Synthesis of Phosphorus and Sulfur Heterocycles via Ring-Closing Olefin Metathesis†

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† This review is dedicated to the memory of the late Professor Adrian M. Docken (1913−2003) from Luther College in Decorah, IA, whose dedication and love of chemistry serves as an inspiration to us all.

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1. Introduction

Organophosphorus[1] compounds continue to receive widespread attention due to their ubiquity in biological systems[2] and their potential to serve as novel pharmaceutical,[3] agricultural,[4] and chemical agents.[5] Among these, a number of phosphorus heterocycles (*P*-heterocycles) displaying potent biological activity have emerged. Notable examples include cyclophosphamide,[3b−d] an extensively studied six-membered *P*-heterocycle that continues to be a valuable therapeutic agent in the treatment of cancer; haptens for the development of catalytic antibodies;[6] and several phosphorus analogues of sugars.[7] In addition, several *P*-heterocycles possessing utility as chiral auxiliaries,[8] Lewis bases,[9] and catalysts[10] have become standard reagents in asymmetric synthesis. Likewise, a vast number of *S*-heterocycles displaying both biological activity[11,12] and synthetic utility[13] also exist. Most notably among these are sulthiame,[14] displaying anti-epileptic properties; brinzolamide,[15,14] a recently approved drug for the treatment of glaucoma; and the well-known cyclic sulfonamide chiral auxiliary, Oppolzer's sultam.[13a]

Until 1996, general methods to access *P*-heterocycles employing transition metal-catalyzed processes were primarily limited to Pd(0)-catalyzed protocols.[16] Similarly, traditional modes of forming *S*-heterocycles[17] have now been augmented by recent transition metal-catalyzed strategies.[12b,18] Despite the wealth of research on organophosphorus and organosulfur compounds, there is an ongoing search for new, efficient approaches to the synthesis of *P*- and *S*-heterocycles. In this context, a powerful reaction has emerged over the past decade that has fundamentally changed the outlook on carbo- and heterocycle chemistry: ring-closing olefin metathesis (RCM).[19]

The recent advent of olefin metathesis[20] as a common synthetic tool has led to numerous advances in both small-molecule and polymer chemistry. Specifically, RCM has become a routine transformation for the construction of small-, medium-, and large-ring-containing systems. The best known precatalysts for RCM reactions include ruthenium-benzylidene complexes **A**[21] and **B**,[22] developed by Grubbs and coworkers, and molybdenum-carbene complex **C**,[23] de-

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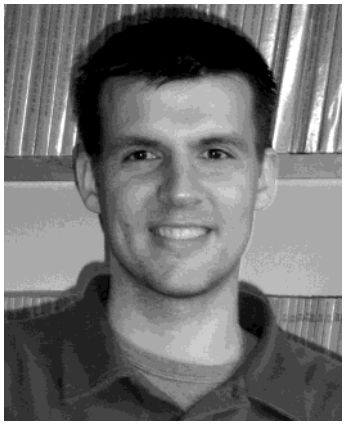


Matthew D. McReynolds, born in 1975 in Oklahoma City, OK, received his B.S. degree in 1998, with a major in chemistry from Southern Nazarene University (Bethany, OK) under the direction of Gene E. Heasley. In the summer of 1997, undergraduate research at the University of Kansas in the Department of Chemistry as an NSF-REU fellow prompted him to pursue his graduate work at KU under the guidance of Paul R. Hanson. In January 2004, he completed his doctoral studies, which centered on the application of ring-closing metathesis for the construction of biologically and synthetically relevant phosphorus heterocycles. Currently, he is working as an NIH postdoctoral fellow in the laboratories of Justin Du Bois at Stanford University, where he is pursuing his interests in transition metal catalysis, desymmetrization methodology, and alkaloid total synthesis.

Joseph Dougherty was born in Silver Spring, MD. He obtained his Bachelor of Special Studies in Chemistry from Cornell College in Mt. Vernon, IA, in 1996. He subsequently joined the research group of Paul R. Hanson for his graduate studies at the University of Kansas, completing his Ph.D. in 2003. His research focused on the use of ring-closing metathesis reactions to access novel sulfamides and related compounds. He is currently a postdoctoral research associate at West Virginia University under the mentorship of George O'Doherty.

Paul R. Hanson was born in 1963 in Mason City, IA, and graduated from Hampton High School in Hampton, IA, in 1981. He received his B.S. degree in 1985 from Luther College (Decorah, IA) with a major in chemistry under the direction of Adrian Docken. In 1993, he obtained his Ph.D. in chemistry from the University of Minnesota under the mentorship of Thomas R. Hoye. From 1993 to 1996, he served as an NIH postdoctoral fellow at Stanford University under the guidance of Barry M. Trost. In 1996, he was hired as an assistant professor of chemistry at the University of Kansas, and he was promoted to associate professor in 2001. His current interests lie in the development of new approaches to the synthesis of phosphorus and sulfur heterocycles with biologic and synthetic utility, natural product synthesis, and the design of high-load oligomers with tunable properties for use in facilitated synthesis.

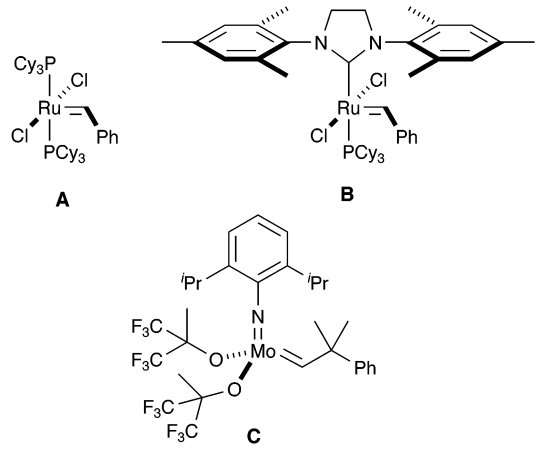


Figure 1.

scribed by Schrock and co-workers (Figure 1). Alkylidene **C** was the first precatalyst to gain extensive use in RCM and has displayed exceptional reactivity toward many diene substrates, including sterically encumbered and electron-deficient olefins. Yet, the limited functional group tolerance of **C**, coupled with its air and moisture sensitivity, warranted continued efforts toward more robust olefin metathesis catalysts. Consequently, ruthenium-based systems **A** and **B** have become the precatalysts of choice for many applications due to their relative tolerance to oxygen and moisture and their broad functional group compatibility. While the "first-generation Grubbs catalyst" **A** is less active than molybdenum-alkylidene **C**, the "second-generation Grubbs catalyst" **B** often rivals or exceeds the activity of **C** and is now commonly used for a wide variety of substrates, including polysubstituted, sterically demanding, or electron-deficient alkenes. However, as it will be evidenced in the following review, instances remain where ruthenium catalysts are insufficient, and catalyst **C** can be used as a viable alternative. Finally, recent advances in the development of derivatives of **A**−**C**,[19,20] including the robust Hoveyda ruthenium catalysts[24] and asymmetric molybdenum[19e,25] and ruthenium[26] complexes, have opened new doors of opportunity in the field of RCM.

The RCM reaction has facilitated the production of various cyclic structures, including a broad range of heterocycles.[19,20,27] Accordingly, the assembly of *P*- and *S*-heterocycles has become considerably more straightforward through the application of this technology. Since the presence of a suitably reactive diene is the basic prerequisite for RCM, there is great potential to derive a host of structurally unique *P*- and *S*-heterocycles, as well as cyclic phosphorus and

sulfur architectures that, at present, would be more difficult to obtain by way of alternative methods.

The following review will summarize through the year 2003 the reported efforts to construct *P*- and *S*-heterocycles via RCM. The examples cited have been limited to those that describe the incorporation of either phosphorus or sulfur atoms within the unsaturated heterocyclic products. The need to generate phosphorus and sulfur substrates possessing diene appendages for RCM has facilitated improved methods for their synthesis. Due to the often-facile nature of RCM reactions, procedures used to access RCM precursors frequently highlight the synthetic sequences. Therefore, many reports summarized herein outline routes to the acyclic diene substrates. Reaction conditions for RCM generally involve 0.05−5 mol % precatalyst, refluxing solvent (typically dichloromethane or benzene), and low concentrations of substrate (0.01−0.05 M). An attempt has been made to note instances where the choice of catalyst and/or reaction conditions has exerted a substantial effect on the outcome of the RCM reaction. In general, this review is organized into phosphorus and sulfur categories and further divided according to each functional group subclass.

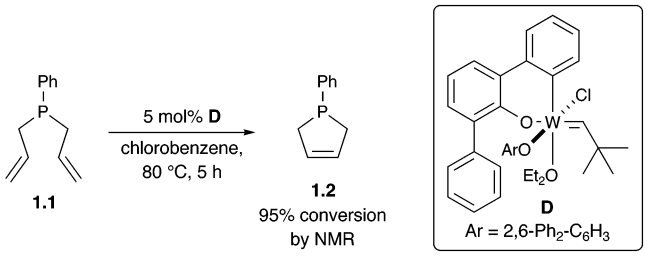
2. Phosphorus Heterocycles

2.1. Phosphines

2.1.1. Seminal Example Using Tungsten-Based Catalyst

In 1995, Basset and co-workers described the first RCM to a *P*-heterocycle[28] by utilizing tungsten alkylidene **D** developed previously in their laboratory.[29] In the presence of 5 mol % **D**, smooth conversion of diallylphenylphosphine (**1.1**) to 1-phenyl-3-phospholene (**1.2**) was achieved in chlorobenzene at 80 °C (Scheme 1). Initially, phosphine binding to tungsten was expected to deactivate the catalyst and prevent RCM. The authors suggest that steric interactions between the substrate and the congested metal center, along with the rigidity of the cyclometalated framework of the catalyst, contribute to the unusual activity of **D** toward dienes possessing a vicinal heteroatom. Other substrates that undergo RCM with **D** include allyl ethers and allyl sulfides, the latter of which shall be outlined in section 3.1 of this review.

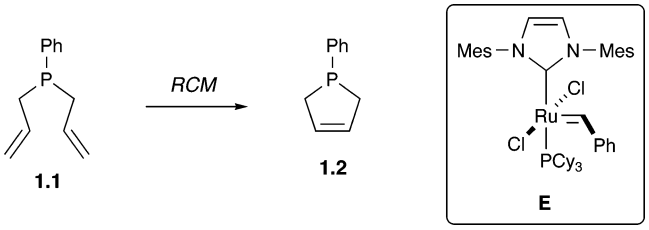
Scheme 1



2.1.2. Example Using Molybdenum-Based Catalyst

Recent studies in 2003 by Gouverneur and co-workers[30] have demonstrated that, while ruthenium-based complexes such as Grubbs catalysts **A** and **B** and catalyst **E**[31] developed by Nolan and co-workers were unreactive toward **1.1** (Table 1, entries 1−3), the Schrock molybdenum-based catalyst **C** effectively promoted cyclization to give excellent conversion to cyclic phosphine **1.2** (entry 4). Previous mechanistic investigations from the Grubbs laboratory established that phosphine dissociation precedes olefin binding in ruthenium-catalyzed olefin metathesis.[32] In accord with this hypothesis, Gouverneur and co-workers suggested that the phosphine moeity in **1.1** hinders the dissociative pathway by competing with olefin binding to ruthenium-based catalysts. Conversely, various competition experiments, as well as the successful RCM of **1.1**, led the authors to conclude that weakly donating phosphines of sufficient size do not inhibit Schrock molybdenum complex **C**.

Table 1



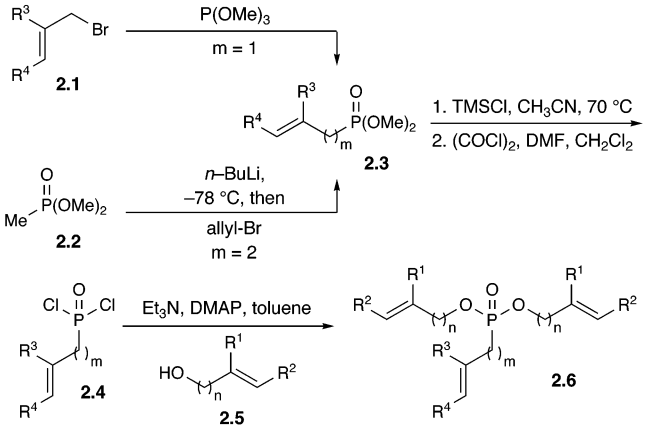
entry	catalyst (mol %)	solvent	*T* (°C)	time (h)	conversion (%)
1	**A** (4)	CH_2Cl_2	40	20	0
2	**B** (8)	CH_2Cl_2	40	72	0
3	**E** (8)	$PhCH_3$	80	72	0
4	**C** (12.5)	$PhCH_3$	60	84	95

2.2. Phosphonates, Phosphinates, and Phosphine Oxides

2.2.1. Phosphonates, $RP(O)(OR')_2$

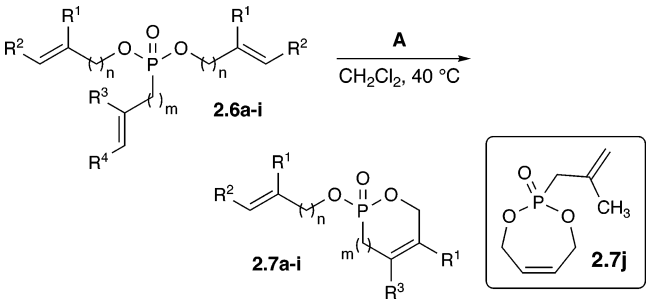
In 1998, the first examples of RCM to *P*-heterocycles utilizing Grubbs' ruthenium-benzylidine **A** were accomplished on phosphonate substrates **2.6** (Scheme 2).[33] Dimethyl allylphosphonate derivatives **2.3** ($m = 1$) were obtained using standard Arbuzov methods, while alkylation of **2.2** with allyl bromide yielded dimethyl homoallylphosphonate ($m = 2$).

Scheme 2



Phosphonates **2.6a**−**i** were subjected to RCM mediated by catalyst **A** to give *P*-heterocyclic products **2.7a**−**i** (Table 2). The effects of varying olefin sub-

Table 2



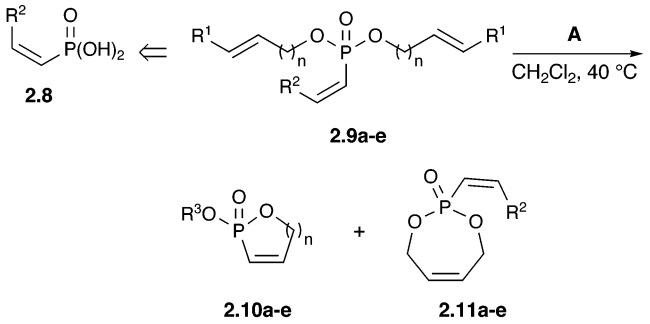
entry	triene	*m*	*n*	R^1	R^2	R^3	R^4	mol % **A**	time	yield (%)
1	**2.6a**	1	1	H	H	H	H	3	30 min	74
2	**2.6b**	1	1	H	Me	H	H	3	30 min	99
3	**2.6c**	1	2	H	H	H	H	3	8 h	74
4	**2.6d**	2	1	H	H	H	H	3	30 min	75
5	**2.6e**	1	1	Me	H	H	H	9	24 h	52
6	**2.6f**	1	1	H	Me	Me	H	12	48 h	0[a]
7	**2.6g**	1	1	Me	H	Me	H	21	48 h	0
8	**2.6h**	1	1	H	H	H	Me	3	30 min	78
9	**2.6i**	1	1		Me	H	Me	15	48 h	68

[a] 68% **2.8**.

stitution and subsequent product ring size were evaluated. Yields of the six- or seven-membered cyclic phosphonates are generally good to excellent, and no metathesis was observed between allyloxy appendages, with the exception of **2.6f**, which gave **2.7j** as the sole product (entry 6).

In a subsequent report,[34] a related study was conducted on acyclic vinylphosphonates **2.9a**−**e** (Table 3), which were prepared from vinylphosphonic acid derivatives **2.8** using methods similar to those outlined in Scheme 2. RCM using **A** proved to be more troublesome when compared to the reactions with the analogous allyl- and homoallylphosphonates described previously. Cyclization of **2.9d** was particularly sluggish, to afford only 30% of the desired *P*-heterocycle **2.10d** and 56% recovered starting material (entry 4).

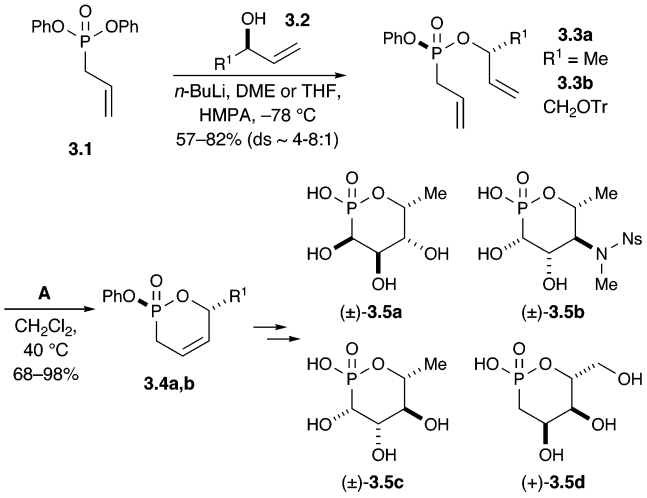
Table 3



entry	triene	*n*	R^1	R^2	mol % **1**	time	yield (%) **2.10**	yield (%) **2.11**
1	**2.9a**	1	H	H	6	6 h	44 (R^3 = H)	31 (R^2 = H)
2	**2.9b**	1	Me	H	18	4 d	54 (R^3 = H)	6 (R^2 = H)
3	**2.9c**	2	H	Me	6	7 h	16 (R^3 = H)	54 (R^2 = Me)
4	**2.9d**	1	Ph	H	21	7 d	30 (R^3 = cinnamyl)	0
5	**2.9e**	2	H	H	3	2 h	79 (R^3 = homoallyl)	0

In 2001, RCM was exploited en route to the synthesis of various phosphonosugars where the phosphonate moiety serves as an anomeric carbon surrogate.[35] Diastereoselective addition of secondary allylic alcohols **3.2** to diphenyl allylphosphonate (**3.1**) employing the Moriarty protocol[36] gave acyclic phosphonates **3.3** in moderate to good yields with modest to good selectivity (4−8:1) (Scheme 3). RCM mediated by **A** yielded cyclic phosphonates **3.4** as versatile synthetic templates possessing an allylic cyclic phosphonate, a stereogenic phosphorus center, and a labile phenylphosphonate ester. These attributes were utilized in the stereoselective synthesis of a variety of phosphonosugars **3.5**, including nonracemic phosphonic acid (+)-**3.5d**.

Scheme 3



Van Boom and co-workers reported an increase in yield and efficiency of RCM to cyclic vinylphosphonates using the more active second-generation Grubbs catalyst **B**.[37] Metathesis precursors **4.2** were prepared from vinylphosphordiamidite **4.1** in high yields over three steps (Scheme 4). In each case, employing precatalyst **B** substantially improved reaction times and yields en route to cyclic vinylphosphonates **4.3a**−**c** when compared to the same reactions conducted with **A**, respectively (Table 4).

Scheme 4

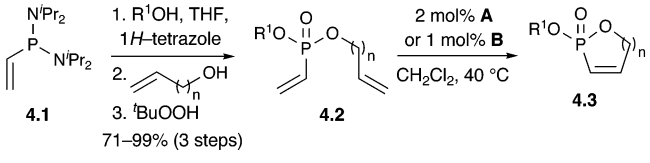
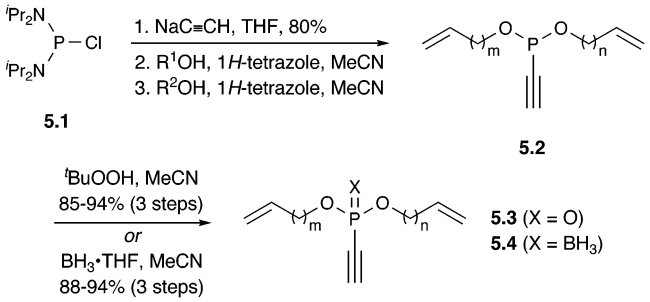


Table 4

entry	substrate	R^1	*n*	RCM cat.	time	yield (%)
1	**4.2a**	allyl	1	**A**	6 h	44
				B	30 min	>99
2	**4.2b**	Bn	1	**A**	4 d	25
				B	15 min	>99
3	**4.2c**	Bn	2	**A**	4 d	85
				B	20 min	>99

In 2001, van Boom and co-workers extended this work to ene−yne metathesis of alkynyl phosphonates and alkynyl phosphonate boranes.[38] Addition of sodium acetylide to chlorophosphine **5.1** and conden-

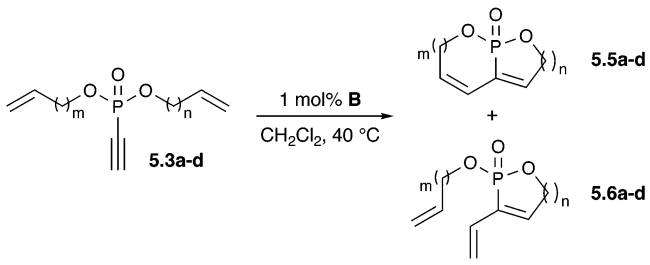
Scheme 5



sation of various alkenyl alcohols provided symmetric or unsymmetric phosphines **5.2** (Scheme 5). In situ oxidation with *tert*-butyl hydroperoxide or protection with BH_3·THF gave the target alkynyl phosphonates **5.3** or boranes **5.4**, respectively.

The results for RCM of phosphonates **5.3a**−**d** with precatalyst **B** are summarized in Table 5, while phosphonate boranes **5.4** will be discussed in section 2.4.2. RCM of diallyl alkynylphosphonate (**5.3a**) gave exclusively monocyclic product **5.6a** (entry 1). Lengthening of the olefin component increases bicyclic phosphonate formation (entries 2 and 3), with the bicyclo[5.5.0]phosphonate **5.5d** obtained as the only product when $m = 2$ and $n = 3$ (entry 4).

Table 5

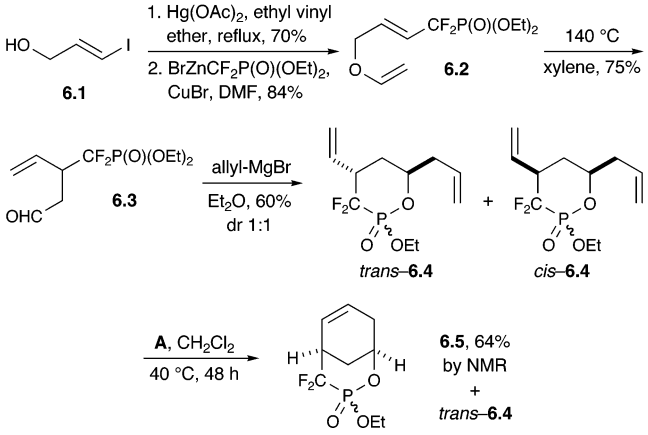


entry	substrate	*m*	*n*	time (h)	yield (%) 5.5	5.6
1	**5.3a**	1	1	4	0	98
2	**5.3b**	2	1	3	66	23
3	**5.3c**	2	2	0.5	76	18
4	**5.3d**	2	3	3	83	0

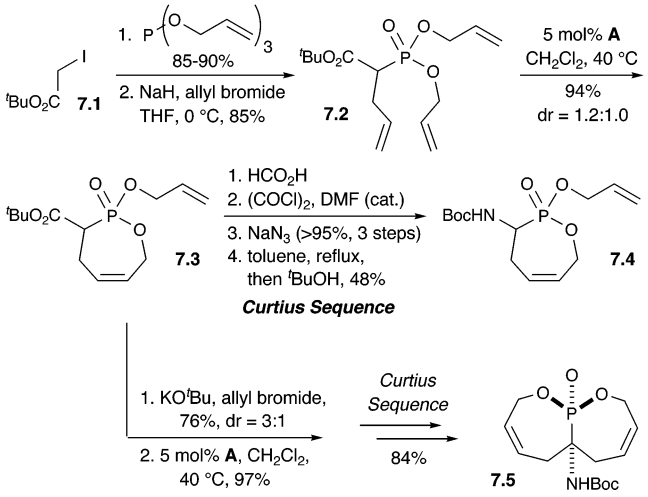
Percy and co-workers reported the synthesis of bicyclo[3.3.1]phosphonate **6.5** as part of a study focused on novel approaches to secondary difluorophosphonates (Scheme 6).[39] Subjection of a cis/trans mixture of **6.4** to metathesis conditions in the presence of **A** promoted ring-closure of the cis diastereomers, leading to **6.5**, while *trans*-**6.4** was unreactive toward RCM.

Application of RCM in the synthesis of conformationally constrained α-aminophosphonates was disclosed in 2002.[40] Acyclic diallyl phosphonate **7.2** was obtained from an Arbuzov reaction between triallyl phosphite and *tert*-butyl iodoacetate (**7.1**), followed by monoalkylation with allyl bromide (Scheme 7). RCM with **A** smoothly generated seven-membered phosphonate **7.3**, and subsequent Curtius rearrangement of the requisite acyl azide afforded the constrained α-aminophosphonate **7.4**. Similarly, the bicyclo[5.5.0]-α-aminophosphonate **7.5** could be generated from **7.3** via allylation, RCM, and subjection to the aforementioned Curtius sequence.

Scheme 6

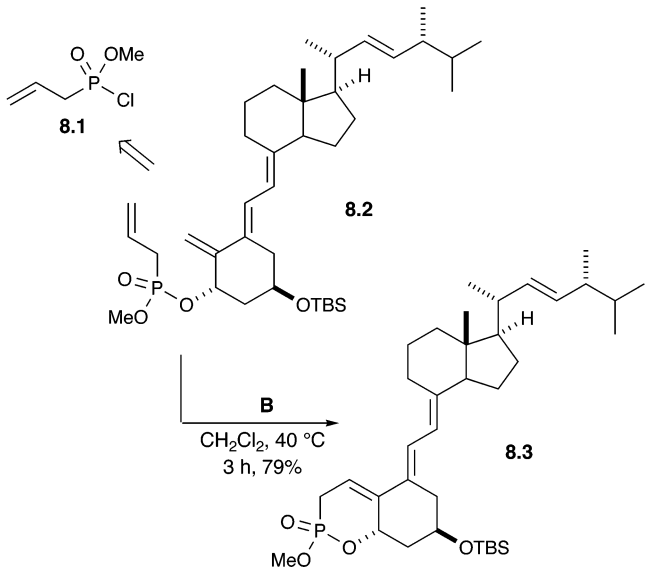


Scheme 7



A recent communication by Barrett and co-workers described the synthesis of **8.3**, a cyclic phosphonate-containing analogue of 1α-hydroxyvitamin D_2[41] (Scheme 8). Coupling of the requisite secondary alcohol of **8.2** with methyl allylphosphonyl monochlo-

Scheme 8

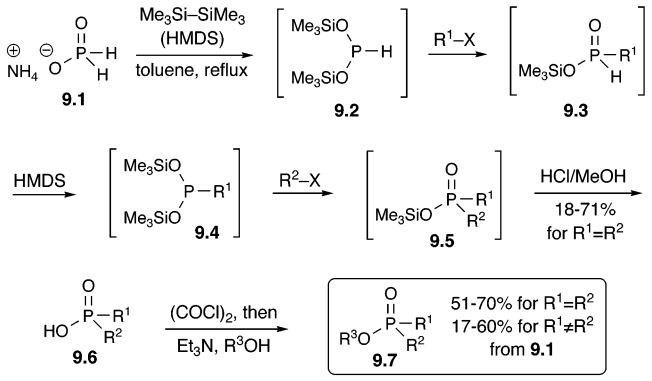


ridate (**8.1**) yielded **8.2**. RCM mediated by **B** in refluxing methylene chloride gave cyclic phosphonate **8.3**.

2.2.2. Phosphinates, $R_2P(O)OR'$

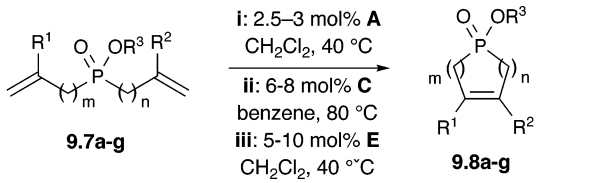
In 1999, Mioskowski and co-workers utilized RCM for the synthesis of *P*-heterocyclic phosphinates.[42] Both symmetric and unsymmetric diene phosphinates **9.7** were assembled according to the two-step procedure outlined in Scheme 9.

Scheme 9



The efficacy of RCM with cyclic phosphinates **9.7a**−**g**, which are varied by olefin length and substitution, was evaluated using **A** (conditions i, Table 6) or the Schrock molybdenum catalyst **C** (conditions ii). Phosphinic acid **9.7a** did not undergo metathesis using either catalyst (entry 1). Conversely, benzyl phosphinates **9.7b**−**d** cyclized to give good to excellent yields of the corresponding five-, six-, and seven-membered products, respectively (entries 2−4). While RCM of monomethallyl derivative **9.7e** was sluggish, to give only moderate yields of product (entry 5), larger substituents such as a phenyl group (entry 6) or disubstitution at R^1 and R^2 (entry 7) completely inhibited metathesis under either of the conditions i or ii. In 2000, Mioskowski and co-workers successfully circumvented these troublesome cyclizations[43] (entries 1, 6, and 7) by employing Nolan catalyst **E**[31] (conditions iii, entries 8−10, respectively).

Table 6

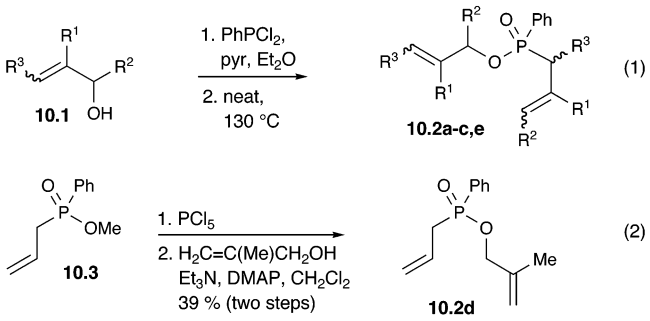


9.7a-g → **9.8a-g**

entry	substrate	*m*	*n*	R^1	R^2	R^3	conditions	yield (%)
1	**9.7a**	1	1	H	H	H	i	0
							ii	0
2	**9.7b**	1	1	H	H	Bn	i	80
							ii	80
3	**9.7c**	1	2	H	H	Bn	i	96
4	**9.7d**	2	2	H	H	Bn	i	97
5	**9.7e**	1	1	Me	H	Bn	i	50
							ii	50
6	**9.7f**	1	1	Ph	H	Bn	i	0
7	**9.7g**	1	1	Me	Me	Bn	i	0
							ii	0
8	**9.7a**	1	1	H	H	H	iii	>99
9	**9.7f**	1	1	Ph	H	Bn	iii	>99
10	**9.7g**	1	1	Me	Me	Bn	iii	88

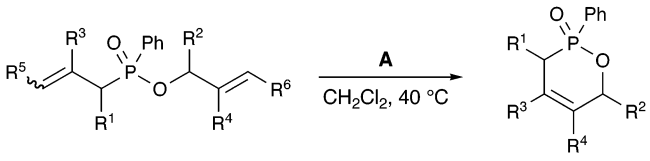
In 2000, Gouverneur and co-workers examined the synthesis of various classes of *P*-heterocycles using catalyst **A**.[44] Included in this study were cyclic phosphinates in which the phosphoric oxygen was incorporated into the heterocyclic framework. Differentially substituted acyclic phosphinates **10.2** were accessed via a [2,3]-sigmatropic Arbuzov rearrangement strategy (Scheme 10, eq 1) or simple condensation of methallyl alcohol to the phosphonyl chloride of **10.3** (eq 2).

Scheme 10



Cataylst **A** successfully promoted RCM to six-membered cyclic phosphinates **10.3a**−**c** from acylic substrates **10.2a**−**c** possessing terminal olefin, allylic, and/or α-phosphonyl substitution (Table 7). In accord with previous studies, substitution at R^3 or R^4 either diminished (entry 4) or prevented (entry 5) ring-closure using complex **A**.

Table 7



10.2a-e → **10.4a-e**

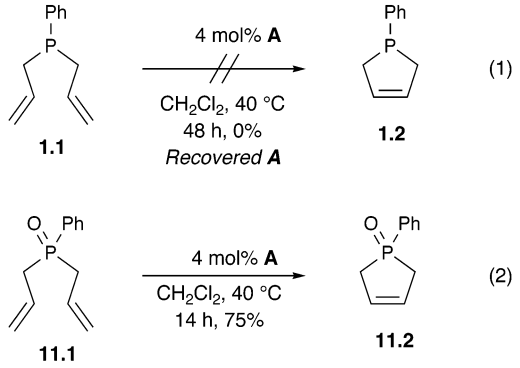
entry	substrate	R^1	R^2	R^3	R^4	R^5	R^6	mol % **A**	time	yield (%)
1	**10.2a**	H	H	H	H	H	H	4	16 h	92
2	**10.2b**	H	Me	H	H	Me	H	8	21 h	84
3	**10.2c**	Me	H	H	H	H	Me	8	3 d	95
4	**10.2d**	H	H	H	Me	H	H	10	3 d	31
5	**10.2e**	H	H	Me	Me	H	H	6	5 d	0

2.2.3. Phosphine Oxides, $RP(O)R'_2$

In 1999, Gouverneur and co-workers successfully utilized catalyst **A** for RCM to cyclic phosphine oxides.[45] In contrast to results obtained by Bassett and co-workers with tungsten catalyst **D** (Scheme 1), the authors found that ruthenium-based complex **A** did not promote ring-closure of phosphine **1.1** (Scheme 11, eq 1). However, the analogous phosphine oxide **11.1** cyclized without incident to afford five-membered *P*-heterocycle **11.2** in good yield (eq 2).

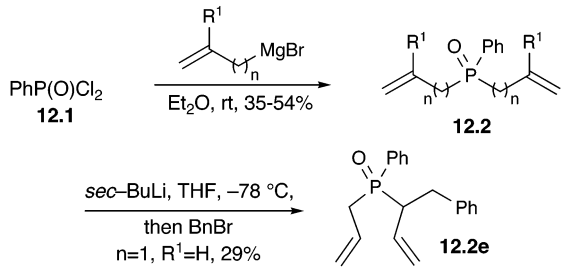
With this result in hand, the authors examined the scope of acyclic phosphine oxide substrates that would participate in RCM under similar conditions.

Scheme 11



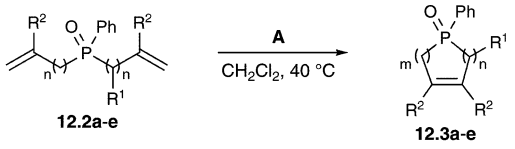
Standard Grignard additions to phenylphosphonic dichloride (**12.1**) gave diene phosphine oxides **12.2** (Scheme 12). Subsequent deprotonation and alkylation gave the α-phosphonyl-substituted variant **12.2e**.

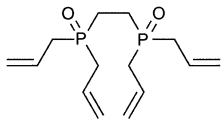
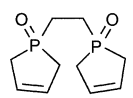
Scheme 12



Metathesis of **12.2** afforded five-, six-, and seven-membered cyclic products **12.3a**−**c** in good to excellent yields (Table 8, entries 1−3). Phosphine oxide **12.2d**, substituted at R^2, was completely unreactive toward RCM (entry 4). Allylic branching in substrate **12.2e** did not inhibit the cyclization event (entry 5). Another noteworthy example involved tetra-ene **12.4**, which yielded the bis-phosphine oxide **12.5** as the major product, with no evidence of eight-membered ring formation (entry 6).

Table 8



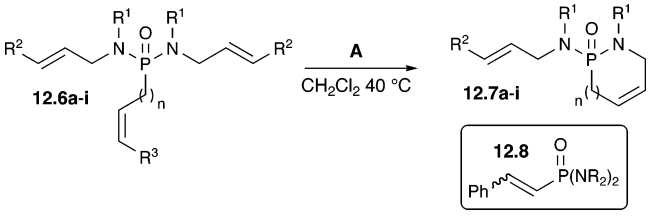
entry	substrate	m	n	R^1	R^2	mol % **A**	time (h)	yield (%)
1	**12.2a**	1	1	H	H	4	14	75
2	**12.2b**	1	2	H	H	2	12	74
3	**12.2c**	2	2	H	H	6	48	89
4	**12.2d**	1	1	H	Me	8	48	0
5	**12.2e**	1	1	Bn	H	4	24	81
6	 **12.4**					10	72	 36% of **12.5**

2.3. Phosphonamides, Phosphonamidates, and Phosphonamidic Anhydrides

2.3.1. Phosphonamides, $RP(O)(NR'_2)_2$

The first application of RCM to heterocycles containing a phosphorus−nitrogen bond was described in 1999.[34] Symmetric phosphonamides **12.6a**−**i** were obtained from the corresponding phosphonic dichlorides by simple condensation of the requisite primary or secondary amines (Table 9). Metathesis of *N*-substituted allyl phosphonamides ($n = 1$) gave excellent yields of the corresponding six-membered *P*-heterocycles (entries 1 and 3), while cyclization of the analogous N−H substrates was comparatively sluggish, to afford moderate yields of product (entries 2 and 4). Good yields were generally obtained for vinyl phosphonamides ($n = 0$) where the allylic amine component is unsubstituted (R^2 = H, entries 5−7). Substrates with phenyl substitution at the olefin terminus yielded appreciable quantities of **12.8** resulting from cross-metathesis between styrene and the vinyl phosphonyl moiety (entries 8 and 9).

Table 9



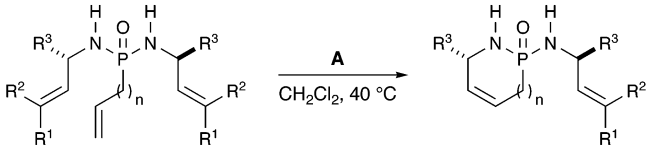
entry	triene	*n*	R^1	R^2	R^3	mol % **A**	time	yield **12.7** (%)
1	**12.6a**	1	Me	Ph	H	3	1.5 h	99
2	**12.6b**	1	H	Ph	H	18	48 h	48
3	**12.6c**	1	Me	H	H	3	2 h	93
4	**12.6d**	1	H	H	H	21	48 h	45
5	**12.6e**	0	H	H	H	9	6 h	74
6	**12.6f**	0	Me	H	H	3	5 h	76
7	**12.6g**	0	Me	H	Me	3	2 h	87
8	**12.6h**	0	H	Ph	H	9	24 h	68[a]
9	**12.6i**	0	Me	Ph	H	21	7 d	13[b]

[a] 17% **12.8g**. [b] 12% **12.8h**, 60% **12.6h**.

An innovative extension of this approach involved the RCM-mediated desymmetrization of nonracemic, pseudo-C_2-symmetric phosphonamides **12.9** en route to *P*-heterocycles containing a stereogenic phosphorus atom (Table 10).[46] The desymmetrization of isopropyl-terminated substrates (R^1 or $R^2 = {}^i$Pr) led to moderate diastereoselection regardless of olefin geometry (entries 1−3). Comparatively, excellent diastereoselectivities of up to 15:1 were observed for the desymmetrization of substrates having an *E*-configured phenyl group at the olefin terminus, yielding five-membered cyclic vinylphosphonamides **12.10d**−**f** ($n = 0$, entries 4−6). RCM to six-membered cyclic allylphosphonamides ($n = 1$) resulted in almost complete loss of selectivity (entries 7 and 8).

In 2000, Gouverneur and co-workers used RCM to access five-, six, and seven-membered cyclic phosphonamides.[44] Acyclic dienes **13.1**−**13.3** were produced via the coupling of various amines to phosphonyl chloride reagents (Scheme 13). For the

Table 10

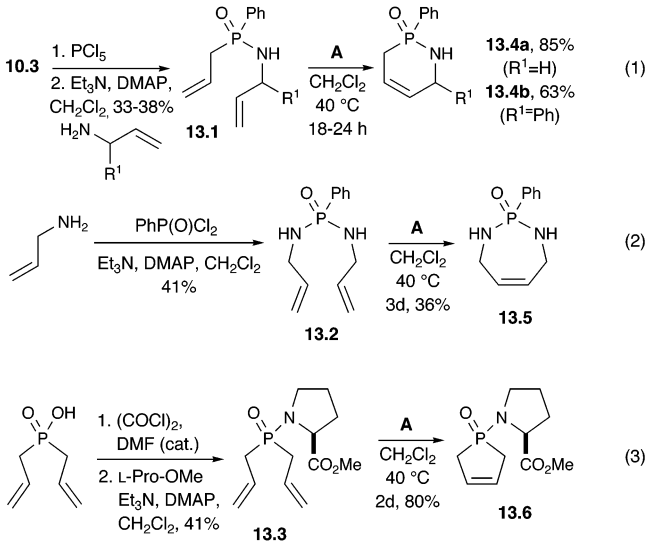


12.9a-h 12.10a-h

entry	triene	*n*	R^1	R^2	R^3	yield (%)	ds
1	**12.9a**	0	H	^{i}Pr	Me	64	2.6:1
2	**12.9b**	0	H	^{i}Pr	^{i}Pr	80	5.0:1
3	**12.9c**	0	^{i}Pr	H	Me	61	3.9:1
4	**12.9d**	0	Ph	H	Me	69	12:1
5	**12.9e**	0	Ph	H	^{i}Pr	66	15:1
6	**12.9f**	0	Ph	H	^{i}Bu	63	15:1
7	**12.9g**	1	Ph	H	Me	50	1.3:1
8	**12.9h**	1	Ph	H	^{i}Bu	51	1.8:1

synthesis of six-membered *P*-heterocycles with catalyst **A**, yields diminished when the allylic amine olefin was more sterically hindered by α-amino substitution (**13.4b** vs **13.4a**, eq 1). Cyclization of N−H phosphonamide **13.2** was sluggish, to give low yields of seven-membered phosphonamide **13.5** (eq 2). Although prolonged reaction times were required, good yields were obtained for RCM of L-proline-derived **13.3** (eq 3).

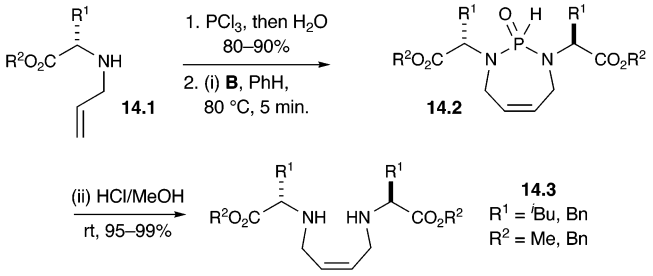
Scheme 13



Phosphorus heterocycles containing acid-labile P−N bonds have been utilized as temporary tethers for the rapid synthesis of *Z*-olefinic 1,4-diamines.[47] For example, condensation of 2 equiv of *N*-allylated amino ester **14.1** with phosphorus trichloride and subsequent water hydrolysis afforded phosphorus(III)-tethered amines (Scheme 14). Facile RCM with **B** gave pseudo-C_2-symmetric phosphorus acid diamide **14.2**. Following mild, in situ cleavage of the phosphorus tether (*P*-tether) with methanolic HCl, 1,4-diamines **14.3** were isolated in excellent yields after simple acid/base extraction.

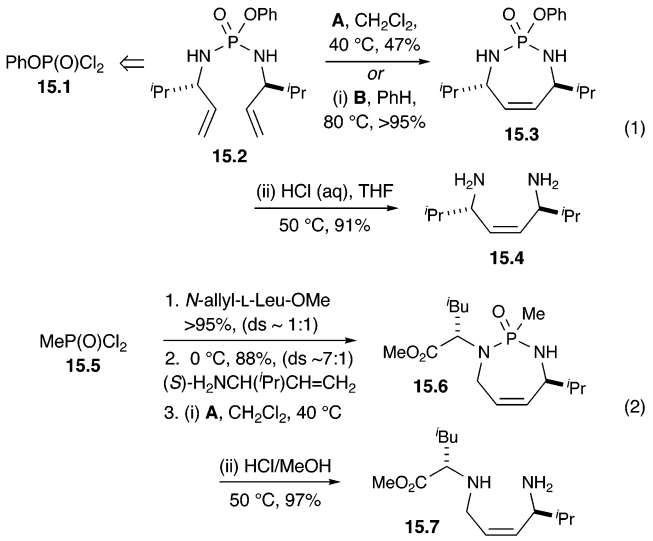
In the same study, phosphorus(V) reagents were also employed as temporary tethers. Only partial conversion of sterically hindered **15.2** was achieved with **A**,[48] but the more reactive catalyst **B** gave nearly

Scheme 14



quantitative yields of cyclic phosphonamide **15.3** (eq 1, Scheme 15). The utility of these functionalized 1,4-diamines was demonstrated in the synthesis of structurally diverse analogues of DMP 323,[49] a potent inhibitor of HIV protease developed by DuPont Merck Laboratories.[50]

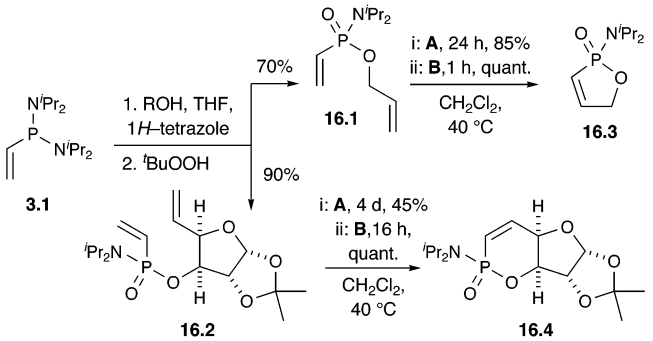
Scheme 15



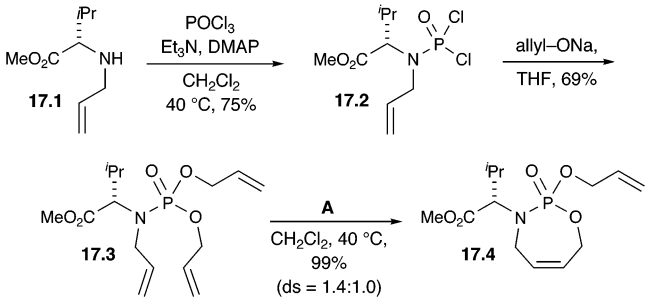
2.3.2. Phosphonamidates, RP(O)(NR′$_2$)(OR′′)

In 2000, RCM approaches to phosphonamidates were first described by van Boom and co-workers.[37] Coupling of alcohols to phosphoramidite **3.1** catalyzed by 1*H*-tetrazole, followed by oxidation, gave acyclic phosphoramidates **16.1** and **16.2** (Scheme 16). RCM was conducted with catalysts **A** and **B**, with catalyst **B** improving both yield and reaction time in each case. Most notably, sterically congested tricyclic phosphonamidate **16.4** was produced in quantitative yield when **B** was used, whereas only 45% conversion after 4 days was achieved with catalyst **A**.

Scheme 16



Scheme 17



Efforts to assemble amino acid-derived *P*-heterocycles via RCM led to the synthesis of seven-membered phosphonamidate **17.4**[48] (Scheme 17). Interestingly, RCM with **A** was completely chemoselective in promoting ring-closure between the allylamino and one of the allyloxy appendages, thereby furnishing **17.4** in excellent yield as a mixture of diastereomers. Metathesis of the allyloxy groups was not observed.

A recent report by Sørensen and co-workers described the utility of RCM in the synthesis of cyclic phosphonamidates as potent matrix metalloproteinase (MMP) inhibitors (Figure 2).[51] Following ring-closure of (±)-**17.5** with catalyst **A**, installation of the hydroxamic acid group furnished a number of potent MMP inhibitors (±)-**17.6**. For six-membered derivatives ($n = 1$), the authors noted that the unsaturated inhibitors containing a cyclic olefin moiety exhibited increased potency relative to their saturated counterparts.

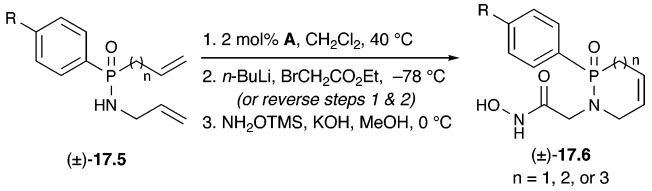
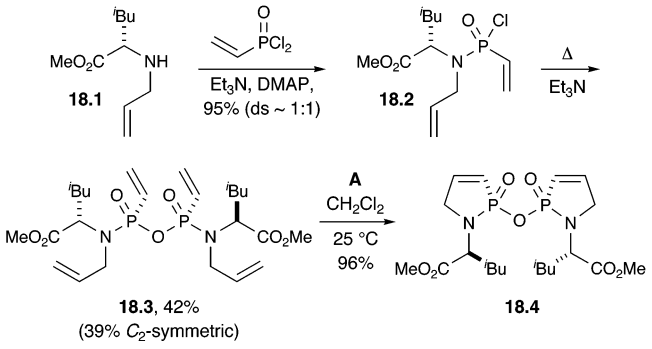


Figure 2.

2.3.3. Phosphonamidic Anhydrides, R(NR′2)P(O)–O–(O)P(NR′2)R

In 2000, a new method for the synthesis of phosphonamidic anhydrides was reported.[52] Phosphonamidic monochloridate **18.2** was generated through the coupling of allylated aminoesters **18.1** with vinylphosphonic dichloride (Scheme 18). Upon heating in Et_3N, **18.2** readily dimerized to afford a separable mixture of "pseudo-*meso*" **18.3** and the corresponding C_2-symmetric diastereomers. In the presence of **A** at room temperature, cyclic phosphonamidic anhydride **18.4** was formed in excellent yields with no evidence of nine-membered-ring formation.

Scheme 18

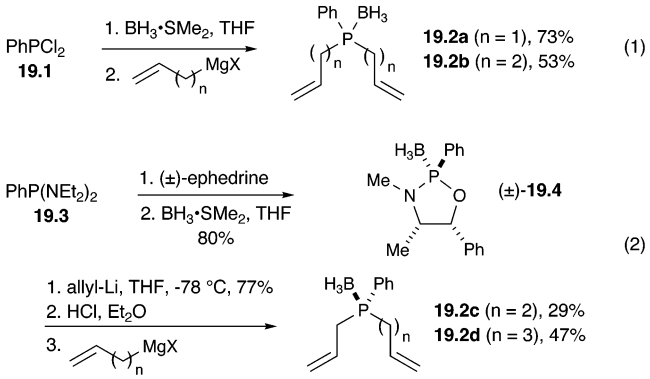


2.4. Phosphine, Phosphonate, and Phosphonamidate Boranes

2.4.1. Phosphine Boranes, RP(BH3)R′2

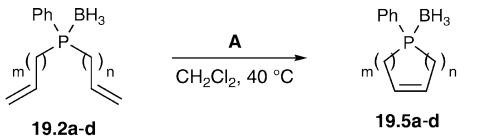
As discussed in section 2.2.3, Gouverneur and co-workers discovered that catalyst **A** was unable to effect RCM upon phosphine dienes.[45] As a result, the authors focused their efforts on evading this problem by protecting the phosphine as its borane adduct.[53] Symmetric phosphine boranes **19.2a** and **19.2b** were acquired by protecting dichlorophenylphosphine with $BH_3{\cdot}SMe_2$ complex and alkylating under standard Grignard conditions (Scheme 19, eq 1). Utilizing a protocol developed by Genêt and Jugé,[54] addition of allyllithium to oxaphospholidine-borane (±)-**19.4**, chlorination, and alkylation produced unsymmetric phosphine boranes **19.2c** and **19.2d** (eq 2).

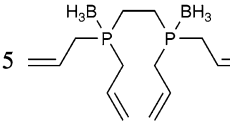
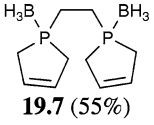
Scheme 19



Five- and six-membered phosphine-borane heterocycles were generated in good to excellent yields using catalyst **A** (Table 11, entries 1 and 3). Cyclization of the symmetric substrate **19.2b** was slow and afforded only moderate yields of seven-membered

Table 11



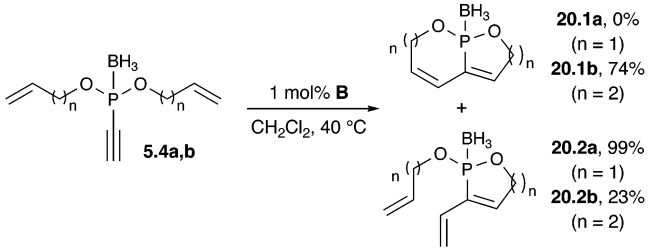
entry	substrate	m	n	mol % **A**	time (h)	yield (%)
1	**19.2a**	1	1	2	14	81
2	**19.2b**	2	2	12	49	63
3	**19.2c**	1	2	4	9	95
4	**19.2d**	1	3	4	9	94
5	 **19.6**			14	90	 **19.7** (55%)

product (entry 2), while the unsymmetric isomer **19.2d** underwent metathesis readily to the corresponding seven-membered heterocycle **19.5d** (entry 4).

2.4.2. Phosphonate Boranes, $RP(BH_3)(OR')_2$, and Phosphonamidate Boranes, $RP(BH_3)(NR'_2)(OR'')$

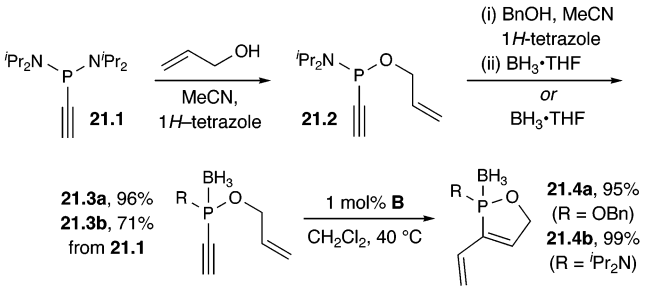
In 2001, van Boom and co-workers utilized ene−yne metathesis to access bicyclic phosphonate boranes in concert with their studies toward bicyclic phosphonates.[38] Acyclic RCM precursors **5.4a** and **5.4b** were produced according to the route outlined previously in Scheme 5. When $n = 1$ for **5.4a**, RCM using **B** gave only monocyclic product **20.2a** (Scheme 20). A mixture of bicyclic and monocyclic species was generated when $n = 2$, with bicyclic **20.1b** being the major product.

Scheme 20



The authors applied this method to target exclusively monocyclic phosphonate and phosphonamidate boranes. Acyclic ene−ynes **21.3** were generated using standard phosphoramidite chemistry (Scheme 21). In the presence of catalyst **B**, excellent yields were obtained of the monocyclic diene phosphonate and phosphonamidate boranes **21.4a** and **21.4b**, respectively.

Scheme 21

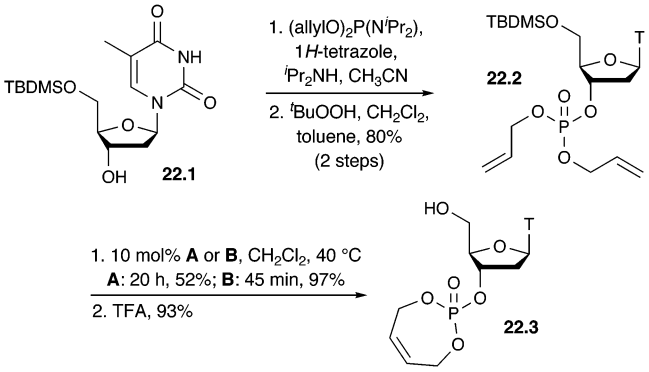


2.5. Conformationally Restricted Di- and Trinucleotides

In 2000, Nielsen and co-workers described the first examples of RCM to cyclic phosphates in their efforts to generate conformationally restricted dinucleotides.[55a] Acyclic phosphate **22.2** served as a model system for RCM and was produced from thymidine-derived secondary alcohol **22.1** using phosphoramidite coupling chemistry (Scheme 22). Ring-closure was significantly more facile using **B** (45 min, 97%) when compared to cyclization under the same conditions with catalyst **A** (20 h, 52%).

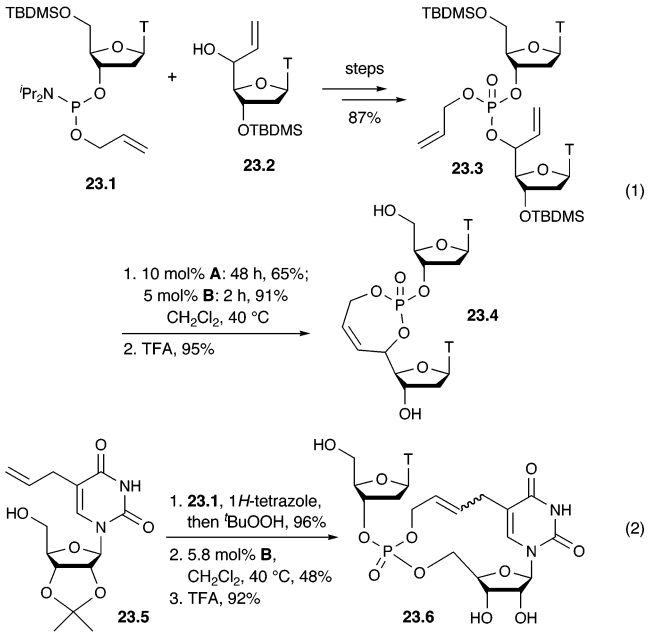
Phosphoramidite **23.1** was coupled with thymidine-derived allylic alcohol **23.2**, and subsequent RCM with catalyst **B** again proved to be more efficient (Scheme 23, eq 1). Removal of the silyl protecting

Scheme 22



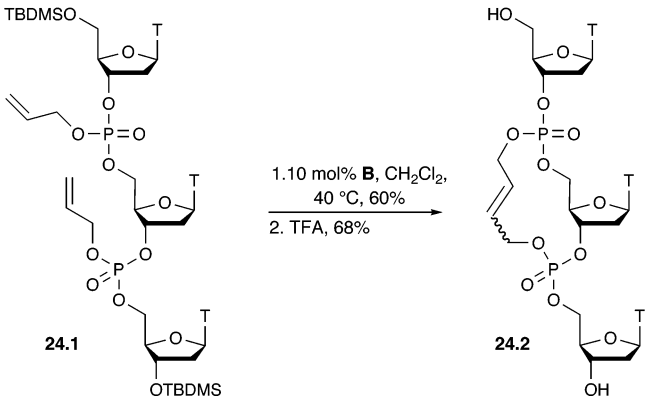
groups with trifluoroacetic acid provided conformationally restricted dinucleotide **23.4**. In related studies,[55c,d] the 14-membered dinucleotide **23.6** was isolated as a 10:1 mixture of *E*/*Z* diastereomers after RCM with **B** (eq 2).

Scheme 23



Nielsen and co-workers have also produced conformationally restricted trinucleotides using RCM.[55c] Bis-phosphate **24.1** underwent metathesis using 10 mol % **B** to afford the 13-membered trinucleotide **24.2** after protecting group removal (Scheme 24).

Scheme 24

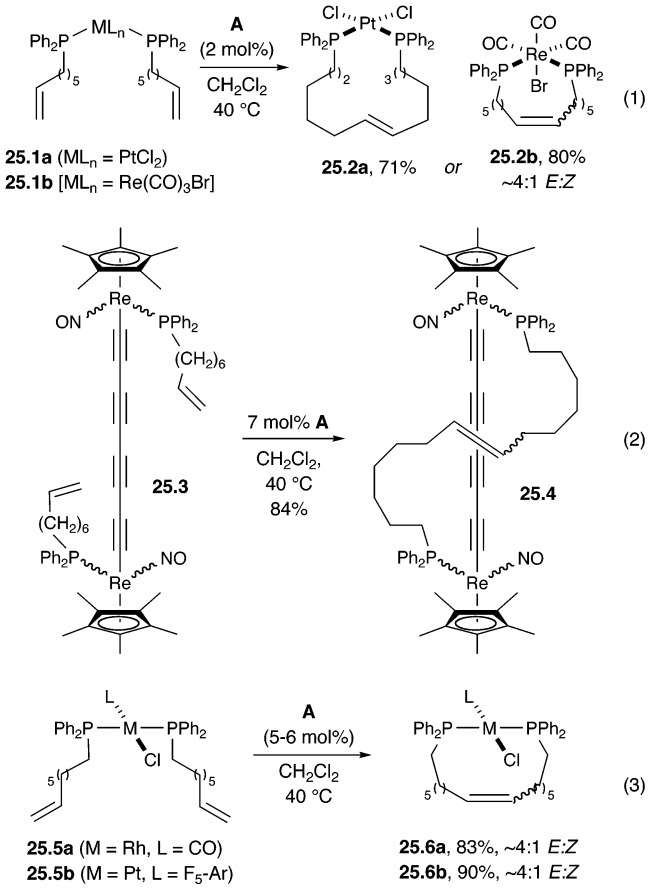


2.6. Phosphorus Metallocycles

2.6.1. Macrocyclic Phosphine Organometallic Complexes

Gladysz and co-workers have delineated numerous RCM strategies to macrocyclic phosphine-containing transition metal complexes[56−61] (Scheme 25). Catalyst **A** effectively promoted macrocyclization in various metal coordination spheres to yield 15-membered platinum and rhenium complexes **25.2**[56,57] (eq 1), as well as 26-membered dirhenium phosphine species **25.4**[58,59] (eq 2). Trans-spanning rhodium and platinum metallocycles **25.6** were accessed using a similar approach[57,60] (eq 3), and a recent systematic study by the same authors[61] evaluated the effect of olefin chain length and substitution upon this type of macrocyclic RCM event. For each of the examples outlined in Scheme 25, it is worth noting that the metal effectively serves as a phosphine protecting group, thereby allowing ruthenium-based catalyst **A** to retain RCM activity toward these phosphine diene substrates.

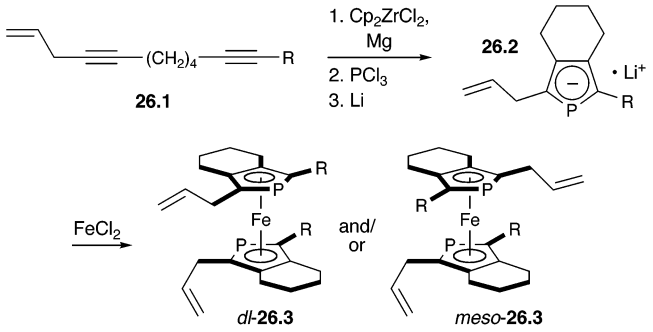
Scheme 25



2.6.2. Diphosphaferrocenophanes

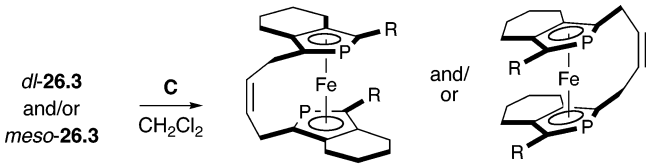
In 2003, Ogasawara, Hayashi, and co-workers described the synthesis of 1,1′-diphospha[4]ferrocenophanes by RCM using the Schrock molybdenum catalyst **C**.[62] Using a procedure developed by Fagan and Nugent,[63] ene−diynes **26.1** were converted to the corresponding *P*-chlorophospholes (Scheme 26). Reduction to the lithium phospholides **26.2**, followed by addition to $FeCl_2$, provided *dl*- and/or *meso*-diallyldiphosphaferrocenes **26.3**.

Scheme 26



The authors initially attempted to effect RCM of **26.3** with either ruthenium-based catalyst **A** or **B**. No ring-closure was observed after 24 h, with only starting material **26.3** being isolated in >90% recovery. The authors suggest that **A** and **B** were being deactivated through binding of the phosphine moieties in **26.3** to the ruthenium metal centers. Conversely, the Schrock molybdenum catalyst **C** was found to successfully promote cyclization to give phosphine metallocyles *dl*- and/or *meso*-**26.4** (Table 12). A notable difference in reactivity of **26.3c** when R = Ph was observed, as RCM was relatively expeditious, even at room temperature. The authors suggest that $\pi-\pi$ interactions between the phenyl substituents place the allylic appendages in close proximity, thereby assisting ring-closure. This hypothesis was supported by crystallographic analysis of *meso*-**26.4c**, which revealed that the phenyl groups were almost parallel, with a dihedral angle of 7.6°.

Table 12



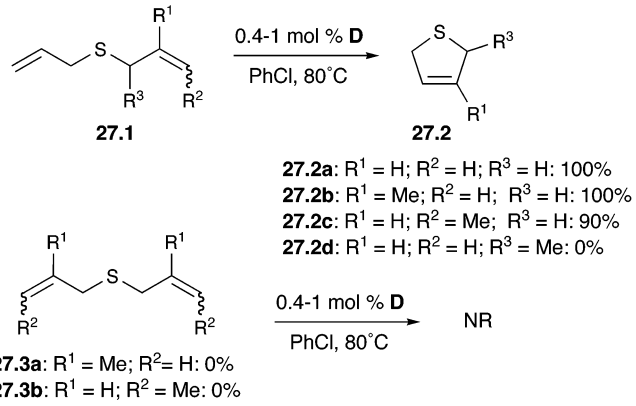
entry	diene	R	mol % **C**	temp (°C)	time (h)	yield **26.4** (%)
1	*meso*-**26.3a**	Me	20	40	48	77
2	*dl*-**26.3b**	^{t}Bu	20	40	36	51
3	*dl*- and *meso*-**26.3c**	Ph	10	23	15	44 (*dl*) 39 (*meso*)
4	**26.3e**	allyl	20	40	36	33 (*dl*) 31, 26.5 (R = $CH_2CH{=}CHCH_2$)

3. Sulfur Heterocycles

3.1. Sulfides, R–S–R′, and Disulfides, R–S–S–R′

In 1995, Basset and co-workers reported the first example of RCM on a sulfide-containing system using catalyst **D**[28] (Scheme 27). Diallyl sulfide (**27.1a**) cyclized smoothly to 2,5-dihydrothiophene (**27.2a**) in quantitative yield. Methyl substitution at either R^1 or R^2 did not hinder RCM, as **27.2b** and **27.2c** were formed in 100% and 90% yield, respectively. Secondary sulfides, with methyl substitution at the allylic position R^3 (**27.1d**) and symmetric dimethyl substitution at either R^1 or R^2 (**27.3a** and **27.3b**), inhibited cyclization, yielding no product.

Scheme 27



In 1996, Armstrong and co-workers also found molybdenum catalyst **C** to be effective in the RCM of sulfides.[64] Again, diallyl sulfide (**27.1a**) was converted to 2,5-dihydrothiophene (**27.2a**) in >99% yield utilizing **C** in toluene at room temperature. Attempts to effect metathesis with Grubbs catalyst **A** in toluene or neat proved unsuccessful, and only byproducts consistent with catalyst decomposition were observed. These results supported the conclusion that catalyst **A** is poisoned by sulfide substrates.

Lee and co-workers[65] extended the scope of sulfide RCM utilizing catalyst **C** to synthesize an array of cyclic sulfides and disulfides (Scheme 28, Table 13).[65] Both simple and substituted sulfides and disulfides were viable substrates in RCM reactions. However, olefinic substitution (R^1 and R^2) on the disulfide precursors **28.1c** and **28.1d** proved to be problematic for metathesis, as RCM of **28.1d** (R^1 = Me) yielded **28.2d** in only 15% yield (entry 5).

Scheme 28

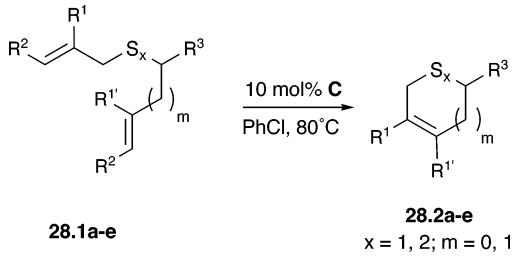


Table 13. RCM of Sulfides and Disulfides with Catalyst C or B

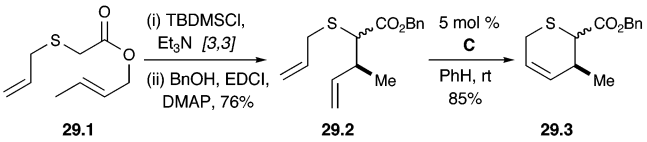
entry	cat.	substrate	*x*	*m*	R^1	$R^{1'}$	R^2	R^3	yield (%)
1	**C**[a]	**27.1a**	1	0	H	H	H	H	99
2	**C**[a]	**28.1a**	1	1	H	H	H	Ph	97
3	**C**[a]	**28.1b**	2	0	H	H	H	H	77
4	**C**[a]	**28.1c**	2	0	H	H	Me	H	54
5	**C**[a]	**28.1d**	2	0	Me	H	H	H	15
6	**B**[b]	**27.1a**	1	0	H	H	H	H	100
7	**B**[b]	**28.1e**	1	1	H	H	H	H	100
8	**B**[b]	**28.1b**	2	0	H	H	H	H	100[c]
9	**B**[b]	**28.1c**	2	0	H	H	Me	H	6

[a] 10 mol % **C**, C_6D_6, 20 °C for 1 h. [b] 5 mol % **B**, C_7D_8, 80 °C. [c] CD_2Cl_2 reflux.

In 2002, Mioskowski demonstrated the utility of the second-generation Grubbs catalyst **B** en route to similar cyclic sulfides and disulfides (Table 13, entries 6−9).[66] Olefinic substitution was again problematic, as RCM of the dicrotyl disulfide **28.1c** gave only limited amounts of **28.2c** (entry 9). Unsurprisingly, diallyl sulfides with substitution at R^3 and olefinic substitutions at both R^1 and $R^{1'}$ (dimethallyl sulfide) were also unreactive to **B**, and therefore unresponsive to all catalysts tested.

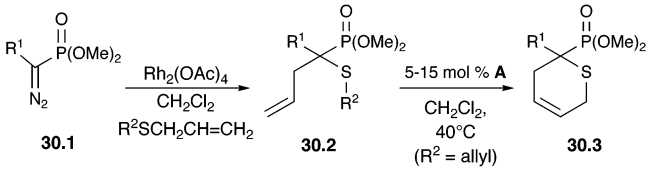
In 1998, Piscopio and co-workers reported the RCM of the secondary sulfide **29.2** as part of a [3,3]-sigmatropic rearrangement/RCM sequence affording a variety of six-membered heterocycles (Scheme 29).[67] Ester-substituted sulfide **29.2** was cyclized utilizing 5 mol % of catalyst **C** in benzene to give sulfide **29.3** in 85% yield.

Scheme 29



A sequential ylide rearrangement/RCM strategy was utilized to generate cyclic α-thiophosphonates **30.3a**−**c** (Scheme 30).[68] Metathesis of the acyclic α-thiophosphonates **30.2a**−**c** using catalyst **A** generated the cyclic α-thiophosphonates **30.3a**−**c** in moderate to excellent yields. The yields of the products were dependent on the steric and electronic nature of the α-substituent. It is interesting to note that the metathesis of substrate **30.2a** (R^1 = H) was sluggish and gave a poor yield of **30.3a**, while the metathesis of substrate **30.2c** ($R^1 = CO_2{}^tBu$) produced the cyclic α-thiophosphonate **30.3c** in quantitative yield. The yield improvement seen for this substrate could be attributed to a rate enhancement due to the bulky, geminal, disubstituted phosphonoacetate **30.2c**. Plausibly, the "blocking" effect of the *tert*-butyl ester may also prevent the lone pairs of the sulfide from poisoning the ruthenium alkylidene in the RCM reaction.

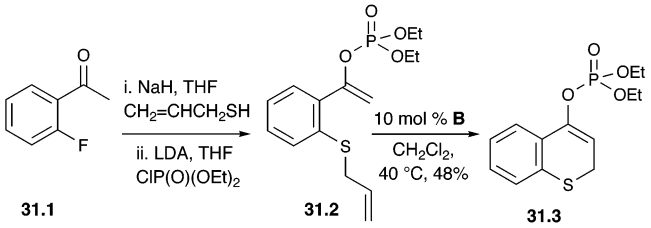
Scheme 30



30.3a: R^1 = H: 15 mol %, 3 d, 19%
30.3b: $R^1 = CO_2Me$: 5 mol %, 1.5 h, 78%
30.3c: $R^1 = CO_2{}^tBu$: 5 mol %, 20 h, 99%

In 2003, a variety of enolphosphate-containing heterocycles were synthesized via RCM, including cyclic sulfide **31.3** (Scheme 31).[69] The pathway to 2*H*-thiochromenyl enol phosphates was carried out beginning with the nucleophilic aromatic substitution of sodium allylmercaptide with 2-fluoroacetophenone (**31.1**). Subsequent enol phosphate generation delivered metathesis precursor **31.2**. Subjection of this enol phosphate to RCM conditions was successful in producing the 2*H*-thiochromen-4-yl enol phosphates **31.3**, albeit in modest yield (48%). However, oxidation

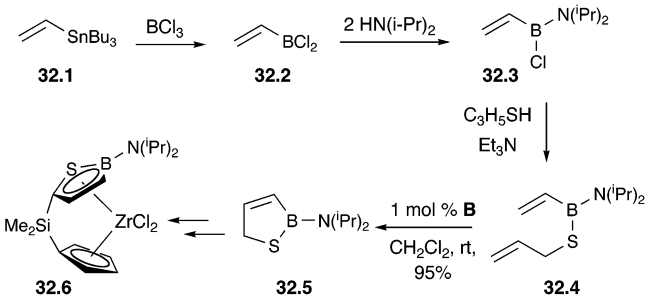
Scheme 31



of **31.2** had a noticeable effect on the subsequent RCM event (section 3.2.1).

Ashe and co-workers reported the metathesis of 1,2-thioboralide **32.4**, which was converted to a π-donating ligand for use in zirconium complex **32.6** (Scheme 32).[70] Starting from vinyl stannane **32.1**, 1,2-thioboralide **32.4** was produced in good yield over three steps. RCM proved highly effective, as borane **32.4** was cyclized using only 1 mol % of catalyst **B** at room temperature to give 1,2-thioboralide **32.5** in 95% yield.

Scheme 32

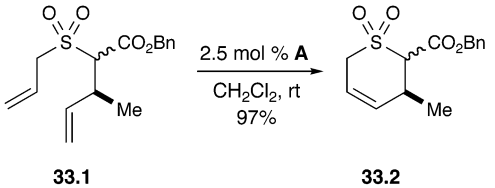


3.2. Sulfones and Sultones

3.2.1. Sulfones, R–SO$_2$–R′

Sulfones have proven to be much more compatible RCM substrates than sulfides. While the potential for sulfonyl oxygen coordination to ruthenium in catalyst **A** has been reported,[71] the sulfonyl group is less likely to induce catalyst poisoning. The initial example of sulfone metathesis, reported by Piscopio and co-workers,[67] was an extension of the aforementioned sequential [3,3]-sigmatropic rearrangement/RCM sequence represented in Scheme 29. Ester-substituted sulfone **33.1** underwent facile RCM, utilizing 2.5 mol % of catalyst **A** to yield the corresponding cyclic sulfone **33.2** in 97% yield in CH_2Cl_2 (Scheme 33).

Scheme 33



In 2002, Yao reported the first thorough study of sulfone RCM.[72] A number of structurally diverse sulfones were prepared, as represented in Scheme 34. Initially, diallyl sulfone **34.4a** was treated with 2 mol % of **A** in refluxing CH_2Cl_2 to give the five-membered

Scheme 34

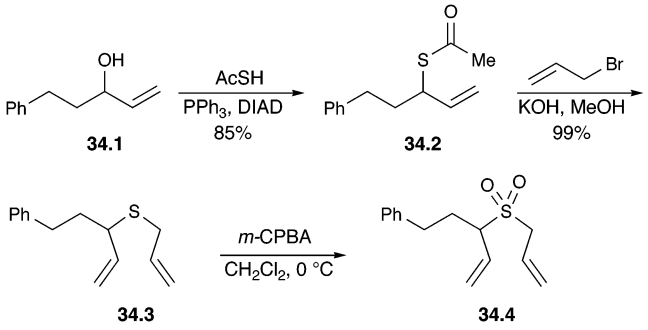
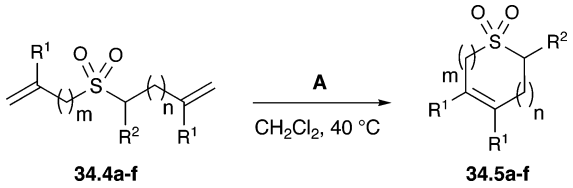


Table 14



entry	diene	*m*	*n*	R^1	R^2	time	yield (%)
1	**34.4a**	1	0	H	H	1 h	95
2	**34.4b**	1	0	H	CH_2CH_2Ph	1 h	99
3[a]	**34.4c**	1	0	Me	H	24 h	99
4	**34.4d**	1	1	H	Ph	2 h	100
5	**34.4e**	2	1	H	Ph	3.5 h	98
6	**34.4f**	3	1	H	Ph	24 h	85

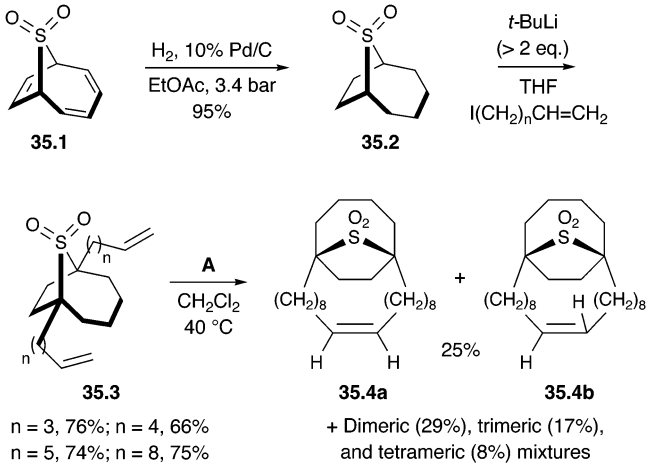
[a] Catalyst **B**.

cyclic sulfone **34.5a** in 95% yield (Table 14, entry 1). Allylic substitution had no effect on metathesis, as secondary cyclic sulfone **34.5b** was generated in 99% yield (entry 2). Methyl substitution at R^1 required the use of catalyst **B** and resulted in a quantitative yield of **34.5c** (entry 3). This exemplifies the facile nature of sulfone metathesis with respect to the analogous sulfide, which has yet to be generated via RCM (vide supra). Substituted six-membered and seven-membered sulfones were also formed without incident (entries 4 and 5). Metathesis of the eight-membered case **34.4f** required a higher catalyst loading (6 mol %) and a 24 h reaction time, affording **34.5f** in 85% yield (entry 6). The five-membered cyclic sulfones found use as masked Diels–Alder dienes formed by chelotropic elimination of SO_2. The larger ring compounds were converted to cyclic dienes via the Ramberg–Backlund reaction.

Paquette and co-workers reported a sulfone RCM involving bridged bicyclic sulfones possessing alkenyl groups at both bridgehead carbons.[71] In this study, the authors sought to determine the optimal chain length (*n*) for facile metathesis to generate strained paddlanes, a class of tricyclic compounds notable for having all four bridges originating from just two bridgehead carbons (Scheme 35). In addition, it was their intent to highlight the power of the sulfone group to serve as a polar "relay" group in olefin metathesis.

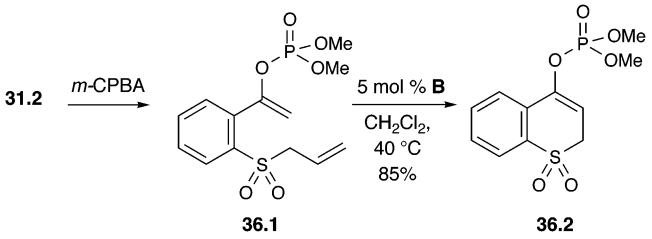
As an extension of the aforementioned sulfide-based enolphosphate metathesis (Scheme 31), it was found that simple oxidation of sulfide **31.2** to the corresponding sulfone **36.1** greatly enhanced subsequent metathesis. Using catalyst **B**, enol phosphate

Scheme 35



36.1 underwent cyclization smoothly to afford the enol phosphate-substituted sulfone **36.2** in 85% yield (Scheme 36).[69] This study was consistent with results observed by Yao in the generation of cyclic sulfones with **B**.

Scheme 36



3.2.2. Sultones

The RCM of vinylic and allylic sultonates has provided access to synthetically useful cyclic sulfonates (sultones).[73] Sultones of varying sizes have been generated utilizing both Grubbs catalysts **A** and **B**, though catalyst **B** has been proven to be more effective. In two independent reports, both Metz and co-workers[74] and Cossy and co-workers[75] synthesized analogous groups of unsubstituted sultones. Sulfonate starting materials were derived from the condensation of olefinic alcohols with vinyl and allyl sulfonyl chlorides (Scheme 37). The two studies both primarily employed catalyst **B**, differing in the use of solvent and temperature (refluxing CH_2Cl_2 vs C_6H_6, 70 °C). Vinyl sulfonate **37.3a** was cyclized to the five-membered sultone **37.4a** with high efficiency in 100% and 94% yield, respectively (Table 15, entry 1). The six-membered sultone **37.4b** was also isolated in excellent yields via both methods (entry 2). The RCM of the substituted vinyl methallyl sulfonate **37.3c** required higher temperatures and was closed more efficiently in C_6H_6 (100%) than in CH_2Cl_2 (69%, entry 3). Interestingly, RCM with catalyst **B** enabled the generation of the seven-membered vinylsultone **37.4d** in higher yield than the seven-membered allylsultone **37.4e** (entries 4 and 5). General trends displayed more facile metatheses of medium-sized rings with β,γ-unsaturated substrates rather than their α,β-unsaturated analogues.

Cossy and co-workers also reported the use of RCM to synthesize sultones derived from secondary alcohols, as summarized in Table 16.[75] Due to their instability, crude sulfonates **38.3**, generated from the coupling of sulfonyl chlorides **38.1** and secondary alcohols **38.2**, were subjected to RCM conditions without purification (Scheme 38). The products derived from RCM were six- and seven-membered sultones **38.4** in good yields over two steps. A variety of protected alcohols as well as an ester were among the compatible functionalities.

Scheme 37

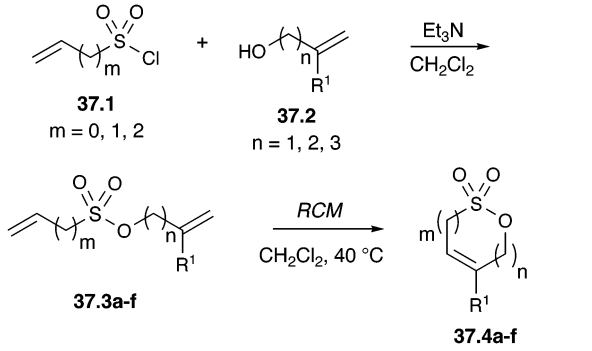


Table 15

entry	diene	*m*	*n*	R^1	% yield[a]	% yield[b]
1	**37.3a**	0	1	H	100	94
2	**37.3b**	0	2	H	90	99
3	**37.3c**	1	1	Me	100	69
4	**37.3d**	0	3	H	na	94
5	**37.3e**	1	2	H	100	76
6	**37.3f**	1	3	H	94[c]	82

[a] Catalyst **B**, C_6H_6, 70 °C; Cossy and co-workers.[75] [b] Catalyst **B**, CH_2Cl_2, reflux; Metz and co-workers.[74] [c] Catalyst **A** was used.

Scheme 38

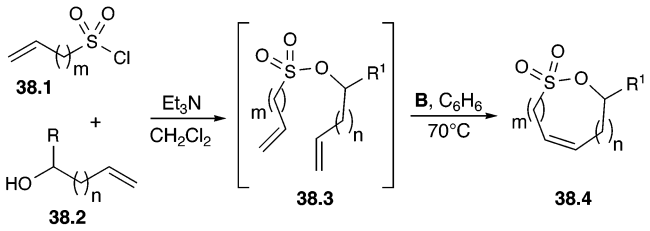


Table 16

entry	diene	*m*	*n*	R^1	yield (%)
1	**38.3a**	0	1	$(CH_2)_3OBn$	76
2	**38.3b**	0	1	CO_2Et	54
3	**38.3c**	1	0	CH_2OPiv	74
4	**38.3d**	1	0	$CH_2OTBDPS$	65
5	**38.3e**	1	1	$(CH_2)_3OBn$	65

3.3. Sulfonamides and Sulfamides

3.3.1. Sulfonamides (Sultams), $R–SO_2–NR'_2$

In 1999, the first examples of sulfonamide metathesis involving the efficient synthesis of simple five-, six-, and seven-membered cyclic sulfonamides (sultams) employing 1.5−6 mol % of catalyst **A** in refluxing CH_2Cl_2 were reported.[76] The precursors were derived from the coupling of nitrogen nucleophiles to styryl-, vinyl-, and allyl-sulfonyl chlorides (Scheme 39). The styryl sulfonamides were ideal

Scheme 39

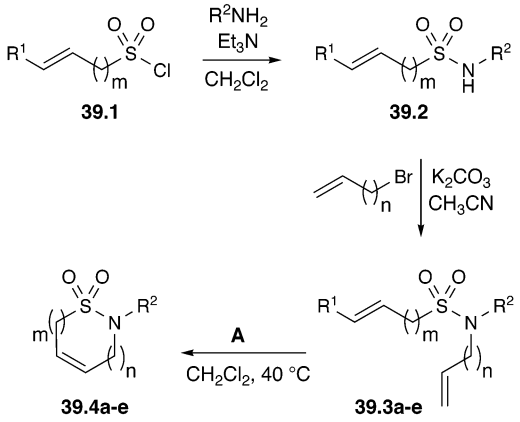


Table 17

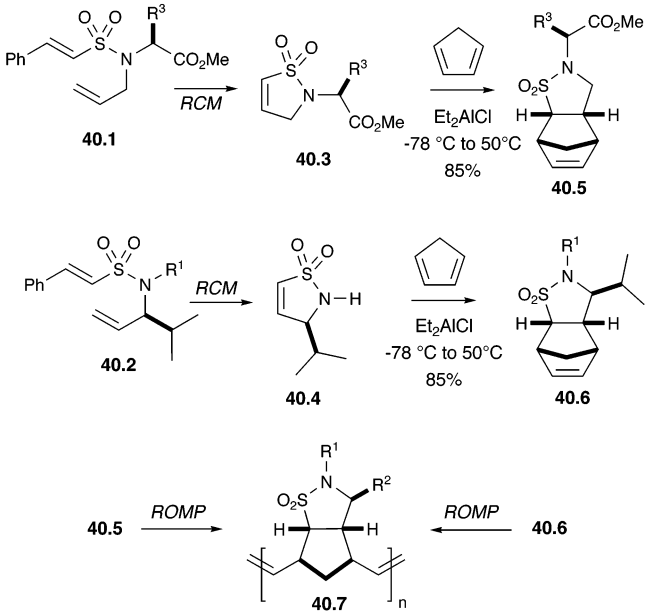
entry	diene	*m*	*n*	R^1	R^2	yield (%)
1	**39.3a**	0	1	Ph	H	90
2	**39.3b**	0	1	Ph	Bn	88
3	**39.3c**	0	2	Ph	Bn	65
4	**39.3d**	1	1	H	H	91
5	**39.3e**	1	2	H	Bn	91

substrates due to the regeneration of the benzylidene catalyst **A** following the metathesis event. Initial results showed that sulfonamides **39.3a**,**b** (Table 17, entries 1 and 2) underwent metathesis smoothly over 24 h to yield five-membered cyclic sulfonamides **39.4a**,**b** in excellent overall yields of 90% and 88%, respectively (entries 1 and 2). In contrast to early reports on the RCM involving free N−H amine substrates poisoning the catalyst, free sulfonamide N−H substrates did not have a deactivating effect on the catalyst. Exocyclic nitrogen substitution was not necessary for efficient RCM on these substrates. Six- and seven-membered sulfonamides were also generated with good efficiency. Though the cyclization of vinyl sulfonamide **39.3c** (entry 3) was sluggish, the metatheses of allyl sulfonamides **39.3d** and **39.3e** (entries 4 and 5) were facile, to give **39.4d** and the seven-membered cyclic sulfonamide **39.4e** in high yields (91% for both).

In addition to the simple cases shown in Table 17, amino ester-derived sulfonamides bearing both internal and external substitution, **40.1** and **40.2**, were shown to be compatible substrates in a strategy employing both RCM and ring-opening metathesis polymerization (ROMP) (Scheme 40).[77] Cyclic amino acid-derived α,β-unsaturated γ-sultams **40.3** and **40.4**, containing exocyclic or γ-endocyclic stereogenic centers, respectively, were generated via RCM. These sultams underwent stereoselective Diels−Alder reaction with cyclopentadiene under Lewis acid catalysis (Et_2AlCl), yielding tricyclic sulfonamides **40.5** and **40.6 w**ith good levels of endo selectivity in each case and with complete facial selectivity in the case of **40.6**. Ensuing ROMP generated sulfonamide oligomers of general structure **40.7**, possessing a broad solubility profile in various solvents.

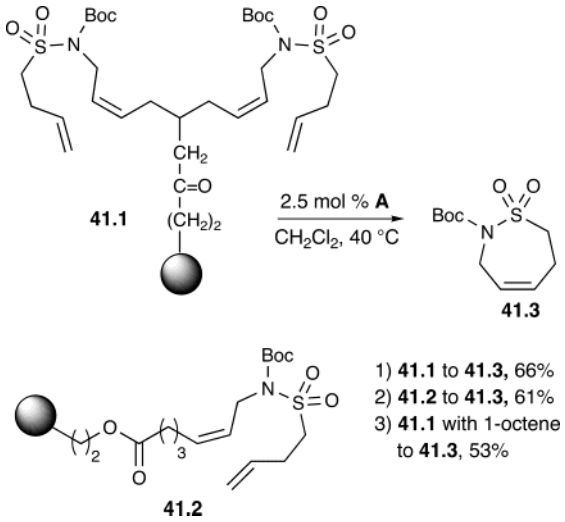
In 2000, Brown and co-workers reported a cyclorelease RCM strategy during a study of solid-phase synthetic methods toward cyclic sulfonamides.[78] The

Scheme 40



metathesis event was utilized to cleave a Boc-protected, seven-membered cyclic sulfonamide from a solid support. The potential difficulty found in the deployment of cyclorelease RCM was thought to arise from catalyst deactivation as a direct result of becoming bound to the resin following the metathesis event. Double-armed and single-armed polystyrene-bound precursors **41.1**, and **41.2**, respectively (Scheme 41), were successfully used to test the efficacy of this method, and optimal results were obtained with 2.5% of **A** in refluxing CH_2Cl_2. Single-armed substrate **41.2** gave *N*-sulfonamide **41.3** in 61% yield, while double-armed substrate **41.1** afforded **41.3** in 66% yield. Use of 1-octene as a double-bond cofactor to aid in catalyst release from the resin was found to be insignificant, as the yield of **41.3** decreased to 53%, indicating that the resin-bound catalyst was not a major hindrance to the reaction.

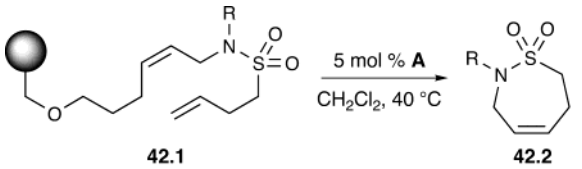
Scheme 41



With this methodology in hand, the researchers generated a small library of unsubstituted and *N*-substituted cyclic sulfonamides (Scheme 42). Sul-

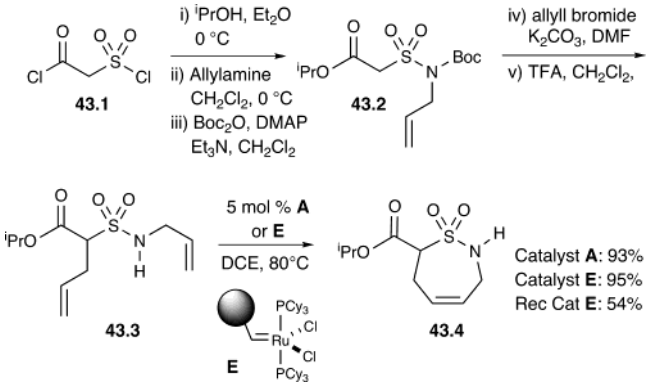
fonamides **42.2a**−**c** were synthesized in overall yields of 49−59%, revealing a viable solid-phase method for synthesizing cyclic sulfonamides.

Scheme 42



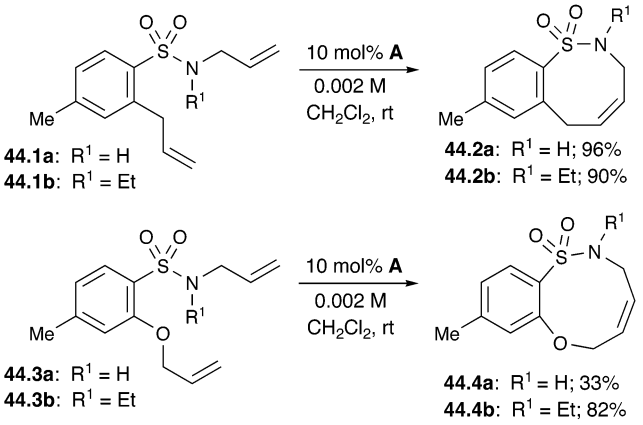
Also within the realm of solid-phase synthesis, Termin and co-workers reported use of RCM to access seven-membered cyclic sulfonamides.[79] The study compared the catalyst **A** with its polystyrene-bound variant **E** (Scheme 43).[80] The advantages of the resin-bound catalyst are the facile chromatographic removal of the RCM impurities from the final products and the ability for catalyst recycling. Sulfonamide **43.3** was synthesized in five steps, starting from commercially available chlorosulfonylacetyl chloride (**43.1**). Reaction of acid chloride **43.1** with 1 equiv of isopropyl alcohol in ether at 0 °C, followed by reaction with a secondary or hindered amine, afforded selective reaction at the sulfonyl chloride. Use of the isopropyl ester was deemed necessary to retain selective amino addition. Protection with Boc_2O afforded **43.2** in good yield. Subsequent selective mono-C-allylation and deprotection of the Boc group generated the requisite sulfonamide **43.3**. RCM was carried out with catalysts **A** and **E** in refluxing dichloroethane, using 1-hexene as a cofactor to aid in the regeneration of **E**. Catalyst **A** generated cyclic sulfonamide **43.4** in 93% yield, while resin-bound catalyst **E** generated **43.4** in 95% yield. While comparable in efficiency, **E** was considered more valuable due to the ease of product purification. The only drawback to this approach was the catalyst behavior upon reuse. When **E** was recycled and redeployed, it was much less effective than previously reported,[80] resulting in the production of cyclic sulfonamide **43.4** in only 54% yield.

Scheme 43



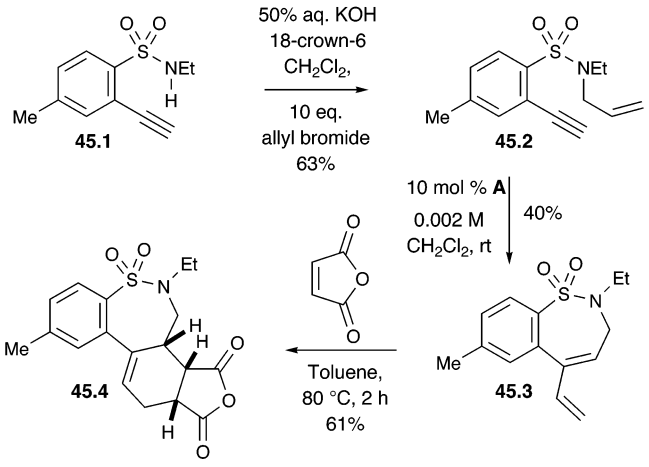
In efforts to synthesize novel benzannulated cyclic sulfonamides, Snieckus and co-workers exploited RCM as the penultimate step in a directed ortho-metalation/RCM methodology.[81] Sulfonamides **44.1a** and **44.1b** were synthesized via directed ortho-metalation followed by allylation in the case of **44.1b** (R^1 = Et) (Scheme 44). All metatheses were carried out with 10 mol % of catalyst **A** in CH_2Cl_2 at room temperature. Initially, sulfonamide **44.1a** was cyclized to give the eight-membered, benzannulated sulfonamide **44.2a** in 96% yield. Nitrogen substitution had little effect on RCM efficiency, as cyclic sulfonamide **44.2b** was generated in 90% yield. Oxygenated sulfonamides were also synthesized in modest to good yields. The metathesis of unsubstituted sulfonamide **44.3a** yielded only 33% of the corresponding nine-membered product **44.4a**, while RCM of the *N*-ethyl-substituted sulfonamide **44.3b** afforded the bicyclic sulfonamide **44.4b** in 82% yield. Any attempts to cyclize sulfonamides with disubstituted olefins gave only products arising from cross-metathesis of the monosubstituted alkenes.

Scheme 44

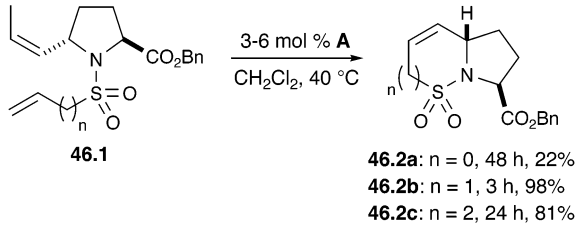


In this same study, Snieckus and co-workers also carried out an ene−yne metathesis to yield diene **45.3** armed for subsequent Diels−Alder reaction (Scheme 45). Thus, allylation of the acetylenic sulfonamide **45.1** under phase-transfer catalysis yielded the ene−yne sulfonamide **45.2**. RCM under standard conditions resulted in the production of diene sulfonamide **45.3** in modest yields. Attempts to employ an ethylene atmosphere, previously reported by Mori and co-workers[82] to improve ene−yne metathesis, were found to be detrimental. Final Diels−Alder reaction

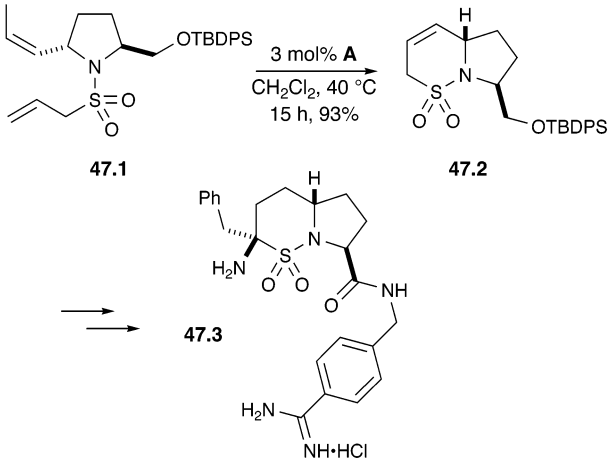
Scheme 45



Scheme 46



Scheme 47



carried out in toluene led to the structurally complex sulfonamide **45.4** in good yield.

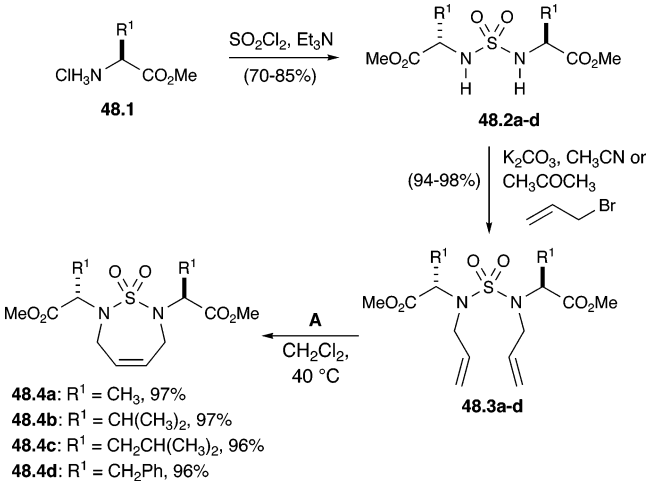
In 2003, Hannesian and co-workers carried out the synthesis of bicyclic, constrained proline analogues (Scheme 46), culminating in the synthesis of the sulfonamide variant **47.3** of a potent thrombin inhibitor (Scheme 47).[83] Metathesis of sulfonamides **46.1a**−**c** with catalyst **A** in refluxing CH_2Cl_2 gave the resulting bicyclic sulfonamides **46.2a**−**c** in modest to excellent yields (Scheme 46). While bicyclo[3.3.0]-sulfonamide **46.2a**, possessing a 5,5-ring system, was generated in only 22% yield, bicyclo[4.3.0]sulfonamide **46.2b**, possessing a 6,5-ring system, was isolated in 98% yield, and bicyclo[5.3.0]sulfonamide **46.2c** in 81% yield. Sulfonamide **47.1** also underwent efficient RCM, producing the bicyclo[4.3.0]sulfonamide **47.2** in 93% yield (Scheme 47). Sulfonamide **47.2** was then converted to the potential thrombin inhibitor **47.3**.

3.3.2. Sulfamides, $R_2N–SO_2–NR'_2$

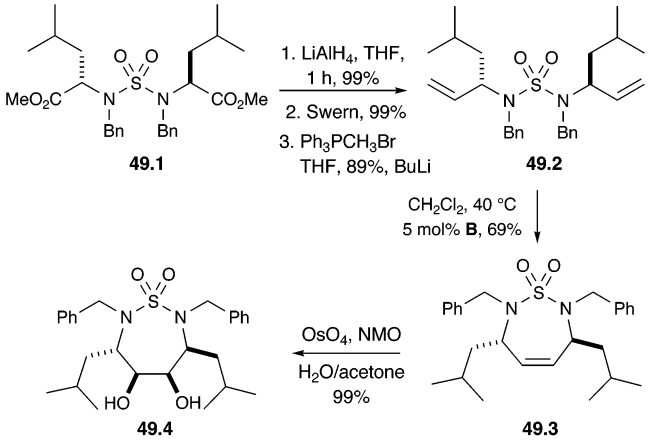
In 2000, RCM strategies were developed to generate symmetric and unsymmetric cyclic sulfamides[84,85] related to the potent HIV-protease inhibitor DMP 323 developed at DuPont Merck.[50] A route to several C_2-symmetric sulfamides derived from amino esters is outlined in Scheme 48. RCM using catalyst **A** gave excellent yields of the C_2-symmetric cyclic sulfamides **48.4a**−**d**. Attempts to derive unsymmetric sulfamides in this manner resulted in unacceptably low yields. In addition, attempts to directly couple secondary amines (allylated amino esters) to SO_2Cl_2 were not successful.

In a newly related route, shown in Scheme 49,[85] the robust nature of the sulfamide group is exemplified in a three-step protocol, converting each of the homotopic ester moieties in **49.1** to the terminal olefins residing in **49.2** that are armed for RCM.

Scheme 48



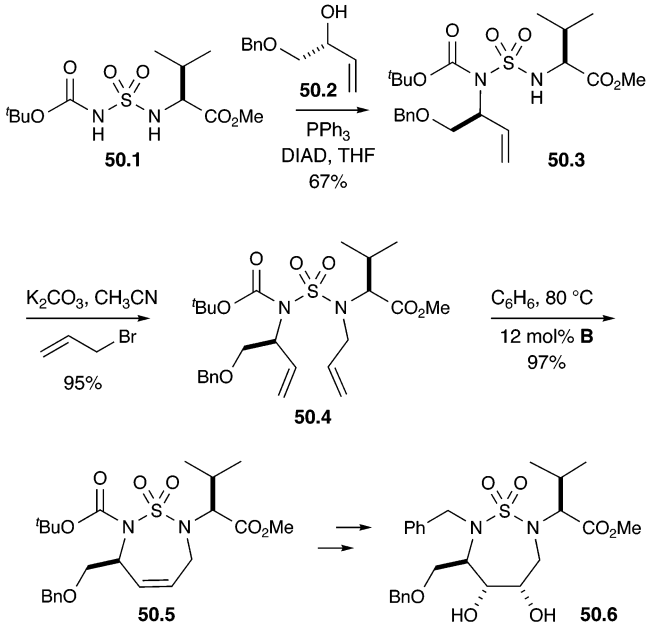
Scheme 49



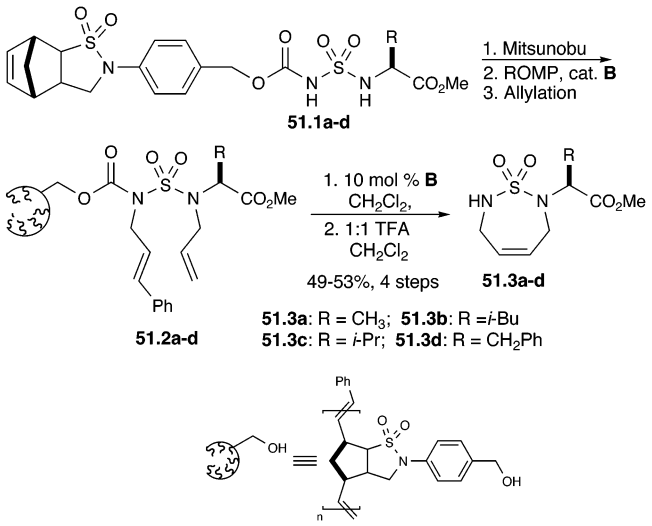
Metathesis with 5 mol % of **B** generated cyclic sulfamide **49.4** in 69% yield. Subsequent dihydroxylation produced the cyclic sulfamide diol in 99% yield.[85]

Unsymmetric sulfamides were also generated with high efficiency (Scheme 50).[84,85] RCM precursors were

Scheme 50



Scheme 51

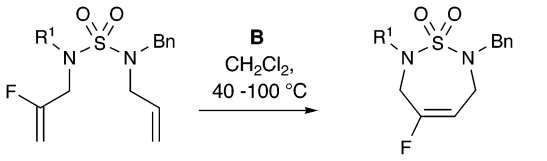


accessed using a three-component coupling reaction involving ^{t}BuOH, chlorosulfonyl isocyanate (CSI), and an amine. In these examples, the sulfamoyl nitrogen was exploited for its ability to act as a nucleophile in the Mitsunobu reaction, effectively delivering stereogenic centers in either the endo- or exocyclic position. In the most elaborate example, Mitsunobu alkylation of sulfamide **50.1**, with the readily prepared nonracemic secondary allylic alcohol **50.2**,[86] generated sulfamide **50.3** in good yield and with good S_N2 regioselectivity. Standard allylation, followed by RCM with 12 mol % of **B**, produced the cyclic sulfamide **50.5** in excellent yield. Further elaboration afforded the differentiated sulfamide diol **50.6** in good yield and with high diastereoselectivity in the final dihydroxylation step.

In 2003, a solution-phase pathway toward cyclic sulfamides using high-load soluble ROMP supports was developed (Scheme 51).[87] The methodology revolves around a ring-opening metathesis polymerization phase trafficking (ROMPpt) strategy. The major advantage of this pathway is that it combines favorable solution-phase reaction kinetics with the ease of purification of solid-phase pathways. Oligomeric sulfamides **51.1a**−**d**, featuring a norbornenyl-tagged Wang-like protecting group (NWPG), were first allylated with phenyl-protected olefins under Mitsunobu conditions. ROMP with catalyst **B**, simple filtration to separate the oligomer-bound sulfamide from Mitsunobu byproducts, and allylation afforded the oligomeric-bound sulfamides **51.2a**−**d**. RCM with 10 mol % of **B** and subsequent sulfamide liberation with trifluoroacetic acid afforded sulfamides **51.3a**−**d** in 49−53% yield over four steps in >90% purity. The pathway was also successful utilizing a more readily derived norbornenyl-tagged sulfamoyl carbamate. Overall, this strategy exploits ROMP in the presence of phenyl-protected olefins and RCM in the presence of an oligomeric olefinic backbone.

In 2003, Brown and co-workers reported an RCM approach on vinyl fluoride-containing dienes using catalyst **B**.[88] In this approach, RCM proceeded efficiently to give six- and seven-membered cyclic vinyl fluorides, including sulfamides such as **52.2** (Scheme 52). RCM was first carried out on the Boc-protected

Scheme 52



52.1a, R^1 = Boc
52.1b, R^1 = H
52.1c, R^1 = Bn
52.1d, R^1 = Me
52.1e, R^1 = Et

52.2a, R^1 = Boc, (90%)
52.2b, R^1 = H, (79%)
52.2c, R^1 = Bn, (78%)
52.2d, R^1 = Me, (77%)
52.2e, R^1 = Et, (85%)

sulfamide **52.1a**, which cyclized smoothly (3 h) in refluxing CH_2Cl_2 with 6 mol % **B**. The monosubstituted sulfamide **52.1b** also underwent ring-closure in refluxing CH_2Cl_2 (7 h), yielding **52.2b**, whereas the *N*-alkyl sulfamides **52.1c**−**e** underwent RCM more slowly and required higher temperatures. The authors note that no special high-dilution conditions were required to avoid cross-metathesis, and all of the desired *N*,*N*-disubstituted sulfamides were obtained in good to excellent yields (77−90%).

4. Conclusion

In conclusion, with the advent of well-defined metathesis catalysts, RCM has emerged as an effective method for the synthesis of *P*- and *S*-heterocycles. With proper choice of catalyst, almost any functional group or "subclass" within the realm of *P*- and *S*-heterocycles can be obtained. When coupled with "diversity-oriented synthesis", this technological advance will undoubtedly enable the generation of new, structurally unique heterocycles exhibiting biological potential. Metathesis to these heterocycles, in concert with the heritage of phosphorus and sulfur compounds as reagents in synthesis, could produce conformationally constrained reagents exhibiting different reactivity profiles relative to acyclic parent compounds. Furthermore, newer advances in catalyst development will only broaden the type of *P*- and *S*-heterocycles that can be made in the future, overall producing a powerful arsenal for both drug and reagent development for years to come.

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