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The Rauhut–Currier reaction: a history and its synthetic application

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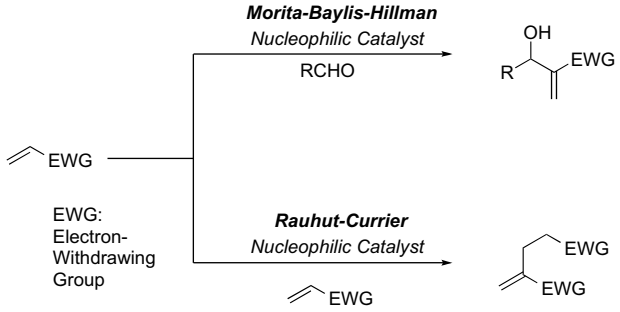
Contents

1. Introduction[1]

Carbon–carbon bond formation is of fundamental importance in organic synthesis, with much research focused on control of reaction efficiency, stereoselectivity, and chemoselectivity.[2] Among the many methods established for the formation of new C–C bonds, nucleophilic conjugate addition reactions constitute a significant and synthetically useful method, with the ability to build rings, set multiple stereocenters, and process a wide variety of substrates.[3] Furthermore, for almost half a century, the use of enones as latent enolates has provided a successful entry into reactions whose mechanisms are more commonly associated with enolates.[4] The Morita–Baylis–Hillman (MBH) and Rauhut–Currier (RC) reactions, in a sense, merge the concepts of conjugate addition and latent enolate generation. Each process comprises an independent class of transformations that encompasses the ability to generate a new C–C bond in an atom economical manner. As will be described below, each may combine the power of nucleophilic catalysis to access latent enolates as a result of formal conjugate addition. While the MBH reaction involves the coupling of the activated alkene/latent enolate with an aldehyde, the RC reaction (also known as the vinylogous MBH reaction)[5] involves the coupling of one active alkene/latent enolate to a second Michael acceptor, creating a new C–C bond between the α-position of one activated alkene and the β-position of a second alkene under the influence of a nucleophilic catalyst (Scheme 1).



Scheme 1. Comparison of the MBH and RC reactions.

A vast array of literature has been established regarding the MBH reaction, reflecting its potential to greatly affect organic

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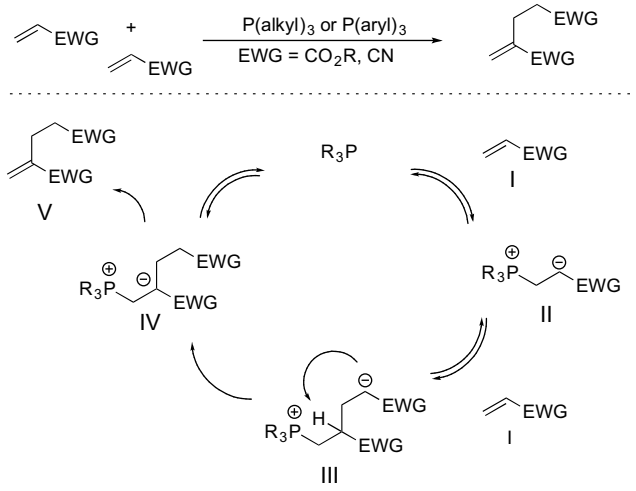
synthesis by providing densely functionalized products with a new stereogenic center that serve as substrates for a multitude of subsequent transformations.[6] The RC reaction, on the other hand, has received much less attention due, in part, to low reactivity of substrates and difficulty in controlling the selectivity of the cross-coupling reaction. While the development of the reaction has not been rapid, great advancement has been made in recent years, providing the synthetic community with new opportunities for efficient C–C bond formations.[7] Herein, the development of the RC reaction will be presented from its initial documentation to the current state-of-the-art. Derivatives of this coupling reaction, such as alternative electrophilic and nucleophilic partners, will also be discussed. Finally, its application in the synthesis of natural products will be described, as the success of this transformation has recently begun to impact complex molecule synthesis.

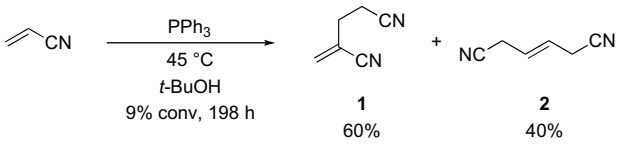
2. Overview of the intermolecular Rauhut–Currier reaction

In 1963, Rauhut and Currier[8] reported the phosphine-catalyzed dimerization of electron-deficient alkenes, acrylonitrile and ethyl acrylate, in what has become known as the RC reaction (Scheme 2).[9] The transformation is believed to proceed via reversible conjugate addition of a nucleophilic catalyst (e.g., either a trialkylphosphine or a triarylphosphine) to activated alkene **I** to generate zwitterionic species **II**. A Michael reaction of the enolate with a second equivalent of activated alkene **I** generates intermediate **III**, which then undergoes a prototropic shift followed by extrusion of the phosphine catalyst to generate the RC coupling product (**V**).



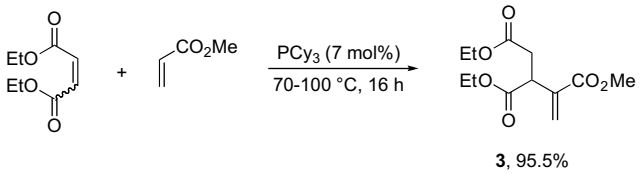
Scheme 2. Proposed mechanism of the RC reaction.

Two years later, Baizer and Anderson,[10] as well as McClure[11] similarly described the successful dimerization of acrylonitrile in the presence of tributylphosphine (PBu_3). The analogous PPh_3-catalyzed dimerization was reported to be less efficient, producing a low yield of α-methyleneglutaronitrile (**1**, 60%) in addition to 1,4-dicyano-1-butene (**2**, 40%), based on 9% conversion of acrylonitrile (Scheme 3). The reaction was performed at 45 °C in *tert*-butyl alcohol (*t*-BuOH) for 198 h.



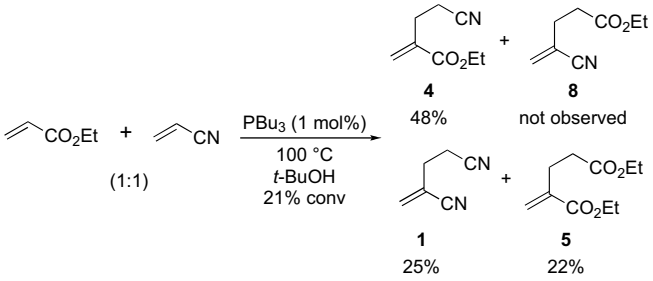
Scheme 3. Dimerization of acrylonitrile by Baizer and Anderson.

In 1969 Morita and Kobayashi[12] reported the first cross-coupling reaction of activated alkenes (methyl acrylate and acrylonitrile) with fumaric/maleic esters (diethyl and dibutyl) in the presence of tricyclohexylphosphine (PCy_3; Scheme 4). They achieved high yield (95.5%) in the coupling of methyl acrylate and diethyl fumarate, to provide addition product 3-butene-1,2,3-tricarboxylic acid 1,2-diethyl-3-methyl ester, **3**. Analogous reactions affording dibutyl (1-cyanovinyl)succinate and dibutyl (1-cyanoethylidene)succinate were presented without yields.



Scheme 4. P(Cy)$_3$-catalyzed coupling reported by Morita and Kobayashi.

McClure[13] presented a similar cross-coupling reaction of ethyl acrylate and acrylonitrile catalyzed by PBu_3 in 1970 (Scheme 5). In the presence of *t*-BuOH at 100 °C, only one of two possible cross-coupled products was obtained, 2-ethoxycarbonyl-4-cyano-1-butene (**4**, 48%), in addition to the products corresponding to homodimerization of both reactants (**5**, 22%; **1**, 25%).

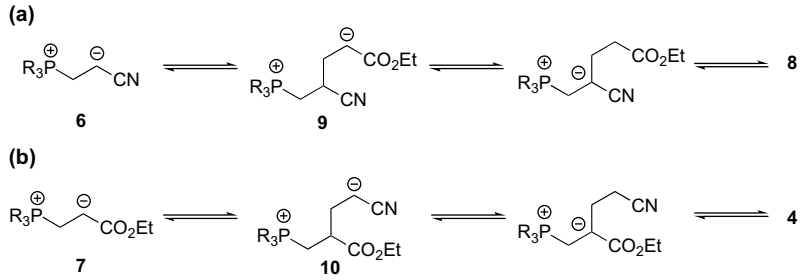


Scheme 5. Cross-coupling in the RC reaction.

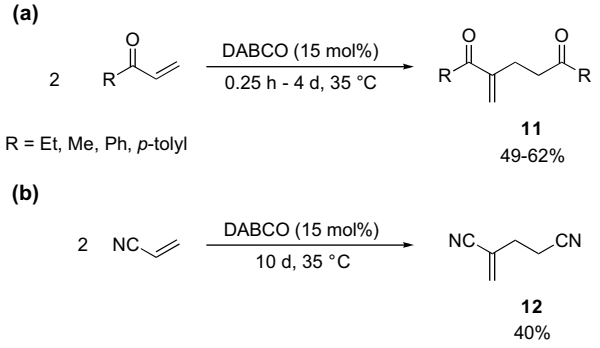
Homodimerization by-products **5** and **1** were isolated in nearly equal amounts, suggesting that both intermediates, **6** and **7**, were formed during the reaction (Scheme 6). The absence of product **8** was thus rationalized by assuming that the subsequent reaction of the phosphonium zwitterions with ethyl acrylate (Scheme 6a) was less favorable than reaction with acrylonitrile (Scheme 6b). The following proton transfer step was also implicated in the selective product formation, with proton transfer being less favored in the case of intermediate **9** than **10**. Ultimate product formation was therefore dependent not on the relative ease of the initial conjugate addition (forming intermediates **6** and **7**), but rather on the ensuing steps in the transformation.

More than 15 years later, various reports of similar processes were established under the influence of amine-based catalysts. In 1986 Amri and Villieras presented an amine-catalyzed variant of the RC transformation.[14] In an investigation of the related MBH reaction, researchers discovered that methyl vinyl ketone (MVK) underwent slow dimerization (7 days) in the presence of 1,4-diazabicyclo[2.2.2]octane (DABCO) to provide 3-methylene-2,6-heptadione.

The DABCO-catalyzed dimerization was extended further by Basavaiah and co-workers to include various α,β-unsaturated ketones and acrylonitrile (Scheme 7).[15] A range of reaction times (15 min, phenyl vinyl ketone; 4 days, methyl vinyl ketone; 10 days, acrylonitrile) were reported with 15 mol % catalyst loading at 35 °C to provide the corresponding 2-methylene-1,5-diketones (**11**) and acrylonitrile dimer (**12**) in moderate to good yields (Scheme 7a and b).

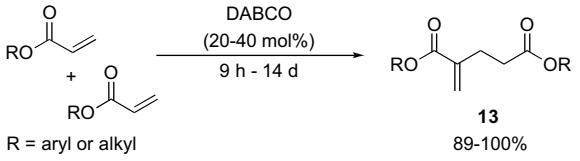


Scheme 6. (a) Pathway to the cross-coupled product **8** (not observed). (b) Pathway to the cross-coupled product **4**.



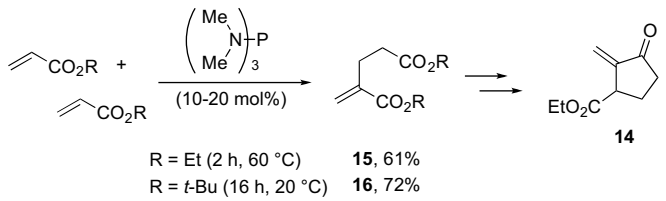
Scheme 7. (a) Amine-catalyzed RC reactions of enones and (b) acrylonitrile.

Drewes and co-workers demonstrated that in the absence of an aldehyde coupling partner in the MBH reaction, acrylate esters will undergo self condensation reactions to afford the corresponding dimers in nearly quantitative yield (89–100%; Scheme 8).[16] The dimerization of a variety of aryl and alkyl functionalized acrylates was promoted by DABCO (20–40 mol %) to provide the esters of α-methyleneglutaric acid (**13**). Under these conditions, however, methyl acrylate was unreactive, even after 30 days.



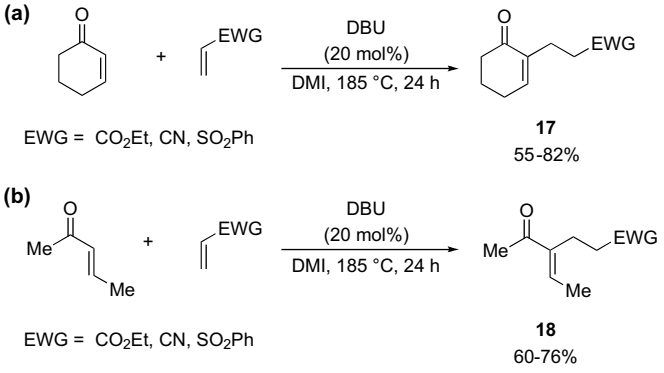
Scheme 8. DABCO-catalyzed dimerization of acrylate esters.

The utility of the dimerization of acrylates was highlighted in the efficient (4 steps) synthesis of (±)-sarkomycin ester **14** from ethyl acrylate by Amri and co-workers (Scheme 9).[17] This large scale application of the RC reaction was performed under the influence of a phosphine-based catalyst, tris(dimethylamino)phosphine (TDAP), which promoted the dimerization of ethyl and *tert*-butyl acrylates in good yields (**15**, 61%; **16**, 72%).



Scheme 9. TDAP-catalyzed RC reaction in the synthesis of (±)-sarkomycin esters.

Hwu and co-workers introduced a related method for the α-alkylation of α,β-unsaturated enones using the tertiary amine 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) with 1,3-dimethyl-2-imidazolidinone (DMI) as the solvent (Scheme 10).[18] Michael acceptors ethyl acrylate, acrylonitrile, and phenyl vinyl sulfone were employed in the cross-coupling reactions with 2-cyclohexen-1-one and 3-pentene-2-one, providing the corresponding α-substituted enones in good yields (**17**, 55–82%; **18**, 60–76%; Scheme 10). This example of the RC reaction to include β-substituted acyclic enones required elevated temperatures of 185 °C for 24 h (Scheme 10b). In the absence of alternative Michael acceptors, the dimerization of 2-cyclohexen-1-one was also possible, providing the corresponding product in 85% yield under identical conditions.



Scheme 10. (a) α-Alkylation of cyclic α,β-unsaturated enones catalyzed by DBU. (b) The analogous reaction with acyclic enones.

Mechanistic work by Hwu and co-workers prompted them to propose that the DBU-catalyzed transformation proceeded via a different pathway than that previously presented for analogous MBH and RC reactions. As shown in Figure 1a, the reaction of 2-cyclohexen-1-one with isobutyraldehyde in the presence of DBU generated the desired aldol adduct **19** in 50% yield, whereas no reaction was detected in the presence of DABCO. In addition, as delineated in Figure 1b, DABCO catalyzes the MBH reaction of methyl vinyl ketone and acetaldehyde to provide **20** (81% yield),[14] but the analogous DBU-catalyzed reaction led only to the recovery of starting material. It was therefore concluded (Fig. 1c) that 2-cyclohexen-1-one, possessing acidic γ-protons, underwent deprotonation by DBU (vs conjugate addition) to provide dienolate intermediate **21**. Subsequent Michael reaction with the desired activated alkene, and finally olefin migration, provided the observed α,β-unsaturated enones (**17**).

Jenner and co-workers presented the dimerization of acrylic esters, nitriles, and ketones under phosphine-based catalysis.[19] In an early report, it was demonstrated that the dimerization of acrylonitrile and methyl acrylate could be promoted with DABCO (10 mol %) at elevated pressure (300 MPa). Attempts to extend this methodology to include sluggish β-substituted analogs, such as

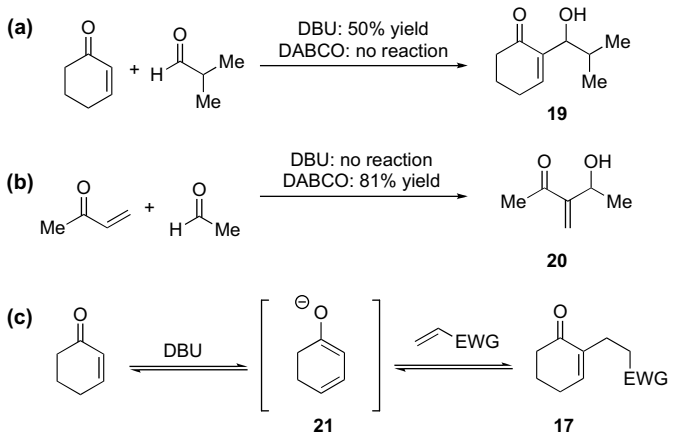
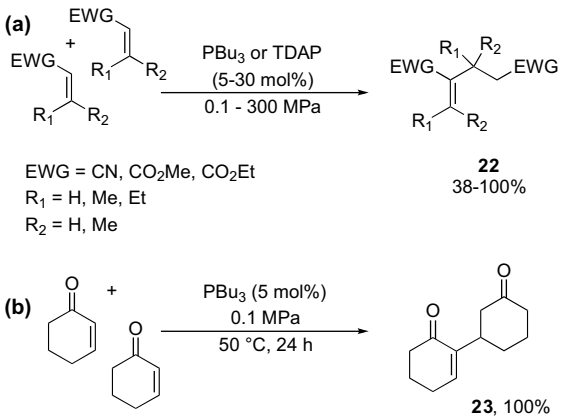


Figure 1. Mechanistic study by Hwu and co-workers. (a) Differential results for MBH reaction when DBU versus DABCO are employed. (b) Opposite reactivity profile with other reaction partners. (c) A mechanistic rationale for the results.

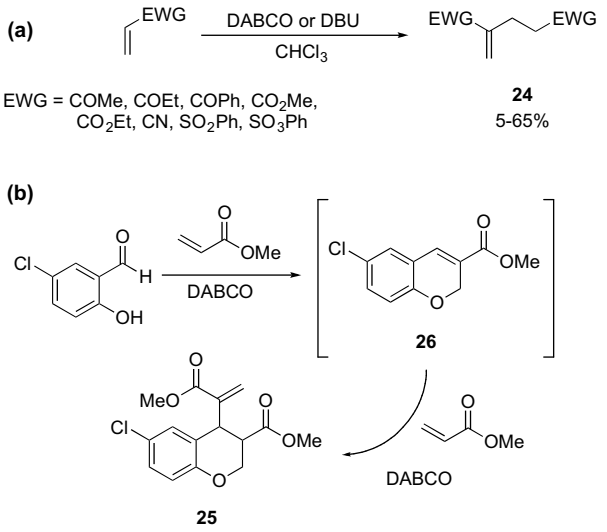
hindered crotonitrile, were unsuccessful with traditional tertiary amine-based catalysts used in the MBH reaction (DABCO and 3-quinuclidinol) at ambient or elevated pressure. On the other hand, quantitative yield of the dimer was achieved using PBu_3 at high pressure (300 MPa) or in slightly lower yield (87%) when using TDAP at ambient pressure (Scheme 11a). While the dimerization of β-substituted derivatives typically required higher pressures, cyclohex-2-en-1-one underwent quantitative dimerization using PBu_3 at ambient pressure (**23**; Scheme 11b).



Scheme 11. (a) Pressure effects on bimolecular RC reactions of acyclic substrates. (b) The analogous reactions with cyclohexenone.

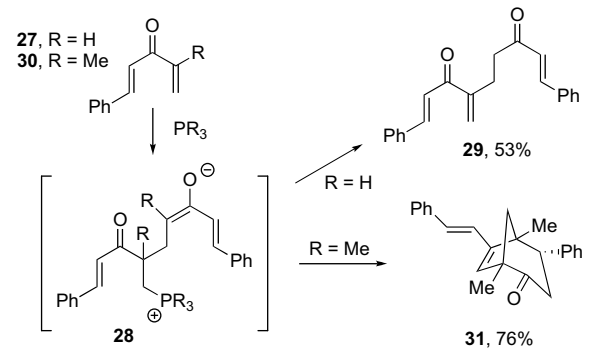
In their study of the MBH reaction, Kaye and co-workers observed a competitive RC transformation leading to alkene dimerization products.[20] Accordingly, they presented a study of the direct dimerization reaction in the absence of an aldehyde coupling partner. Various activated alkenes were examined in the presence of DABCO and DBU and shown to undergo coupling to the corresponding dimers (**24**) in low to moderate yield (5–65%; Scheme 12a). They also reported the isolation of chromane **25** in the MBH reaction of salicylaldehyde and methyl acrylate. Researchers proposed that **25** was the product of an in situ RC transformation of MBH product **26** and a second equivalent of methyl acrylate (Scheme 12b).

The RC transformation has also been employed in the generation of bicyclic systems when followed by a subsequent enolization and aldol reaction.[21] In the case of divinyl ketones, Schaus and co-workers have demonstrated divergent reactivity with differing α-substituted substrates to produce either traditional RC products or



Scheme 12. (a) Dimerization of various activated alkenes with DABCO or DBU. (b) *In* situ RC reaction with MBH product **26**.

bicyclo[3.2.1]octenones with two bridgehead quaternary carbon centers (Scheme 13).[22] When 1,4-diene-3-one **27** was employed in the cyclization reaction in the presence of PPh_3 (100 mol %), facile α-deprotonation of intermediate **28** (R=H) afforded RC product **29** in 53% yield. Alternatively, in the absence of the requisite α-proton (**30**, R=Me), the generated enolate undergoes intramolecular Michael addition and in situ intramolecular Wittig olefination with the α,β-unsaturated ketone to generate bicycle **31** in good yield (76%).



Scheme 13. Divergent reactivity in phosphine-promoted RC reactions.

More recently, Shi and co-workers have expanded upon the intermolecular Michael/Michael cross-coupling with the combination of proline and sodium azide (NaN_3) as catalysts.[23] Among other Lewis bases, such as 4-dimethyl-amino-pyridine (DMAP), PPh_3, DABCO, imidazole, *N*-methylimidazole (NMI), proline was found to be the most effective catalyst and NaN_3 as the co-catalyst for fine-tuning the reaction acidity. This methodology is applicable to a wide range of β-alkyl nitroalkenes (**32**) in coupling to various enones (**33**, Fig. 2) to produce homlogated RC products (**34**). The authors also propose the reaction proceeds through a nucleophilic mechanism as opposed to a general base mechanism, supported both by control experiments and computational studies.

3. Intramolecular Rauhut–Currier reactions

Although the RC transformation was first disclosed in 1963, the reaction remained relatively undeveloped due to lack of selectivity

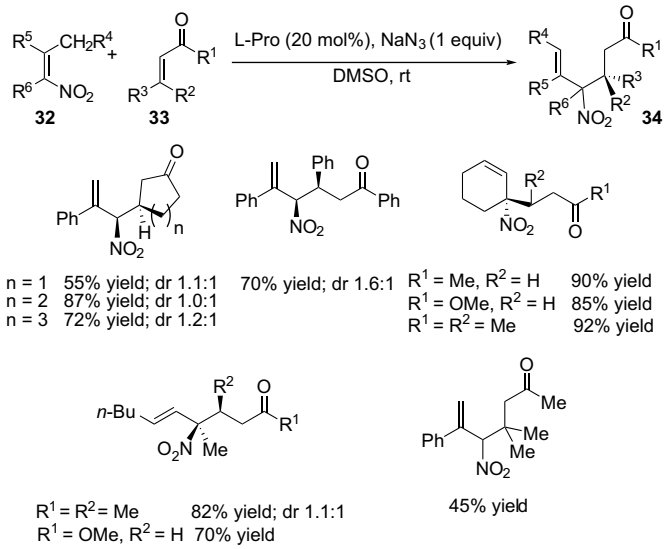
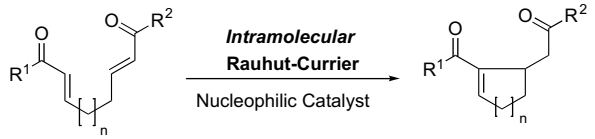


Figure 2. Cross-couplings of nitroolefins and α,β-unsaturated carbonyls via the RC reaction.

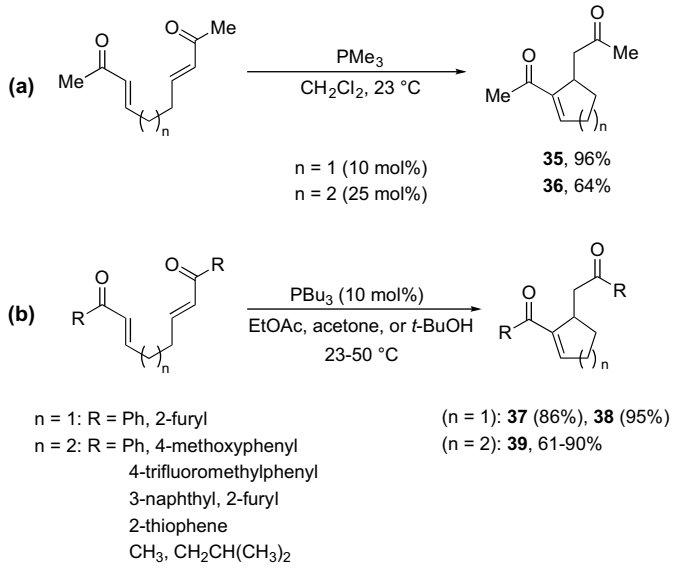
in cross-coupling reactions involving different activated alkenes. In 1999, Moore and Erguden revealed a unique example of an intramolecular transannular RC reaction in the synthesis of natural product waihoensene (vide infra; Section 6).[24] Then, in 2002 the groups of Roush[25] and Krische[26] presented detailed methodology studies where they cleverly resolved the issue of selectivity by tethering coupling partners of differing electrophilicity, thereby creating an *intramolecular* RC reaction (Scheme 14).



Scheme 14. Intramolecular RC reaction.

Both groups demonstrated that trialkylphosphines catalyze the cycloisomerization of five- and six-membered symmetrical and unsymmetrical bis(enones) with high efficiency. Amine-based nucleophiles, such as DABCO, DBU, Et_2NH, and DMAP, commonly employed in the MBH reaction of activated alkenes and aldehydes were demonstrated to be much less efficient than phosphine-based nucleophiles in the intramolecular RC reaction.[25,26] It was proposed that the lack of reactivity of amine-based nucleophiles was due to the softer character of phosphines being more suited to soft activated alkene substrates. Additionally, while trialkylphosphines (10 mol%) were sufficiently reactive to catalyze the transformation, PPh_3 (100 mol%) demonstrated inferior reactivity. The relative order of reactivity of phosphine-based catalysts for the intramolecular RC reaction was empirically determined: $PMe_3>PBu_3>>PCy_3>>PPh_3$. Solvent effects were examined by both research groups, leading to similar conclusions.[25,26] For example, undesired by-product formation (oligomerization and aldol cyclization) could be minimized by varying solvents. Generally, faster reactions were observed when polar protic solvents were employed.[25] It is noteworthy that a single set of reaction conditions was not applicable to different substrate classes, and modifications were required for optimal results in each independent case.

The cyclization reaction of symmetrical bis(enones) was facile in the case of five-membered ring formation leading to the production of various substituted cyclopentenes (Scheme 15). Cyclohexene formation was more difficult, providing slightly lower yields and requiring increased catalyst loading in some cases (25 mol%) to maintain useful reaction rates. Roush and co-workers employed trimethylphosphine (Scheme 15a) in methylene chloride at ambient temperature to provide bis(methyl) substrates **35** (96%) and **36** (64%).[25] Krische and co-workers used PBu_3 in various solvents at ambient and elevated temperatures (23–50 °C) in the analogous cyclization providing aromatic cyclopentene products (**37**, 86% and **38**, 95%, Scheme 15b) as well as a variety of aromatic and aliphatic cyclohexene products (**39**, 61–90%).[26]

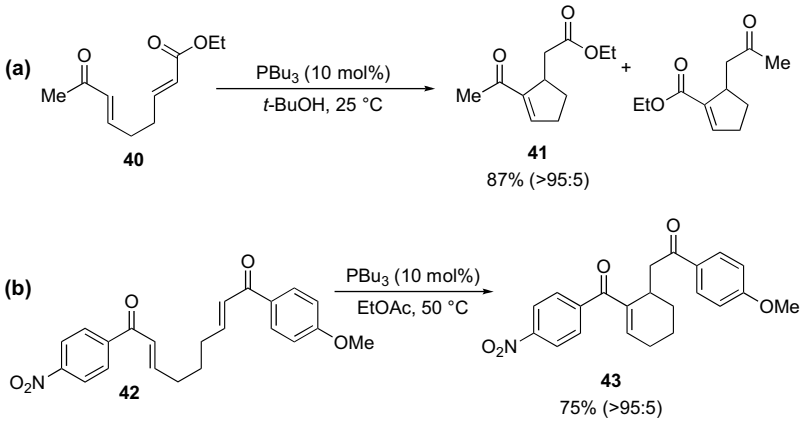


Scheme 15. Cycloisomerization of five- and six-membered symmetrical bis(enones) by Roush (a) and Krische (b).

The regioselectivity of the RC cycloisomerization of unsymmetric substrates was controlled through both electronic and steric differentiation. For example, Krische and co-workers demonstrated high regioselectivity in five- and six-membered ring formation to give single isomeric cyclization products (reported as >95:5, Scheme 16a).[26] In the case of enone-enoate **40**, regioisomeric product **41** was isolated as the sole product in 87% yield. As shown in Scheme 16b, cyclization to provide unsymmetric product **43** from **42** was catalyzed by PBu_3 at elevated temperature (50 °C) in EtOAc in good yield (75%) as a single regioisomeric product as well.

Roush and co-workers discovered similar electronic effects, with the major product of cyclization reflecting chemoselective nucleophilic addition of the phosphine catalyst to the more electrophilic enone, followed by cyclization on the less reactive Michael acceptor (Fig. 3).[25] Various substituted cyclopentenes and cyclohexenes were generated using either PMe_3 or PBu_3 (20–100 mol%) in moderate to excellent yield (32–96%). For example, preparation of compound **44** was achieved in 95% yield, whereas enal-enoate **45** was more difficult to access (38% yield). Enal-enone cyclization to afford cyclohexene product **46** led to a higher yield (55%).

In the comparison of cyclopentene and cyclohexene ring formation of unsymmetric aromatic–aliphatic bis(enones) **47** and **48**, higher chemoselectivity was achieved in the case of cyclohexene formation (7:1 vs 1:1, Scheme 17). It was proposed that trapping of the kinetic phosphine Michael adducts in the rapid five-membered ring formation led to indiscriminate product formation (1:1). Alternatively, the attenuated rate in homologous six-membered ring formation enabled the electronic effects of the different substituents to be reflected in the product distribution (7:1), with cyclization being the product- and rate-determining step.[26]



Scheme 16. Electronic control of product distribution in the RC reaction of unsymmetric substrates by Krische and co-workers.

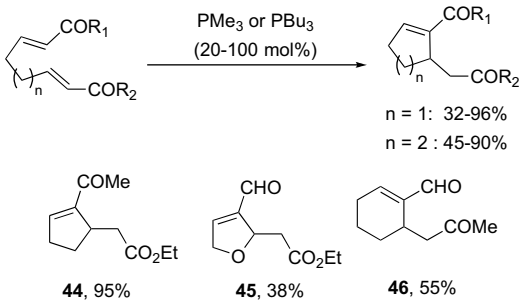
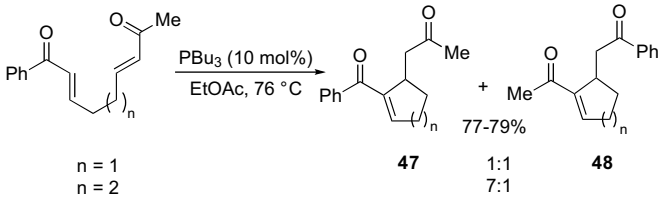
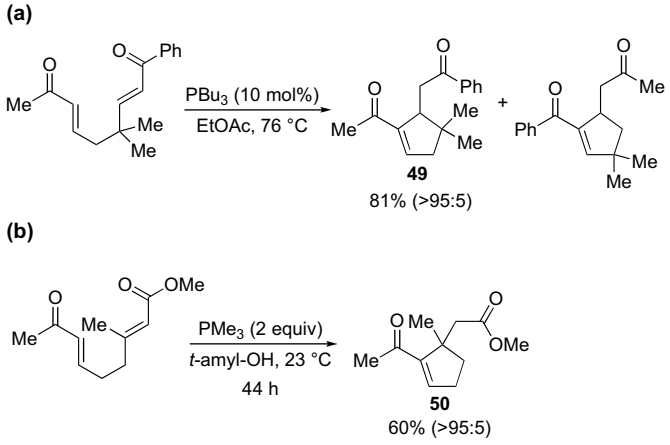


Figure 3. RC cyclization of various unsymmetric substrates by Roush and co-workers.



Scheme 17. Kinetic control of product distribution.

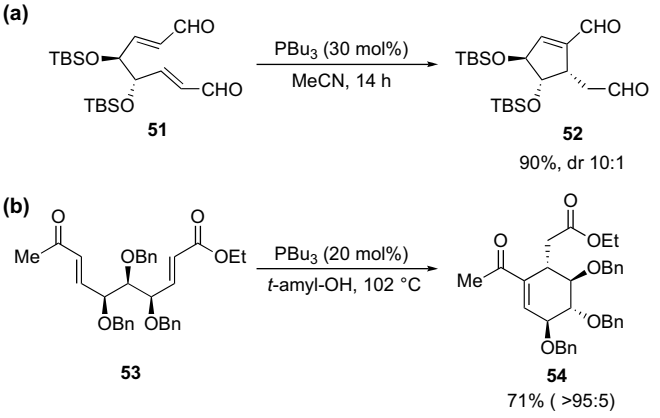
Furthermore, steric effects were evaluated in the synthesis of geminal dimethyl cyclohexene **49** by Krische and co-workers (Scheme 18a).[26] Enone **50** was prepared by Roush and co-workers, establishing the viability of introducing a quaternary center



Scheme 18. (a) The effect of allylic substitution in the RC cyclization. (b) The effect of higher substitution on the RC cyclization.

(Scheme 18b). In both cases, RC transformation proceeded through initial addition to the less hindered enone, with the more hindered site serving as the Michael acceptor in the ring-closing step.

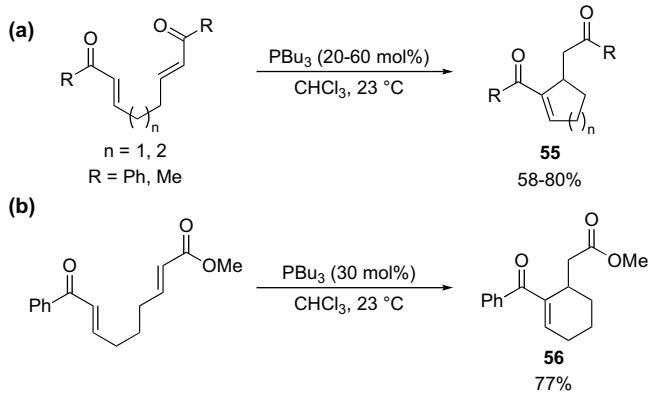
Good diastereoselectivity was achieved (10:1) in the cyclization reaction of bis(enal) **51**, providing the desired cyclized product **52** in excellent yield (Scheme 19a, 90%). Optically pure xylose-derived substrate **53** underwent cyclization to provide pentasubstituted product **54** as a single diastereomer (Scheme 19b, 71%).



Scheme 19. Diastereoselectivity in the RC cycloisomerization reactions to deliver (a) highly substituted cyclopentenes and (b) cyclohexenes.

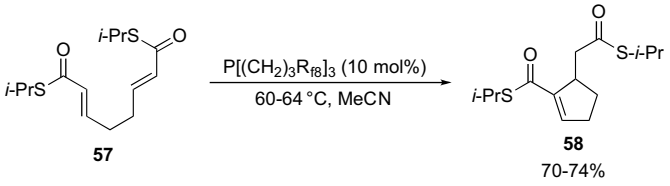
Following the work of the Roush and Krische laboratories, Murphy and co-workers demonstrated a similar tandem Michael/Michael cyclization reaction.[27] Symmetric phenyl and methyl bis(enones) underwent cyclization catalyzed by PBu_3 (20–60 mol %) at ambient temperature to provide the corresponding cyclopentene and cyclohexene derivatives in good yields (58–80%, Scheme 20a). The homologous bis(enone) that would generate a seven-membered ring was resistant to cyclization. Additionally, in analogy to the work of Roush[25] and Krische,[26] bis(enoates) were demonstrated to be unreactive under these reaction conditions, while a crossed enone-enoate substrate was successfully cyclized to provide cyclohexene derivative **56** as the only product in good yield (Scheme 20b, 77%).

Gladysz and co-workers have recently reported the RC cyclizations of bis(thioesters) employing a fluorinated phosphine catalyst.[28] The cycloisomerization of bis(thioenoate) **57** is catalyzed by 10 mol % $P[(CH_2)_3(CF_2)_3CF_3]_3$ ($P[(CH_2)_3R_{f8}]_3$) to give the five-membered cyclopentene **58** in 70–74% yield. In the same report, $P[(CH_2)_3R_{f8}]_3$ is also used to catalyze the MBH reaction in which case the catalyst can be recycled by precipitation on



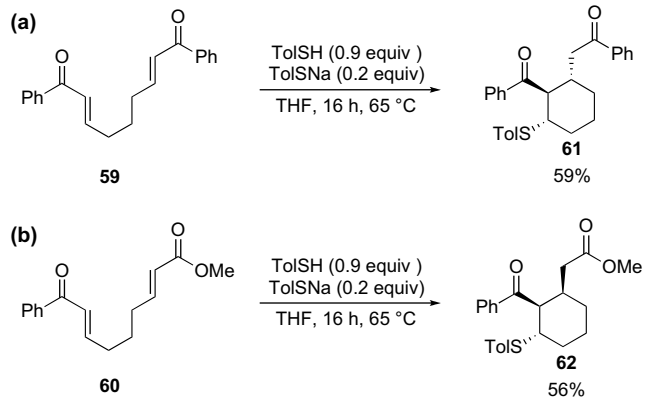
Scheme 20. (a) Symmetrical 'Michael/Michael' reactions reported by Murphy and co-workers (b) An unsymmetrical case reported by Murphy.

a fluoropolymer support, such as Teflon® tape or Gore-Rastex® fiber. In either case the length of the R_{fn} fragment was fine-tuned to achieve solubility at high temperatures (Scheme 21).



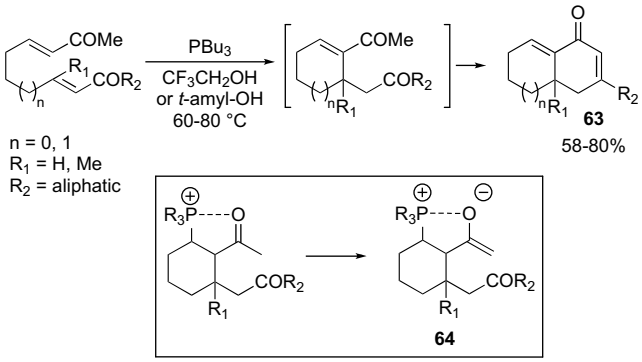
Scheme 21. RC cyclizations of bis(thioesters) catalyzed by fluorinated phosphines.

Murphy and co-workers also examined thiol-mediated catalysis of the identical transformations and discovered that upon exposure to both *p*-TolSH and *p*-TolSNa in refluxing THF, symmetrical bis(phenyl) enone **59** and unsymmetrical enone-enoate **60** underwent cyclization (Scheme 22).[27] Although the reaction conditions did not enable the final catalyst elimination step in the RC reaction, affording products with the catalyst covalently incorporated, they uncovered interesting stereochemical information regarding the corresponding intermediates in the transformation. Substrate **59** afforded cyclized product **61** as a single stereoisomer, with an all-trans relationship of the three contiguous stereocenters (Scheme 22a). Enone-enoate **60**, on the other hand, provided the analogous product **62** with a *syn–anti* relationship of the ring substituents (Scheme 22b). It was suggested that cyclization may be reversible in the case of the symmetrical bis(enone) and non-reversible in the case of the enone-enoate substrate due to the lower acidity of the α-protons of the resultant ester.



Scheme 22. Thiol-catalyzed RC transformation by Murphy and co-workers for (a) symmetrical and (b) unsymmetrical substrates.

In 2005, Roush and co-workers presented a tandem intramolecular RC/aldolization reaction.[29] The secondary aldol reaction was observed as a by-product in their initial study of the RC transformation and was further optimized in this study to provide products **63** in good yield (Scheme 23). The high regioselectivity in the aldol reaction was attributed to an interaction between the phosphonium moiety and the adjacent carbonyl, increasing the acidity of the β-phosphonium-substituted methyl ketone (leading to intermediate **64**) and therefore regioselective deprotonation.



Scheme 23. Tandem intramolecular RC/aldol reaction.

4. Enantioselective Rauhut–Currier reactions

Although the development of the 45-year-old RC reaction has seen substantial progress, it has only recently become the focus of studies aimed at enantioselectivity. In 2007, our laboratory[30] was able to contribute by establishing a method to perform enantioselective RC reactions in high yield and enantioselectivity using convenient reagents and conditions. In so-doing, we were also able to document the use of a simple cysteine (Cys) derivative as an asymmetric catalyst.

These initial studies showed that Cys-based amino acid **65** catalyzes the cycloisomerization of symmetrical and unsymmetrical bis(enones) in the presence of potassium *tert*-butoxide (*t*-BuOK) in acetonitrile (MeCN) with synthetically useful enantioselectivities and yields within 24 h (Fig. 4).[30] Notably, the incorporation of a precise quantity of water (20 equiv) has a dramatic effect on enantioselectivity. Systematic optimization of various reaction parameters, including solvent, concentration, base, and temperature, led to the optimal conditions, which afforded cyclized product **66** in 95% ee and 70% yield. The cycloisomerization was extended to include electron-deficient (**67**, 70%, 93% ee; **68**, 71%, 84% ee) and electron-rich (**69**, 73%, 90% ee) aryl symmetrical bis(enones), as well as aliphatic (**70**, 55%, 90% ee) and heteroaromatic (**71**, 54%, 92% ee) bis(enones) while maintaining high enantioselectivity and good efficiency. The reaction of unsymmetrical substrate **72** resulted in reduced enantioselectivity and yield. Additionally, the use of substoichiometric catalyst loading (20 mol %) provided comparable results, with attenuated rate observed only when a further reduction in catalyst loading was utilized (10 mol %).

In order to provide some insight into the mechanism of stereoinduction, several experiments were performed to guide in the derivation of a heuristic transition state model. First, when the cycloisomerization of bis(enone) **59** was performed under optimized conditions in the presence of 18-crown-6, a non-conjugated by-product **73** (vs **66**) was isolated as the predominant product (26% yield, 84% ee) suggesting that potassium ion chelation was essential in the formation of desired RC product (Scheme 24).

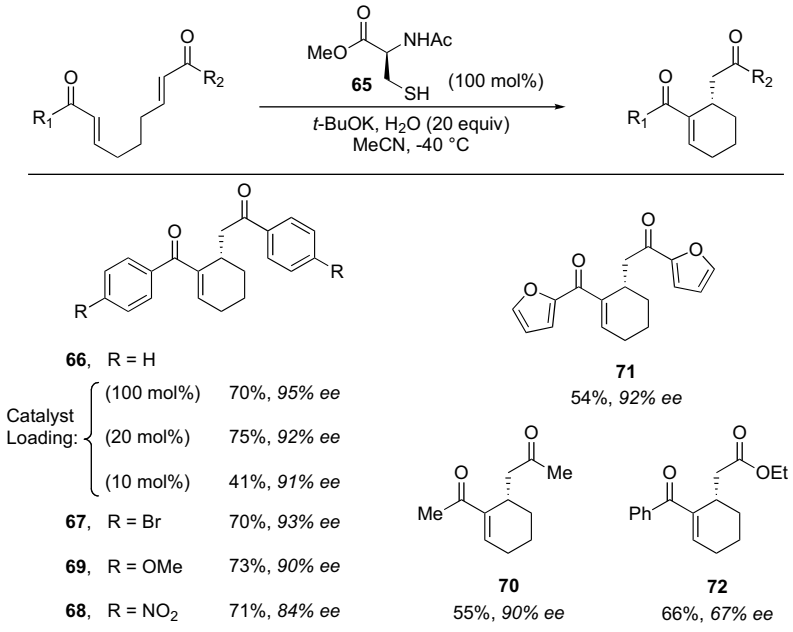
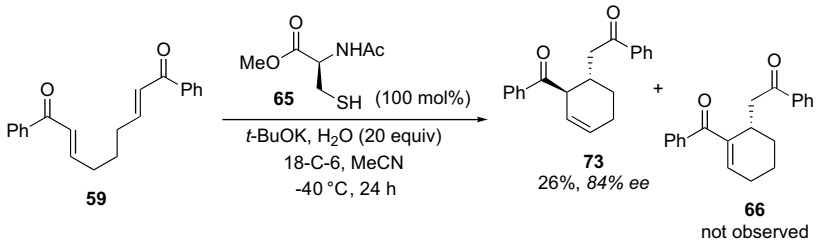
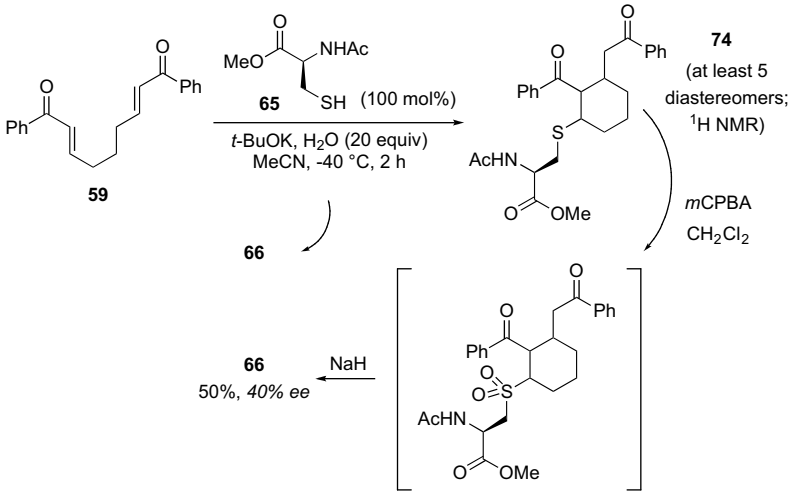


Figure 4. Substrate scope in the enantioselective RC cyclization.



Scheme 24. RC cyclization under optimized conditions with 18-C-6.

In a second experiment, the optimized cycloisomerization reaction was quenched prematurely, after 2 h, providing desired product **66** (29% yield, 95% ee). Significantly, in addition, a mixture of five diastereomers corresponding to intermediate **74** (Scheme 20) was also observed.[30] This mixture was then subjected to oxidation and elimination under irreversible conditions (i. *m*CPBA, ii. NaH), leading to isolation of the desired product **66** with reduced enantioselectivity of 40% ee. These experiments are consistent with reversible carbon–carbon bond formation, and abstraction of the α-H atom leading to catalyst regeneration as the irreversible and stereochemical-determining step (Scheme 25).



Scheme 25. Elimination of Cys-based catalyst under irreversible conditions.

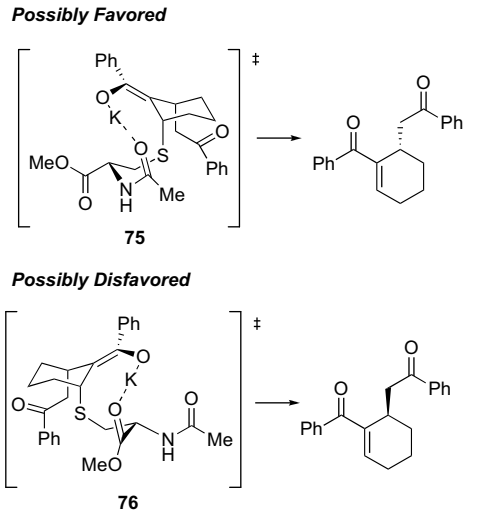
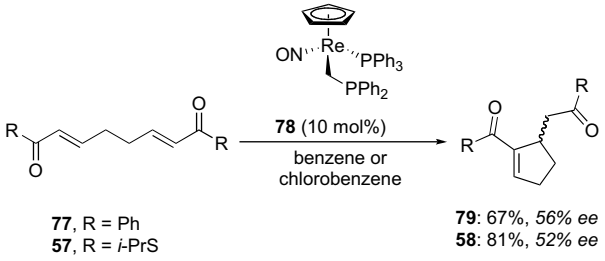


Figure 5. Proposed transition state to account for enantioselectivity.

Based on these experiments, it was suggested that a favored transition state (**75**) could derive from a more stable potassium chelate between the enolate oxygen and the *amide* carbonyl of the catalyst, leading to a faster rate of elimination to deliver **66** with high enantiomeric excess (Fig. 5). An alternative transition state (**76**) could derive from an analogous, less stable chelate involving the ester carbonyl. In both cases, pseudoaxial orientation of the substituents may be preferred in order to (a) minimize allylic strain with the *exo*-methylene-like enolate, and (b) to maintain continuous, proper overlap between the enolate π-system and the σ*-orbital of the departing thiolate moiety.

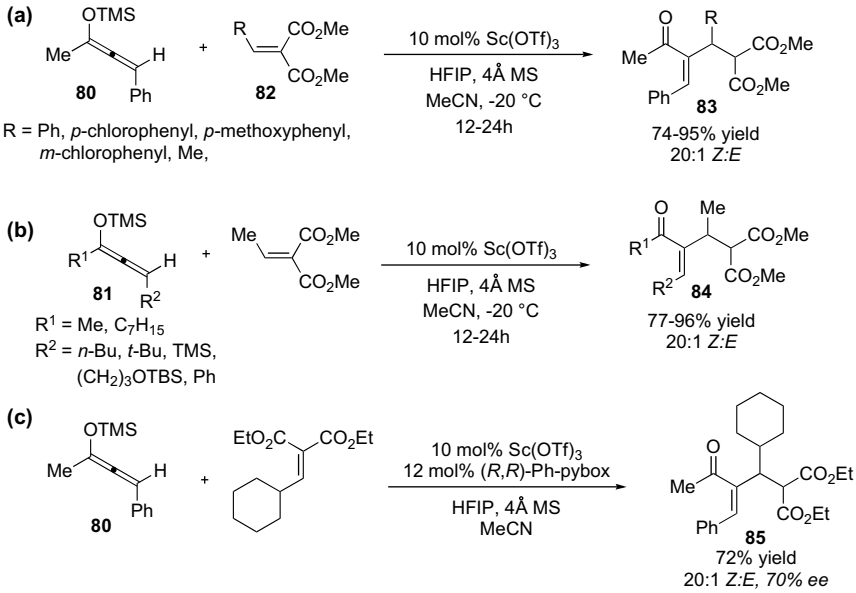


Scheme 26. Rhenium-containing phosphine-catalyzed enantioselective intramolecular RC reaction.

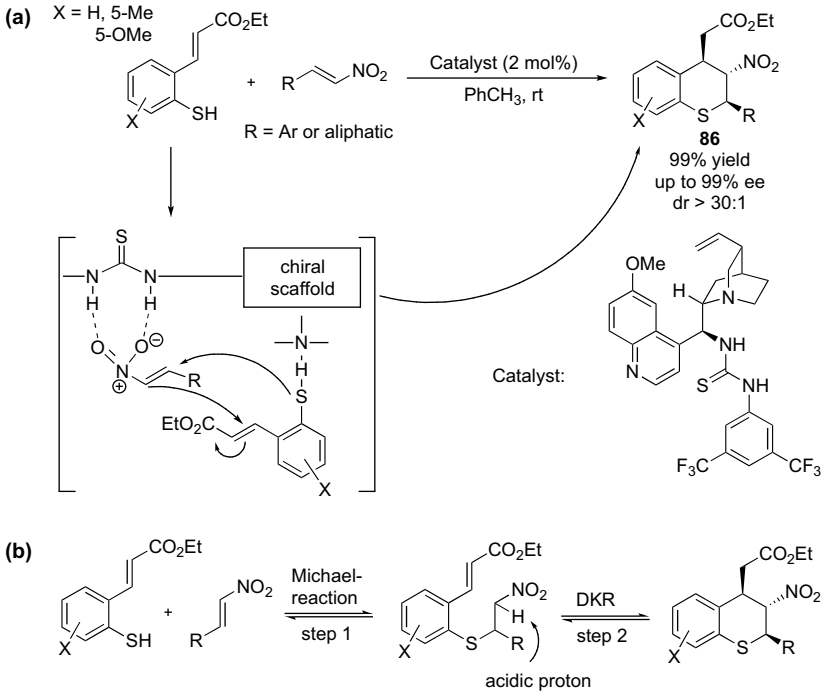
Later in the same year, Gladysz and co-workers presented a phosphine-catalyzed enantioselective intramolecular RC reaction of symmetrical bis(enone) **77** and **57** (Scheme 26).[31] It was proposed that the 18-electron rhenium fragment increased the Lewis basicity and nucleophilicity of the phosphorous donor atom (CH_2PPh_2) in the active catalyst (η^5-C_5H_5)Re(NO)(PPh_3)(CH_2PPh_2) (**78**). Using catalyst **78** (10 mol %), cycloisomerization of the bis(phenylketone) and bis(thioester) provided compounds **79** and **58**, respectively, in good yield (67% and 81%) and with modest enantioselectivities (56% and 52% ee).

In 2008, Scheidt and co-workers reported a unique solution to the intermolecular RC reaction by using silyloxyallenes (α-acylvinyl anion equivalents), such as **80**, under Lewis acid-catalyzed conditions (Scheme 27). Variants were reported that provide RC products in both racemic and enantioenriched form.[32] This method differs from the more typical RC approaches covered in this report in that the nucleophilic component is pre-activated as the silyloxyallene. The reaction is then promoted by a Lewis acid rather than a Lewis base. Optimal results were realized using scandium triflate ($Sc(OTf)_3$) as the Lewis acid in the presence of hexafluoroisopropanol (HFIP) and 4 Å molecular sieves in MeCN at −20 °C (Scheme 27a and b). The method is tolerant of a variety of substituents on the silyloxyallene (**81**) as well as the alkylidene malonate (**82**) to give RC products (**83** and **84**) in high yields (74–99%) and excellent *Z*-selectivity (Scheme 27a and b). Also, introduction of a chiral ligand renders the reaction enantioselective with significant selectivity (Scheme 27c, **85**, 70% ee).

Wang and co-workers have also introduced a one-pot enantioselective Michael/Michael cascade reaction to generate highly functionalized products, in this case thiochromanes (**86**, Scheme 28a).[33] Under optimal conditions, the reaction benefits from low catalyst loadings (2 mol %) and affords a wide range of products in excellent enantioselectivity (up to 99%) and diastereoselectivity (up to 30:1). As proposed by the authors, the reaction mechanism may involve a dynamic kinetic resolution-mediated Rauhut–Currier



Scheme 27. (a and b) Substrate scope for the bimolecular RC reactions of activated siloxyallenes. (c) Demonstration of viability of enantioselective variants.

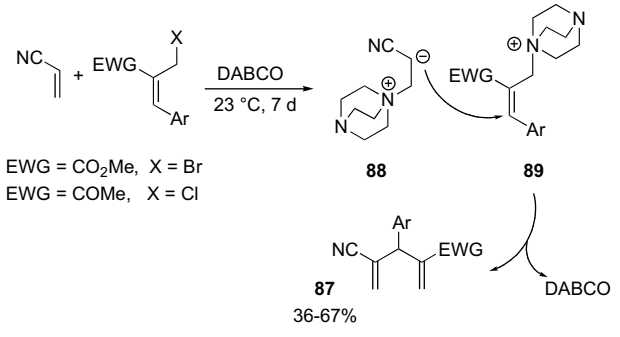


Scheme 28. (a) Modified cinchona-alkaloid-catalyzed RC reaction involving cascade cyclization to deliver thiochromanes. (b) Mechanistic postulate to account for dynamic kinetic resolution.

pathway, where the reversibility of each step allows for the high levels of enantioenrichment that are observed in the products (Scheme 28b).

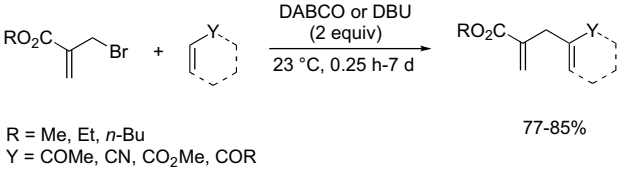
5. Extension to include alternative electrophilic partners

Exciting advances have also been made in the extension of the traditional RC transformation to include alternative non-classical electrophilic partners. In 2001, Basavaiah and co-workers incorporated the use of (*Z*)-allyl halides (chlorides and bromides) as coupling partners in the synthesis of 3-substituted 2,4-functionalized 1,4-pentadienes (Scheme 29).[34] Researchers proposed generation of the desired products (**87**) via unique reactivity in the RC transformation. They suggested that DABCO underwent reaction with both acrylonitrile and the requisite allyl halide to provide intermediates **88** and **89**. Subsequently, **89** underwent S_N2' displacement of DABCO by zwitterionic species **88**. Finally, elimination of a second equivalent of DABCO provided the desired 1,4-pentadienes in moderate to good yields (**87**, 36–67%). Simple allyl bromides, such as 3-bromoprop-1-ene, were unreactive under analogous conditions (23 °C, 7 days). No further studies were presented in support of the proposed mechanism.



Scheme 29. Extension of the RC reaction to include allyl halides as electrophilic partners.

In a later report, Basavaiah and co-workers expanded the scope to produce 2,4-functionalized 1,4-pentadienes without substitution at the 3-position (Scheme 30).[35] In the presence of a tertiary amine (DABCO or DBU), they illustrated the coupling of alkyl 2-(bromomethyl)prop-2-enoates with various activated alkenes, including methyl vinyl ketone, acrylonitrile, alkyl acrylates, and cyclohex-2-en-1-one. DABCO was also employed successfully by Lee and Lee in the coupling of dihalonaphthoquinones with methyl vinyl ketone and methyl acrylate to form α-vinylquinones.[36]



Scheme 30. Synthesis of 2,4-functionalized 1,4-pentadienes.

Krische and co-workers have also presented a two-component catalyst system to combine the nucleophilic features of the MBH-type reaction with the electrophilic features of the Tsuji-Trost reaction to effect a catalytic enone cycloallyation (Fig. 6).[37] In this variant of the RC reaction, an allylic carbonate is activated through π-allyl–palladium complex formation. Contemporaneously, the enone is activated via phosphine addition. A variety of enone–allylic carbonates, including aromatic, heteroaromatic, and aliphatic enones, were subjected to stoichiometric PBu_3 and catalytic quantities of $(Ph_3P)_4Pd$ (1 mol %) to afford the corresponding five- or six-membered ring cycloallylated products in good to excellent yields (**90**, 64–92%). Although enoates were found to be unreactive in this system, the related thioenoates were viable substrates (73% yield).[38]

Still another interesting variant reported by Krische and co-workers involved the use of *p*-nitrophenyl substituted vinyl

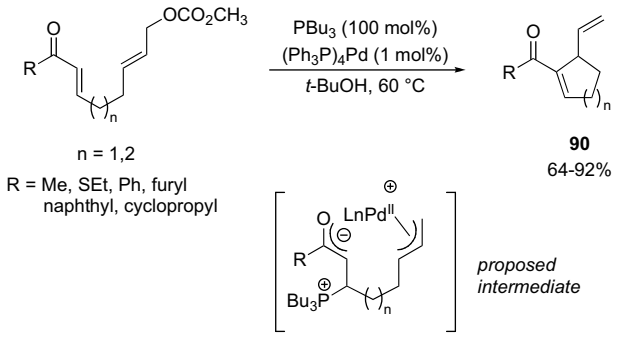
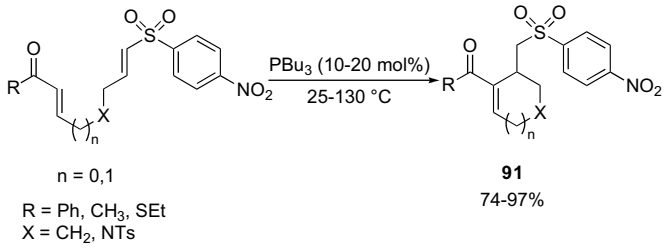


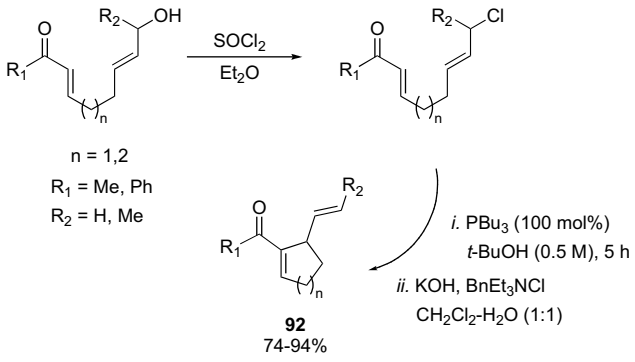
Figure 6. Cycloallylation of enones using the two-component catalyst system employing phosphine and palladium co-catalysts.

sulfones as the electrophilic coupling partner with a variety of enones and thioenoates (Scheme 31).[39] Cyclopentene and cyclohexene products **91** were afforded in good to excellent yield (74–97%) using 10–20 mol % PBu_3.



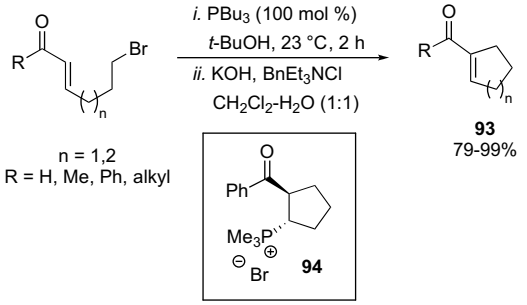
Scheme 31. Extension of the RC reaction to include vinyl sulfone coupling partners.

In work related to Basavaiah's, Krafft and Haxell have demonstrated the direct use of allyl halides as electrophiles in the organomediated intramolecular RC reaction (Scheme 32).[40] PBu_3 (100 mol %) was used to promote the cyclization of various enones with primary and secondary allylic chlorides in *t*-BuOH under phase transfer conditions (KOH, $BnEt_3NCl$) to afford both mono- and disubstituted alkenes **92** in good to excellent yields (74–94%). In analogy to the findings presented by the groups of Roush and Krische, amine-based catalysts (DABCO, quinuclidine, DBU, and DMAP) were found to be inefficient catalysts. The use of allylic mesylates and tosylates was inferior to allylic chlorides, which were generated in situ from the corresponding enone–allylic alcohols using thionyl chloride.



Scheme 32. Intramolecular RC cycloisomerization of enones and allylic leaving groups.

Thus far, the MBH and RC transformations have involved the coupling of activated alkenes with highly reactive sp^2 hybridized carbon electrophiles, including aldehydes, α-keto esters, 1,2-diketones, enones, enoates, vinyl sulfones, allylic carbonates, and allylic halides. In 2005, Krafft and co-workers incorporated a new class of electrophiles into the expanding list of viable coupling partners;[41] researchers successfully promoted the phosphine-catalyzed RC cycloisomerization reaction of activated alkenes with sp^3 hybridized electrophiles (Scheme 33). The formation of both five- and six-membered enone cycloalkylation products **93** was performed in a stepwise procedure in excellent yields (79–99%) using stoichiometric PBu_3 in *t*-BuOH followed by the addition of aqueous base under phase transfer conditions. In a later report, researchers were able to perform the reaction using substoichiometric phosphine (20 mol %) by demonstrating that all the required components of the transformation were compatible, enabling a one-step procedure under similar conditions (KOH, $BnEt_3NCl$, *t*-BuOH–CH_2Cl_2).[42] Comparable results were obtained under lower catalyst loading, with PBu_3 as the optimal catalyst for five-membered ring formation and PMe_3 optimal for six-membered ring formation. The direct reaction of phosphine with the alkyl halide to generate a phosphonium salt was discounted through control experiments.



Scheme 33. Direct intramolecular α-alkylation of enones.

Intermediate ketophosphonium salt **94** was isolated in a later study by the same authors, lending credence to the proposed MBH/RC reaction mechanism.[43] Potential transition state conformations leading to the observed trans-configuration of the intermediate did not include the potentially beneficial oxygen–phosphorous electrostatic interaction. The authors suggested that this interaction, which has been involved in many MBH mechanistic discussions, may not be the overriding influence in defining the stereochemical outcome of the cyclization and may not be necessary for a successful transformation.

Expanding upon the use of sp^3 hybridized electrophiles, Krafft and Wright reported the incorporation of an epoxide as the electrophilic partner in the intramolecular RC transformation, giving rise to homologous aldol adducts.[44] As illustrated in Figure 7, RC

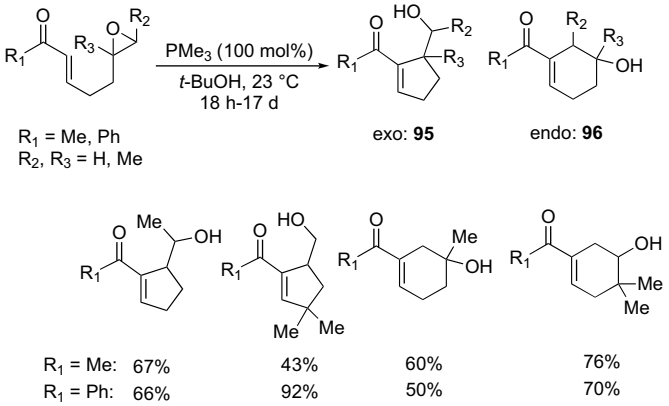
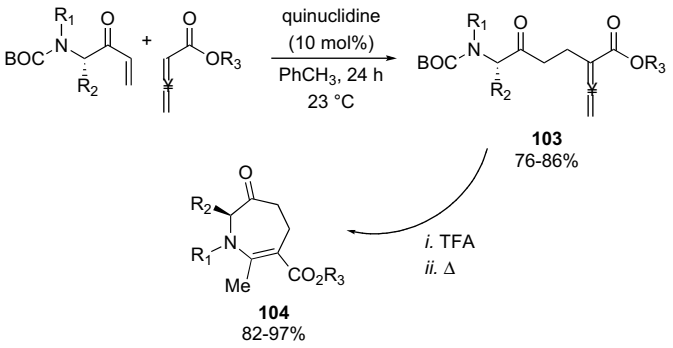


Figure 7. Intramolecular RC cyclization via epoxide ring opening.

cyclization of the epoxy enone could proceed to generate either alcohol **95** (from *exo* ring opening of the epoxide) or alcohol **96** (from *endo* ring opening). Investigation of several phenyl and methyl enones demonstrated that substitution on the epoxide or the tether was required for high *endo*/*exo* selectivity in the cyclization step, providing various cyclopentene and cyclohexene derivatives in good yield (43–92%). A control experiment confirmed that the phosphine was not reacting directly with the epoxide and that the transformation proceeded through the traditional RC mechanistic pathway where conjugate addition of PMe_3 generated a zwitterionic enolate followed by epoxide opening. The final deprotonation/elimination of the catalyst was proposed to be promoted by the resultant alkoxide.

A variant of the RC reaction involving an alternative latent nucleophile (vs the original α,β-unsaturated enone) was presented by our laboratory.[45] Catalyst-dependent, divergent reactivity was demonstrated such that the phosphine-catalyzed reaction of enone **97** and allenic ester **98** afforded the corresponding [3+2]-cycloadduct, in accord with literature precedent.[46] On the other hand, the amine-catalyzed reaction (quinuclidine, 10 mol%) of various α,β-unsaturated carbonyls with allenoate **98** undergoes a traditional RC pathway, providing α,α′-disubstituted allenoates (**99**) in good to excellent yields (50–96%; Scheme 34a). A three-component coupling reaction was demonstrated with several aldehydes **100**, acrylate **101**, and allenoate **98**, affecting a MBH-RC tandem reaction sequence with good yields (**102**, 60–88%; Scheme 34b).

This methodology was expanded to include the coupling of α-amino acid derived vinyl ketones with allenic esters to provide a diverse range of α,α′-disustituted allenoates **103** (76–86%, Scheme 35).[47] Allenic ester products were then elaborated to provide synthetically interesting chiral azacycles (**104**, 82–97%) through a deprotection/7-*endo*-*dig* cyclization–isomerization reaction sequence.

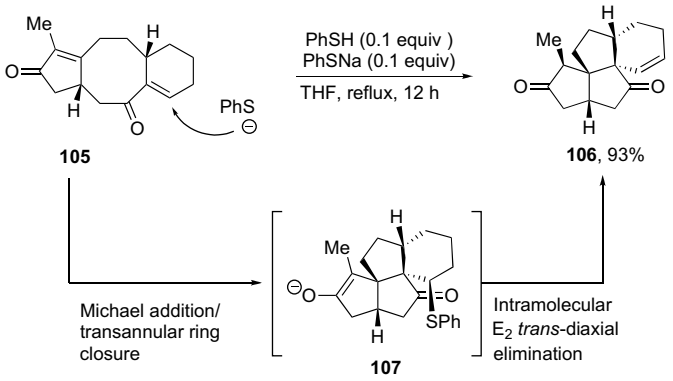


Scheme 35. Synthesis of azepines from allenoate–enone coupling products.

6. Application in total synthesis

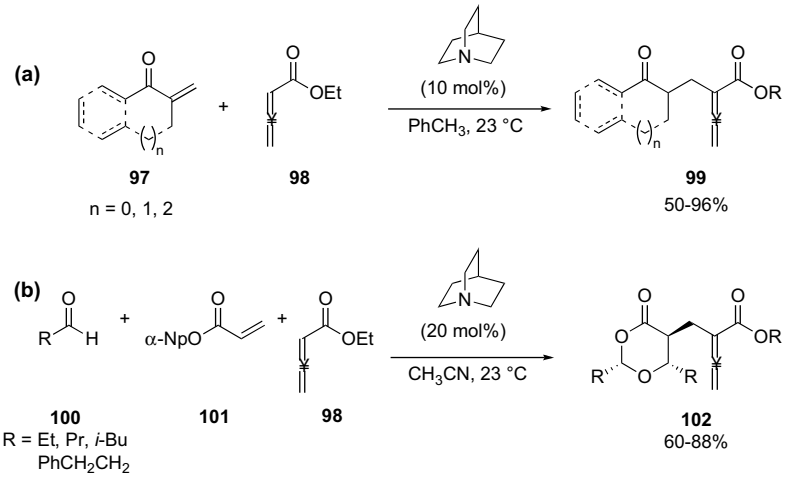
The RC reaction and its relatives have the ability to establish complex ring systems with multiple stereogenic centers. While the development of this transformation has been slow due to highly substrate dependent yields and low reaction rates, the introduction of an intramolecular variant had a great affect on the utility of the reaction, as illustrated by its use in the synthesis of several natural products.

In 1999, Moore and Erguden[24] demonstrated an interesting and unique application of the intramolecular RC reaction in the synthesis of a fused tetraquinane ring system en route to the synthesis of the natural product waihoensene (Scheme 36). The cycloisomerization of tricyclic bis(enone) **105** catalyzed by thiophenol and sodium thiophenolate provided angularly fused tetraquinane **106** in excellent yield (93%). The transformation was believed to proceed through a tandem sequence of reactions, including initial conjugate addition of the thiolate followed by transannular Michael reaction to provide intermediate **107**, and finally an intramolecular E2 trans-diaxial elimination reaction to produce desired product **106** and regenerate the thiophenolate.



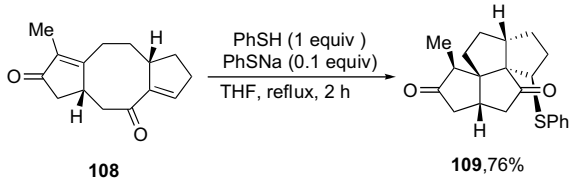
Scheme 36.

Interestingly, in a very similar transformation involving homologous **108** (containing a five-membered ring vs a six-membered ring), the requisite intermediate was no longer in proper



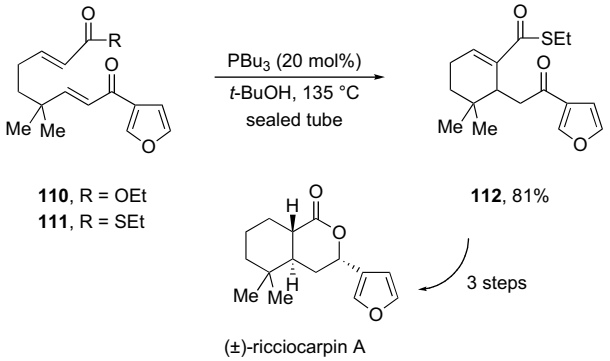
Scheme 34. (a) Coupling of allenic esters and various α,β-unsaturated carbonyl compounds. (b) A three-component coupling involving a tandem MBH/RC sequence.

alignment for the elimination reaction and product **109** was isolated only when a stoichiometric quantity of thiophenol was employed (Scheme 37). The covalent trapping of the catalyst is more representative of general thiol-based catalysis in MBH/RC-type transformations.[6c]



Scheme 37. Synthesis of tetraquinane ring system without elimination of the catalyst.

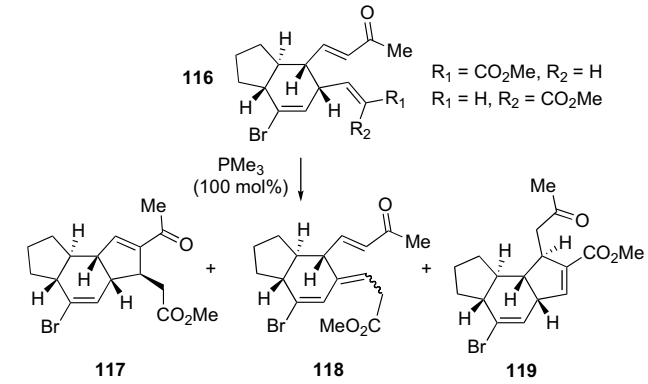
Krische and Agapiou demonstrated the use of highly reactive and chemoselective thioenoates in the RC transformation in the synthesis of the furanosequiterpene lactone (±)-ricciocarpin A (Scheme 38).[48] Although the enoate-enone **110** was unreactive in the phosphine-catalyzed reaction, the analogous thioenoate-enone substrate (**111**) demonstrated heightened reactivity, as well as exquisite chemoselectivity, to provide desired cyclized product **112** in 81% yield. Cyclohexene **112** was elaborated to the natural product in 3 steps.



Scheme 38. Synthesis of (±)-ricciocarpin A by Krische and co-workers.

In 2004, Roush and co-workers reported the total synthesis of (−)-spinosyn A featuring a diastereoselective transannular RC reaction (Scheme 39).[49] An intramolecular Horner–Wadsworth–Emmons macrocyclization reaction followed by a transannular Diels–Alder reaction generated the RC substrate, **113**. The RC ring contraction was effected with PMe_3 (8 equiv) in *t*-amyl-OH solvent.

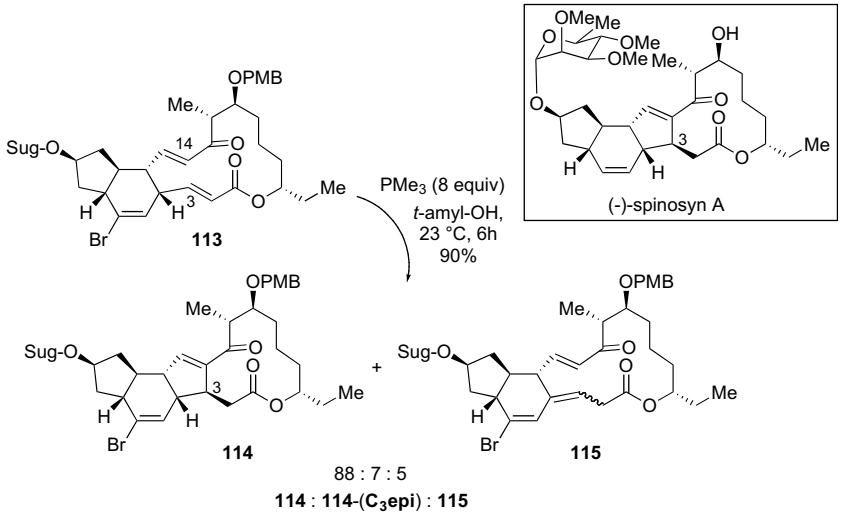
Table 1
RC cyclization with (*Z*)- and (*E*)-enoates



	117	118	119
CH_2Cl_2	59	30	11
t-Amyl-OH	96	Trace	4

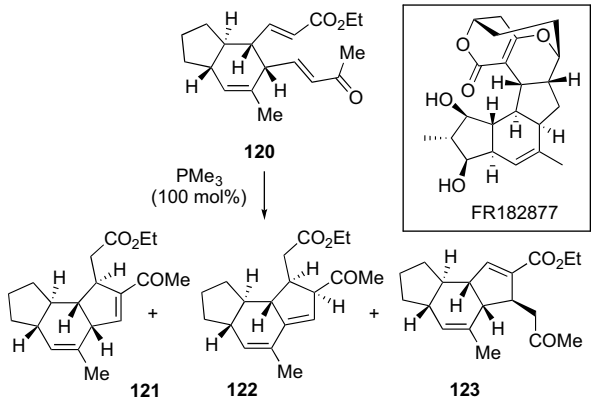
This striking reaction proceeds with excellent diastereoselectivity in the generation of the C3–C14 carbon–carbon bond. Desired product **114** was isolated with only minimal amounts of the C3-epimer or the olefin migration product **115** (88:7:5).

In studies leading up to the successful synthesis of (−)-spinosyn A, Roush and co-workers presented various studies of the transannular RC reaction in the generation of the *as*-indacene core.[50] For example, olefin geometry had a critical effect on the product distribution in the phosphine-catalyzed cyclization of enone-enoate **116** (Table 1). Cyclization of the (*E*)-enoate bicyclic precursor in CH_2Cl_2 provided approximately a 2:1 mixture of desired tricycle **117** and olefin migration by-product **118**, in addition to regioisomeric tricycle **119**. Excitingly, when the alternative (*Z*)-enoate precursor was employed in the cyclization with PMe_3 in *t*-amyl-OH, researchers were able to obtain the desired cyclization product in good yield (86%) and excellent chemoselectivity (96:4), with only trace amounts of the olefin migration by-product. Cycloisomerization of the (*E*)-enoate was examined in various solvents, with CH_2Cl_2 providing the best results. It was proposed that the change in olefin geometry to the (*Z*)-enoate resulted in restricted orbital alignment, which suppressed γ-deprotonation and therefore minimized formation of the olefin migration by-product.



Scheme 39. Synthesis of (−)-spinosyn A by Roush and co-workers.

Table 2
Studies of the intramolecular RC reaction in the synthesis of FR182877

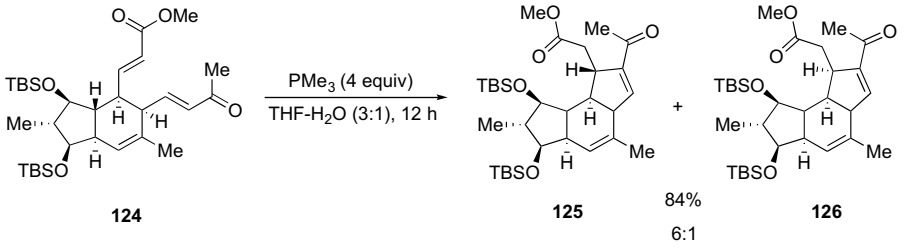


	121	122	123
t-Amyl-OH	58	8	34
THF–H_2O (3:1)	100	0	0
HMPA	0	90	10
CF_3CH_2OH	0	0	100

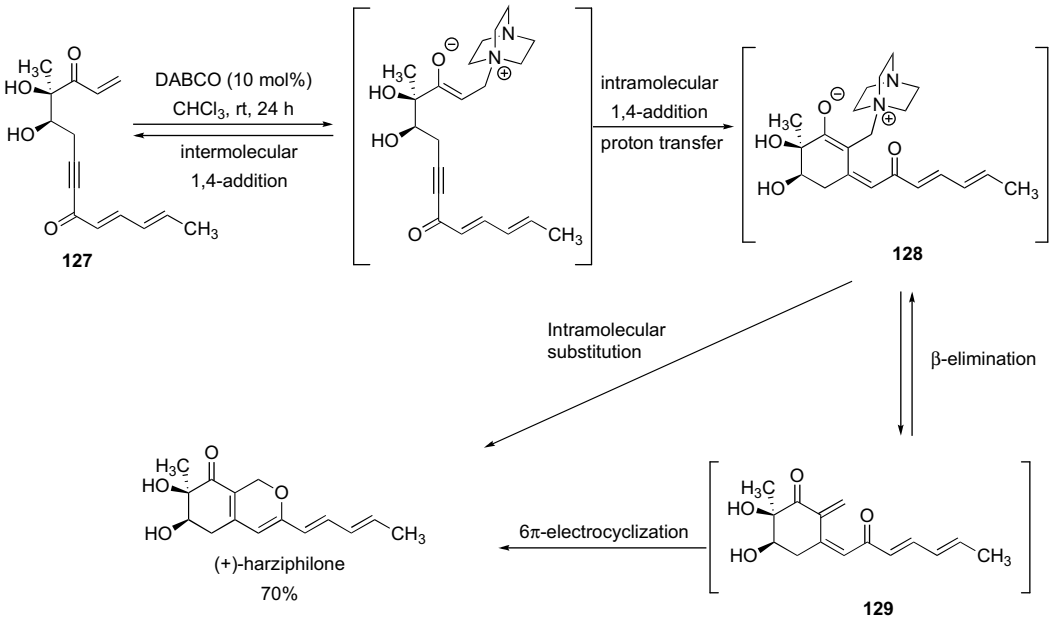
In an effort to synthesize antimitotic agent FR182877, Roush and co-workers illustrated the use of an intramolecular RC cycloisomerization to generate the *as*-indacene ring of this natural product.[51] RC cyclization of enone-enoate **120** under previously optimized conditions (*t*-amyl-OH) was unsuccessful and underscored the substrate dependence of this transformation (Table 2). Optimization of the reaction conditions revealed a dramatic solvent effect. Poor selectivity was obtained among the desired cyclization product (**121**), the olefin migration product (**122**), and regioisomeric product **123** when the reaction was performed in *t*-amyl-OH (58:8:34). On the other hand, exquisite selectivity was obtained when the reaction was performed in THF–H_2O (3:1) with 2 equiv PBu_3 providing exclusively desired product **121**. Interestingly, when the reaction was performed in 2,2,2-trifluoroethanol under otherwise identical reaction conditions, exclusive formation of regioisomeric product **123** was observed. Additionally, in hexamethylphosphoramide (HMPA) olefin migration product **122** was isolated as the major product.

The optimal reaction conditions (THF–H_2O/3:1) were amenable to the more advanced model system **124**. In the synthetic studies toward FR182877, the desired cyclization product **125** was obtained in 84% yield with a 6:1 diastereomeric ratio (**125**–**126**; Scheme 40).

Sorensen and co-workers demonstrated the use of a tertiary amine-catalyzed RC transformation in the successful synthesis of (+)-harziphilone (Scheme 41).[52] Under mild catalysis with DABCO (10 mol %), they were able to promote the selective cyclization reaction to generate the bicyclic natural product. The mechanism of the bicycloisomerization was proposed to proceed via reversible conjugate addition of DABCO to the unsubstituted enone system of **127** followed by intramolecular Michael addition to afford zwitterion **128** after a proton transfer of the generated allenolate ion. The reaction could proceed through a traditional MBH–RC mechanism, such that β-elimination would provide **129** with



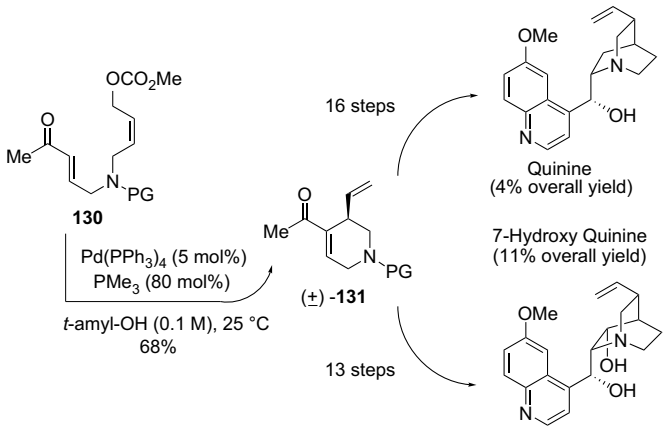
Scheme 40. Advanced model system in the synthetic studies of FR182877.



Scheme 41. Synthesis of (+)-harziphilone by Sorensen and co-workers.

regeneration of the catalyst, enabling a subsequent 6π-electrocyclization to provide the natural product. Alternatively, an intramolecular displacement of DABCO from intermediate **128** could be envisioned to lead directly to (+)-harziphilone.

In 2008, a formal synthesis of (±)-quinine and total synthesis of (±)-7-hydroxyquinine was completed by Krische and co-workers with the use of a merged Morita–Baylis–Hillman–Tsuji–Trost cyclization.[53] Subjecting substrate **130** to optimized conditions lead to the desired six-membered heterocycle in 68% yield (**131**, Scheme 42). Further manipulations from this common intermediate were shown to produce either quinine (16 steps) or 7-hydroxyquinine (13 steps) in good overall yields (4% and 11%, respectively).



Scheme 42. MBH/RC-based approaches to the cinchona family of natural products.

7. Conclusions

The RC reaction and the MBH are of the same vintage, having been introduced within a few years of one another. However, the difficulty in controlling the selectivity of the RC has limited its widespread application. Successful dimerization of various enones and enoates has surely been achieved. Yet, there is great opportunity to improve upon reactivity and scope of viable substrates. Over the past five years, there has been a substantial increase in the power of RC methodology. Perhaps most notably, the advent of the intramolecular variant has dramatically improved the reach of this transformation. Moreover, the development of an enantioselective variant has opened up some doors for this reaction and presented many possibilities in the realm of stereoselective carbon–carbon bond formation. Looking to the future, many opportunities exist for multidimensional expansion of the process. Certainly, the extended application of the RC reaction in complex molecule synthesis will remain the exciting frontier for inspiration in the design of new substrates and catalysts for this powerful class of reactions.

Acknowledgements

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References and notes

1. This manuscript was adapted from the doctoral dissertation of Carrie Aroyan (Boston College, Chestnut Hill, MA 02467; approved in 2008).
2. (a) Dalko, P. I.; Moisan, L. *Angew. Chem., Int. Ed.* **2004**, *43*, 5138–5175; (b) Dalko, P. I.; Moisan, L. *Angew. Chem., Int. Ed.* **2001**, *40*, 3726–3748.
3. For selected reviews, please see: (a) Almaşi, D.; Alonso, D. A.; Nájera, C. *Tetrahedron: Asymmetry* **2007**, *18*, 299–365; (b) Vicario, J. L.; Badía, D.; Carrillo, L. *Synthesis* **2007**, *14*, 2065–2092; (c) Krause, N.; Hoffmann-Röder, A. *Synthesis* **2001**, *2*, 171–196; (d) Sibi, M. P.; Manyem, S. *Tetrahedron* **2000**, *56*, 8033–8061.
4. Stork, G.; Rosen, P.; Goldman, N. L. *J. Am. Chem. Soc.* **1961**, *83*, 2965–2966.
5. Although the term 'vinylogous Morita–Baylis–Hillman' reaction has been used interchangeably with Rauhut–Currier in the literature, we have chosen to refer specifically to the coupling of two activated olefins through 1,4-addition as the Rauhut–Currier reaction, whereas the MBH reaction involves 1,2-addition. We make this distinction to emphasize the multidimensional differences between the two reactions.
6. For selected reviews, please see: (a) Drewes, S. E.; Roos, G. H. P. *Tetrahedron* **1988**, *44*, 4653–4670; (b) Basavaiah, D.; Rao, P. D.; Hyma, R. S. *Tetrahedron* **1996**, *52*, 8001–8062; (c) Basavaiah, D.; Rao, A. J.; Satyanarayana, T. *Chem. Rev.* **2003**, *103*, 811–891.
7. (a) Lee, K. Y.; Gowrisankar, S.; Kim, J. N. *Bull. Korean Chem. Soc.* **2005**, *26*, 1481–1490; (b) Masson, G.; Housseman, C.; Zhu, J. *Angew. Chem., Int. Ed.* **2007**, *46*, 4614–4628.
8. Rauhut, M. M.; Currier, H. (American Cyanamid Co.), U.S. Patent 307,499,919,630,122, 1963; *Chem. Abstr.* **1963**, *58*, 11224a.
9. The RC reaction can also be run using trialkylamines and thiols as nucleophilic catalysts, as discussed throughout the Review.
10. Baizer, M. M.; Anderson, J. D. *J. Org. Chem.* **1965**, *30*, 1357–1360.
11. McClure, J. D., U.S. Patent 3,225,083, 1965.
12. Morita, K.; Kobayashi, T. *Bull. Chem. Soc. Jpn.* **1969**, *42*, 2732.
13. McClure, J. D. *J. Org. Chem.* **1970**, *35*, 3045–3048.
14. Amri, H.; Villieras, J. *Tetrahedron Lett.* **1986**, *27*, 4307–4308.
15. Basavaiah, D.; Gowriswari, V. V. L.; Bharathi, T. K. *Tetrahedron Lett.* **1987**, *28*, 4591–4592.
16. Drewes, S. E.; Emslie, N. D.; Karodia, N. *Synth. Commun.* **1990**, *20*, 1915–1921.
17. Amri, H.; Rambaud, M.; Villieras, J. *Tetrahedron Lett.* **1989**, *30*, 7381–7382.
18. Hwu, J. R.; Hakimelahi, G. H.; Chou, C.-T. *Tetrahedron Lett.* **1992**, *33*, 6469–6472.
19. (a) Jenner, G. *High Press. Res.* **1999**, *16*, 243–252; (b) Jenner, G. *Tetrahedron Lett.* **2000**, *41*, 3091–3094; (c) Su, W.; Mcleod, D.; Verkade, J. G. *J. Org. Chem.* **2003**, *68*, 9499–9501; (d) Hall, C. D.; Lowther, N.; Tweedy, B. R.; Hall, A. C.; Shaw, G. *J. Chem. Soc., Perkin Trans. 2* **1998**, 2047–2054.
20. (a) Kaye, P. T.; Nocanda, X. W. *J. Chem. Soc., Perkin Trans. 1* **2002**, 1318–1323; (b) Kaye, P. T.; Robinson, R. S. *Synth. Commun.* **1996**, *26*, 2085–2097.
21. Couturier, M.; Ménard, F.; Ragan, J. A.; Riou, M.; Dauphin, E.; Andersen, B. M.; Ghosh, A.; Dupont-Gaudet, K.; Girardin, M. *Org. Lett.* **2004**, *6*, 1857–1860.
22. McDougal, S. E.; Schaus, S. E. *Angew. Chem., Int. Ed.* **2006**, *45*, 3117–3119.
23. Sun, X.; Sengupta, S.; Peterson, J. L.; Wang, H.; Lewis, J. P.; Shi, X. *Org. Lett.* **2007**, *9*, 4495–4498.
24. Erguden, J. K.; Moore, H. W. *Org. Lett.* **1999**, *1*, 375–377.
25. Frank, S. A.; Mergott, D. J.; Roush, W. R. *J. Am. Chem. Soc.* **2002**, *124*, 2404–2405.
26. Wang, L.-C.; Luis, A. L.; Agapiou, K.; Jang, H.-Y.; Krische, M. J. *J. Am. Chem. Soc.* **2002**, *124*, 2402–2403.
27. (a) Brown, P. M.; Käppel, N.; Murphy, P. J. *Tetrahedron Lett.* **2002**, *43*, 8707–8710; (b) Brown, P. M.; Käppel, N.; Murphy, P. J.; Coles, S. J.; Hursthouse, M. B. *Tetrahedron* **2007**, *63*, 1100–1106.
28. Siedel, F. O.; Gladysz, J. A. *Adv. Synth. Catal.* **2008**, *350*, 2443–2449.
29. Thalji, R. K.; Roush, W. R. *J. Am. Chem. Soc.* **2005**, *127*, 16778–16779.
30. Aroyan, C. E.; Miller, S. J. *J. Am. Chem. Soc.* **2007**, *129*, 256–257.
31. Seidel, F.; Gladysz, J. A. *Synlett* **2007**, 986–988.
32. Reynolds, T. E.; Binkley, M. S.; Scheidt, K. A. *Org. Lett.* **2008**, *10*, 2449–2452.
33. Wang, J.; Xie, H.; Zu, L.; Wang, W. *Angew. Chem., Int. Ed.* **2008**, *47*, 4177–4179. Note: Although the mechanism is not proposed as a concerted process, the products are formal RC products.
34. Basavaiah, D.; Kumaragurubaran, N.; Sharada, D. S. *Tetrahedron Lett.* **2001**, *42*, 85–87.
35. Basavaiah, D.; Sharada, D. S.; Kumaragurubaran, N.; Reddy, R. M. *J. Org. Chem.* **2002**, *67*, 7135–7137.
36. Lee, C. H.; Lee, K.-J. *Synthesis* **2004**, *12*, 1941–1946.
37. Jellerichs, B. G.; Kong, J.-R.; Krische, M. J. *J. Am. Chem. Soc.* **2003**, *125*, 7758–7759.
38. Keck and co-workers pioneered the use of thioenoates in the MBH reaction, see: Keck, G. E.; Welch, D. S. *Org. Lett.* **2002**, *4*, 3687–3690.
39. Luis, A. L.; Krische, M. J. *Synthesis* **2004**, *15*, 2579–2585.
40. Krafft, M. E.; Haxell, T. F. N. *J. Am. Chem. Soc.* **2005**, *127*, 10168–10169.
41. Krafft, M. E.; Seibert, K. A.; Haxell, T. F. N.; Hirosawa, C. *Chem. Commun.* **2005**, 5772–5774.
42. Krafft, M. E.; Seibert, K. A. *Synlett* **2006**, 3334–3336.
43. Krafft, M. E.; Haxell, T. F. N.; Seibert, K. A.; Abboud, K. A. *J. Am. Chem. Soc.* **2006**, *128*, 4174–4175.
44. Krafft, M. E.; Wright, J. A. *Chem. Commun.* **2006**, 2977–2979.
45. Evans, C. A.; Miller, S. J. *J. Am. Chem. Soc.* **2003**, *125*, 12394–12395.
46. Du, Y.; Lu, X.; Yu, Y. *J. Org. Chem.* **2002**, *67*, 8901–8905.
47. Evans, C. A.; Cowen, B. J.; Miller, S. J. *Tetrahedron* **2005**, *61*, 6309–6314.
48. Agapiou, K.; Krische, M. J. *Org. Lett.* **2003**, *5*, 1737–1740.
49. (a) Winbush, S. M.; Mergott, D. J.; Roush, W. R. *J. Org. Chem.* **2008**, *73*, 1818–1829; (b) Mergott, D. J.; Frank, S. A.; Roush, W. R. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 11955–11959; (c) Methot, J. L.; Roush, W. R. *Adv. Synth. Catal.* **2004**, *346*, 1035–1050.
50. Mergott, D. J.; Frank, S. A.; Roush, W. R. *Org. Lett.* **2002**, *4*, 3157–3160.
51. Methot, J. L.; Roush, W. R. *Org. Lett.* **2003**, *5*, 4223–4226.
52. Stark, L. M.; Pekari, K.; Sorensen, E. J. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 12064–12066.
53. Webber, P.; Krische, M. J. *J. Org. Chem.* **2008**, *73*, 9379–9387.

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