V.; van Delft, F. L.; Tiebes, J.; Rutjes, F. P. J. T. *Eur. J. Org. Chem.* **2006**, 1166.

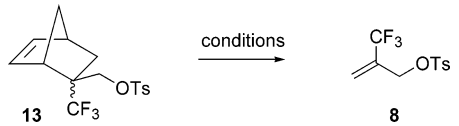
(13) For $LiAlH_4$ reduction of the corresponding fluoroacrylic acid, see: Laue, K. W.; Haufe, G. *Synthesis* **1998**, 1453.

(14) Furuta, S.; Saito, Y.; Fuchigami, T. *J. Fluorine Chem.* **1998**, *87*, 209.

(15) Solomon, M.; Hoekstra, W.; Zima, G.; Liotta, D. *J. Org. Chem.* **1988**, *53*, 5058.

(16) (a) Hanzawa, Y.; Suzuki, M.; Kobayashi, Y. *Tetrahedron Lett.* **1989**, *30*, 571. (b) Hanzawa, Y.; Suzuki, M.; Kobayashi, Y.; Taguchi, T. *J. Org. Chem.* **1991**, *56*, 1718.

TABLE 1. Retro-Diels−Alder Reaction

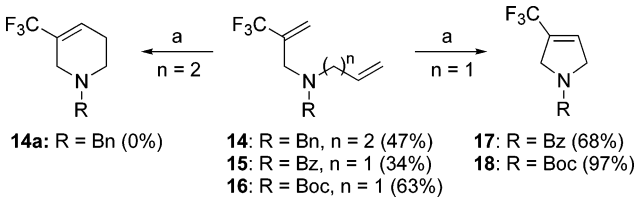


entry	conditions	yield (%)
1	FVT, $T_1 = 120$ °C, $T_2 = 600$ °C, 0.04 mbar, 13 h	95
2	diphenyl ether, 260 °C, 12 h	31
3	diphenyl ether, 190 °C, 5 h	10
4	diphenyl ether, 250 °C, 8 h	82
5	microwave, 185 W, diphenyl ether, $BMIMPF_6$, 232 °C, 30 min	41
6	microwave, 200 W, diphenyl ether, $BMIMPF_6$, 240 °C, 20 min	27
7	microwave, 300 W, diphenyl ether, $BMIMPF_6$, 250 °C, 30 min	trace
8	microwave, 182 W, diphenyl ether, $BMIMPF_6$, maleic anhydride, 240 °C, 50 min	68
9	microwave, 182 W, diphenyl ether, $BMIMPF_6$, 240 °C, 50 min	85

compound is evaporated) and T_2 (the oven where the unimolecular reaction takes place) were varied, while the pressure was kept at 0.04 mbar. The optimum result is depicted in Table 1, where 100−200 mg batches were subjected to $T_1 = 120$ °C and $T_2 = 600$ °C, providing the required tosylate **8** in essentially pure form and excellent yield (entry 1). It was used without further purification for subsequent follow-up chemistry but could also be further purified over a short silica gel column. Although this pathway represents an efficient synthesis of the trifluoromethylated alkylating agent, a drawback is the fact that this procedure is rather laborious and time-consuming and therefore difficult to scale-up.

For this reason, we have been exploring pathways that would provide alternative means for the retro-Diels−Alder reaction. One of the alternatives is a thermal solution-phase reaction using a high-boiling solvent such as diphenyl ether (entries 2−4). Again, a series of reactions was performed to screen several conditions, and it appeared that an optimum was reached at 250 °C with a reaction time of 8 h to give the tosylate **8** in 82% yield after filtration over a short path of silica gel. Although this result by itself was satisfactory, scaling up of this reaction appeared somewhat problematic due to the fact that reaction times had to be optimized again for each experiment. Finally, we also considered using a monomode microwave oven to perform the retro-Diels−Alder reaction (entries 5−9). In view of the vast increase of examples of microwave reactions that show the capacity of this technique for increasing the yield of the products or reducing the reaction time, this particular decomposition event might also benefit from it. Initially we performed the reactions in neat diphenyl ether, but due to the relative apolar character of the solvent, the temperature of the system did not reach sufficiently high temperatures. Therefore, in all cases a small amount of the ionic liquid 1-butyl-3-methylimidazolium hexafluorophosphate ($BMIMPF_6$) was added, so that reflux temperatures could be readily reached. The irradiation power and the reaction times were varied, but also reactions were carried out in open and closed vessels. It appeared that the retro reaction went considerably faster in open vessels, probably due to the fact that the cyclopentadiene escapes from the mixture and the forward reaction is no longer possible. Alternatively, addition of an excess of a trapping reagent (e.g., maleic anhydride (entry 8)) in a closed system did not lead to better results. Eventually optimal conditions were reached, which

SCHEME 3. RCM Examples of Trifluoromethylated Olefins[a]



[a] Reagents and conditions: (a) catalyst **5** (10 mol %), toluene, 100 °C, 24 h for **17** and 2 h for **18**.

were reproducibly repeated at gram scale (entry 9). Thus, tosylate **13** dissolved in 25 mL of diphenyl ether was heated in the presence of six drops of $BMIMIPF_6$ in an open vessel at a power of 182 W for 50 min (temperature of the vessel was 240 °C) to give the tosylate **8** in 85% yield. This latter procedure for the retro-Diels−Alder step now ensures facile and efficient access to this potentially important trifluoromethylated allylating agent. Having reliable access to tosylate **8**, a preliminary investigation was performed to synthesize trifluoromethyl-containing heterocyclic building blocks via RCM (Scheme 3).

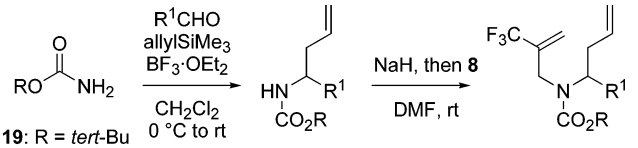
The precursors **14**−**16** were prepared via alkylation of the corresponding amine with tosylate **8** following well-known procedures, involving either *N*-benzylbut-3-en-1-amine, Et_3N, Et_2O, room temperature overnight (for **14**) or NaH, acylating agent, DMF, or rt (for **15** and **16**). Attempts to cyclize **14** to tetrahydropyridine **14a** failed under a variety of conditions, which may be due to the presence of the basic amine functionality. In contrast, in the case of substrates **15** and **16**, the *N*-acylated precursors readily cyclized to the corresponding trifluoromethyl-substituted cyclic building blocks in moderate to good yields of 68% and 97%, respectively, using catalyst **5**, which was added in portions to the reaction mixture in toluene, at 100 °C. This preliminary study gave us an initial idea of the viability of these types of metathesis reactions, and we set out to explore its possibilities for generating potentially biologically active heterocyclic compounds.

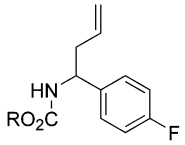
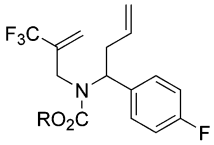
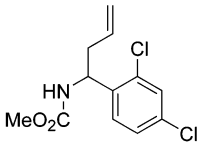
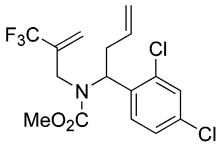
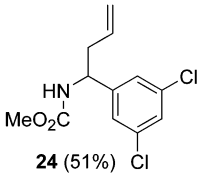
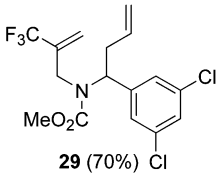
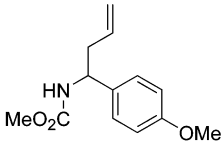
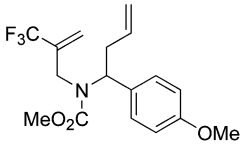
A set of precursor molecules **26**−**30** (Table 2) was prepared from compound **19**−**20** via a one-pot, three-component reaction,[17] which afforded compounds **21**−**25**. This reaction was followed by the introduction of the trifluoromethyl-containing side chain, yielding products **26**−**30**. The first step usually proceeded in moderate to good yields. The low yield (22%) observed in the formation of amide **21** might be due to partial decomposition of the acid-labile *tert*-butyl carbamate. All compounds **21**−**25** were alkylated with tosylate **8** (1 equiv, NaH, DMF, rt), which proceeded uneventfully to produce the metathesis precursors **26**−**30** in moderate to reasonable yields.

Precursor molecules **26** and **27** were then subjected to the previously used RCM conditions (catalyst **5**, toluene) at a somewhat lower temperature of 80 °C to prevent decomposition from taking place. This led to the corresponding trifluoromethyl-substituted cyclic building blocks **31** and **32** in good to excellent yield (Table 3). To investigate whether the reaction times could be decreased, cyclizations of compounds **28**−**30** were performed in a microwave oven at 80 °C and 300 W (entries 3−5). As shown in Table 3, the reaction times indeed were decreased to

(17) (a) Panek, J. S.; Jain, N. F. *J. Org. Chem.* **1994**, *59*, 2674. (b) Veenstra, S. J.; Schmid, P. *Tetrahedron Lett.* **1997**, *38*, 997. (c) Meester, W. J. N.; van Maarseveen, J. H.; Kirchsteiger, K.; Hermkens, P. H. H.; Schoemaker, H. E.; Hiemstra, H.; Rutjes, F. P. J. T. *Arkivoc* **2004**, 122.

TABLE 2. Synthesis of the RCM Precursors



entry	3-CR product (yield)	alkylation product (yield)
1	 **21**: R = *tert*-Bu (22%)	 **26**: R = *tert*-Bu (62%)
2	**22**: R = Me (50%)	**27**: R = Me (56%)
3	 **23** (68%)	 **28** (60%)
4	 **24** (51%)	 **29** (70%)
5	 **25** (30%)	 **30** (46%)

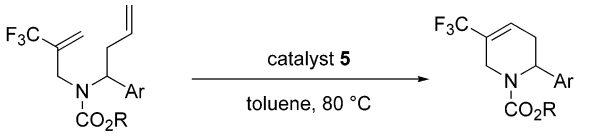
only 30 min, while the yields were largely comparable to those in the first two entries.

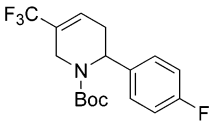
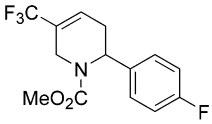
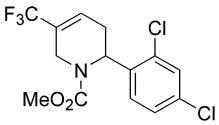
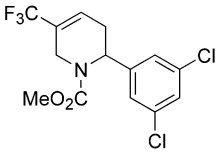
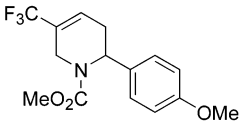
Confident by these successful cyclizations, the RCM was applied to the synthesis of cyclic amino acid derivatives. Precursor **38** was prepared from Boc-protected allylglycine methyl ester (**37**)[18] via alkylation with **8** (NaH, DMF) in 61% yield (Scheme 4). Upon subjection of **38** to similar RCM conditions, this time in toluene at 100 °C, with catalyst **5** added in portions to the reaction mixture, RCM product **39** was obtained in a satisfactory yield of 67%.

Other amino acid derivatives were synthesized next, as shown in Table 4. Thus, allylglycine (**36**, Table 4) was reacted with 5-chloro-2-methoxybenzenesulfonyl chloride (Et_3N, CH_2Cl_2, 1 h, rt) to afford the acid **40** in 80% yield. The acid **40** was then coupled to four different benzylic amines under standard peptide coupling conditions (EDCI, HOBt, CH_2Cl_2, rt), which also proceeded smoothly to afford the amides **41**−**44**. Finally, the trifluoromethylallyl substituent was introduced via coupling with **8** (NaH, DMF, 12 h, rt) leading to RCM precursors **45**−**48**. This step appeared to be somewhat more problematic as is shown by the moderate yields, which is probably due to the fact that there is an amide function present in the molecule.

(18) Collet, S.; Bauchat, P.; Danion-Bougot, R.; Danion, D. *Tetrahedron: Asymmetry* **1998**, *9*, 2121.

TABLE 3. RCM Results[a]



entry	precursor	method	catalyst (mol%)	time (min)	product (yield)
1	**26**	A	4	60	 **31** (99%)
2	**27**	A	4	60	 **32** (80%)
3	**28**	B	3	30	 **33** (63%)
4	**29**	B	3	30	 **34** (79%)
5	**30**	B	5	40	 **35** (80%)

[a] Method A: catalyst 5, toluene, 80 °C. Method B: The reaction was conducted in a microwave, 300 W, catalyst 5, toluene, 80 °C.

This might lead to side reactions, or loss of the base and therefore incomplete conversion.

Precursors **45**−**48** were subjected to the previous RCM conditions (Table 5) and readily proceeded to provide the trifluoromethylated heterocycles **49**−**52** in good to excellent yields.

Considering the versatility of this approach—at various stages, different functionalities can be introduced—and the generally good yields in the cyclization processes, this pathway provides a potentially very useful route to appreciable quantities of highly functionalized trifluoromethyl-containing cyclic amino acid derivatives.

Conclusions

In summary, a detailed account is provided on investigations toward a RCM-mediated pathway leading to trifluoromethyl-substituted heterocycles. This involves the synthesis of a new

SCHEME 4. Synthesis and RCM of Compound 38

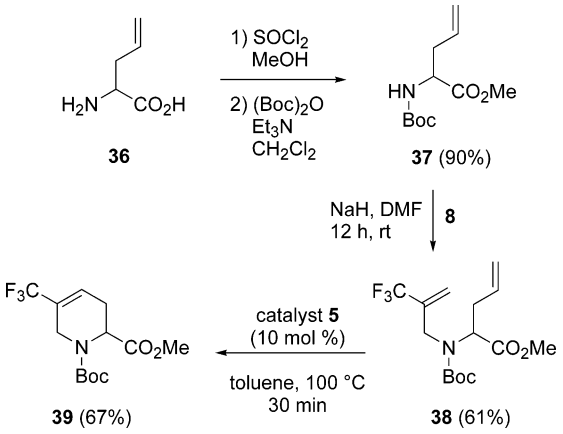
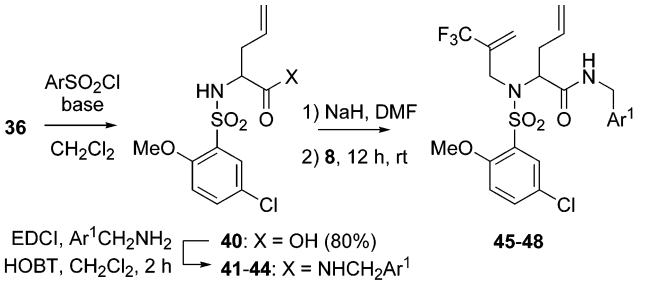
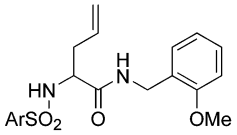
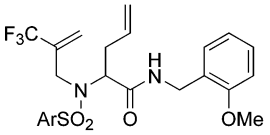
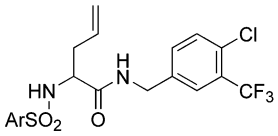
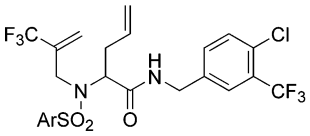
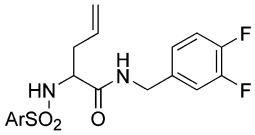
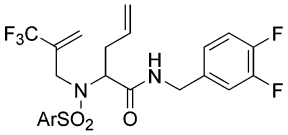
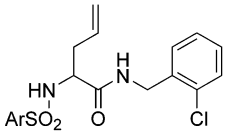
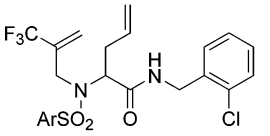


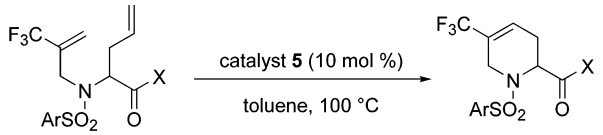
TABLE 4. Synthesis of RCM Precursors

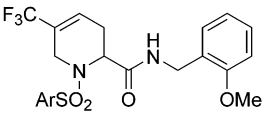
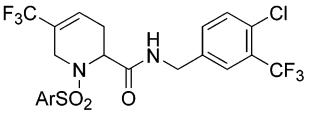
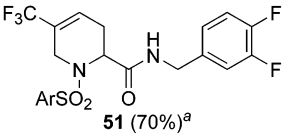
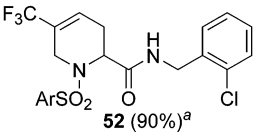


entry	sulfonamide (yield)	amide (yield)
1	 **41** (76%)	 **45** (45%)
2	 **42** (99%)	 **46** (44%)
3	 **43** (87%)	 **47** (60%)
4	 **44** (99%)	 **48** (47%)

(trifluoromethyl)allylating reagent via a Diels−Alder/retro-Diels−Alder strategy, its application in the synthesis of a series of RCM precursors, and eventually the successful cyclization of these precursor molecules to the corresponding nitrogen heterocycles. Thus, we have clearly established that RCM represents a viable pathway to several classes of biologically relevant trifluoromethylated piperidine derivatives.

TABLE 5. RCM Results



entry	RCM precursor	time (min)	RCM product (yield)
1	**45**	60	 **49** (70%)[a]
2	**46**	30	 **50** (98%)[a]
3	**47**	60	 **51** (70%)[a]
4	**48**	60	 **52** (90%)[a]

[a] Ar = 4-Cl-2-MeOC$_6$H$_3$.

Experimental Section

Toluene-4-sulfonic Acid 2-Trifluoromethylallyl Ester (8) via FVT. Compound **13** (410 mg, 1.19 mmol) was introduced in a flash vacuum thermolysis (FVT) instrument under the following conditions: temperature of the first oven was 120 °C, temperature of the second oven was 600 °C, pressure of 0.04 mbar for 4 h. The ester **8** (314 mg, 95%) was obtained as a colorless oil: IR (neat, cm^{-1}) 3118, 3068, 3041, 2962, 1598, 1369, 1176,1132, 1176, 972, 841, 777; ^{1}H NMR (200 MHz, CDCl$_3$) δ = 7.77 (d, J = 8.5 Hz, 2H), 7.34 (d, J = 7.8 Hz, 2H), 5.89 (br s, 1H), 5.73 (d, J = 1.2 Hz, 1H), 4.62 (s, 2H), 2.45 (s, 3H); ^{13}C NMR (75 MHz, CDCl$_3$) δ = 145.3, 132.4, 131.9 (q, J = 31.0 Hz), 129.9, 127.9, 123.5 (q, J = 5.1 Hz), 122.1 (q, J = 270.8 Hz), 65.6, 21.9; HRMS (EI) calcd for C$_{11}$H$_{11}$ F$_3$O$_3$S (M$^+$) 280.0381 found 280.0375.

***N*-Benzoyl-3-trifluoromethyl-2,5-dihydropyrrole (17).** To a solution of **15** (45 mg, 0.167 mmol) in dry toluene (20 mL) was added catalyst **5** (10 mo l%) at 100 °C in small portions. The reaction was complete in 24 h. The mixture was evaporated, and the product was purified using column chromatography (heptane/EtOAc 6:1) to give **17** (28 mg, 68%) as a yellow solid: mp 89−92 °C; IR (neat, cm^{-1}) 3058, 2919, 2867, 1713, 1632,1385, 1303, 1269, 1165, 1122, 1043, 789, 694, 672; ^{1}H NMR (300 MHz, CDCl$_3$, some signals appear as rotamers) δ = 7.52−7.42 (m, 5H), 6.44 + 6.26 (d, J = 1.8 Hz, 1H), 4.61 + 4.36 (br s, 4H); ^{13}C NMR (75 MHz, CDCl$_3$, some signals appear as rotamers) δ = 170.3 + 169.9, 131.6, (q, J = 180 Hz), 132.5, 130.4 +130.3, 130.1 + 129.0 (q, J = 4.9 Hz), 128.6 + 128.5, 126.8 + 126.8, 122.2, 56.0 + 53.3, 53.8 + 51.3; HRMS (EI) calcd for C$_{12}$H$_{10}$F$_3$NO (M$^+$) 241.0715, found 241.0714.

2-(4-Fluorophenyl)-5-trifluoromethyl-3,6-dihydro-2*H*-pyridine-1-carboxylic Acid *tert*-Butyl Ester (31). To a solution of **26** (83

mg, 0.22 mmol) in dry toluene (40 mL) was added catalyst **5** (4 mol %) at 80 °C in small portions. The reaction was complete in 60 min. The solvent was evaporated and the residue purified using column chromatography (heptane/EtOAc 6:1) to give **31** (75 mg, 99%) as a colorless oil: IR (neat, cm^{-1}) 3065, 2980, 2928, 1705, 1601, 1515, 1411, 1312, 1238, 1165, 1109, 983, 849, 763; ^1H NMR (300 MHz, $CDCl_3$) $\delta = 7.16$ (dd, $J = 6.0$, 9.3 Hz, 2H), 6.97 (dd, $J = 8.7$, 8.7 Hz, 2H), 6.5 (br s, 1H), 5.56 (br s, 1H), 4.37 (d, $J = 18.0$ Hz, 1H), 3.32 (d, $J = 18.3$ Hz, 1H), 2.82−2.62 (m, 2H), 1.50 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) $\delta = 161.9$ (d, $J = 243.8$ Hz), 154.4, 135.3, 128.1 (d, $J = 8.0$ Hz), 127.5−127.2 (m), 126.5 (q, $J = 30$ Hz), 122.6 (q, $J = 268.8$ Hz), 115.4 (d, $J = 20.9$ Hz), 81.0, 49.6, 37.4, 28.7, 27.4; HRMS (EI) calcd for $C_{17}H_{19}F_4NO_2$ (M^+) 345.1352, found 345.1352.

2-(4-Fluorophenyl)-5-trifluoromethyl-3,6-dihydro-2*H*-pyridine-1-carboxylic Acid Methyl Ester (32). To a solution of **27** (110 mg, 0.33 mmol) in dry toluene (45 mL) was added catalyst **5** (4 mo l%) at 80 °C in small portions. The reaction was complete in 60 min. The solvent was evaporated and the residue purified using column chromatography (heptane/EtOAc 10:1) to give **32** (80 mg, 80%) as a colorless oil: IR (neat, cm^{-1}) 3065, 2954, 2898, 2855, 1705, 1605, 1515, 1446, 1316, 1247, 1156, 1113, 1022, 966, 858, 767; ^1H NMR (300 MHz, $CDCl_3$) $\delta = 7.18$ (dd, $J = 6.0$, 9.3 Hz, 2H), 6.98 (dd, $J = 8.7$, 8.7 Hz, 2H), 6.5 (br s, 1H), 5.62 (br s, 1H), 4.44 (d, $J = 18.0$ Hz, 1H), 3.78 (s, 3H) 3.36 (d, $J = 20$ Hz, 1H), 2.85−2.64 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) $\delta = 161.9$ (d, $J = 244.1$ Hz), 155.7, 134.8, 128.4 (d, $J = 8.0$ Hz), 127.5 (br s), 126.2 (q, $J = 31$ Hz), 122.5 (q, $J = 269.1$ Hz), 115.5 (d, $J = 21$ Hz), 53.3, 49.9, 37.4, 27.3; HRMS (EI) calcd for $C_{14}H_{13}F_4NO_2$ (M^+) 303.0882, found 303.0883.

5-Trifluoromethyl-3,6-dihydro-2*H*-pyridine-1,2-dicarboxylic Acid 1-*tert*-Butyl Ester 2-Methyl Ester (39). To a solution of **38** (46 mg, 0.14 mmol) in dry toluene (20 mL) was added catalyst **5** (10 mol %) at 100 °C in small portions. The reaction was complete in 60 min. The solvent was evaporated and the residue purified using column chromatography (heptane/EtOAc 10:1 to 6:1) to give **39** (29 mg, 67%) as a colorless oil: IR (neat, cm^{-1}) 2976, 2924, 2872, 1744, 1701, 1403, 1364, 1308, 1251, 1212, 1161, 1113, 1035, 1001, 823, 607; ^1H NMR (300 MHz, $CDCl_3$) $\delta = 6.37$ (s, 1H), 5.11−4.89 (m, 1H), 4.34−4.17 (m, 1H), 3.91−3.76 (m, 1H), 3.71 (s, 3H), 2.84−2.77 (m, 1H), 2.62−2.53 (m, 1H), 1.50 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) $\delta = 171.0$, 155.1, 126.5−126.3 (m), 125.9−125.8 (m), 122.6 (q, $J = 267.9$ Hz), 81.4, 52.7, 50.3, 39.4, 30.0, 28.6; HRMS (EI) calcd for $C_{13}H_{19}F_3NO_4$ $(M + H)^+$ 310.1266, found 310.1260.

1-(5-Chloro-2-methoxybenzenesulfonyl)-5-trifluoromethyl-1,2,3,6-tetrahydropyridine-2-carboxylic Acid 2-Chlorobenzylamide (52). To a solution of **48** (173 mg, 0.31 mmol) in dry toluene (69 mL) was added catalyst **5** (10 mol %) at 100 °C in small portions. The reaction was complete in 60 min. The solvent was evaporated and the residue purified using column chromatography (heptane/EtOAc 3:1 to 1:1) to give **52** (145 mg, 90%) as a white solid: mp = 137−140 °C; IR (neat, cm^{-1}) 3384, 3329, 3071, 2939, 2917, 2846, 1676, 1591, 1572, 1522, 1478, 1440, 1390, 1344, 1305, 1273, 1209, 1163, 1113, 1078, 1015, 960, 897, 839, 814, 751, 644, 589; ^1H NMR (400 MHz, $CDCl_3$) $\delta = 7.92$ (d, $J = 2.8$ Hz, 1H), 7.51−7.48 (m, 1H), 7.38−7.35 (m, 1H), 7.30−7.22 (m, 3H), 7.12 (br s, 1H), 6.9 (d, $J = 8.8$ Hz, 1H), 6.41 (br s, 1H), 4.61−4.45 (m, 4H), 3.84 (s, 1H), 3.79 (s, 3H), 2.95−2.89 (m, 1H), 1.91−1.85 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) $\delta = 167.7$, 154.8, 134.7, 134.6, 134.0, 133.2, 130.7, 129.5, 129.3, 128.8, 127.6 (q, $J = 5.3$ Hz), 126.8, 125.6, 124.1 (q, $J = 31.2$ Hz), 122.1 (q, $J = 271.1$ Hz), 113.6, 56.1, 52.3, 41.6, 38.8, 31.5; HRMS (EI) calcd for $C_{21}H_{20}Cl_2F_3N_2O_4S$ $(M + H)^+$ 523.0473, found 523.0439.

Acknowledgment. Bayer CropScience is gratefully acknowledged for financial support.

Supporting Information Available: Experimental procedures and spectroscopic and analytical data of all the compounds both mentioned and not mentioned in the Experimental Section. This material is available free of charge via the Internet at http://pubs.acs.org.

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