Multicomponent One-Pot Annulations Forming Three to Six Bonds†

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Contents

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I. Introduction

Forming a carbon–carbon bond is one of the most fundamental operations in organic chemistry. Forming *two* carbon–carbon bonds in one reaction vessel is the basis of some of the most often used organic reactions: cycloadditions (e.g., Diels–Alder,[1] ene,[2] dipolar,[3] carbenoid[4]), annulations (e.g., Robinson annulation[5] involving Michael addition followed by aldol condensation), and α,β-dialkylations of α,β-unsaturated carbonyl compounds.[6] Forming *three* to *six* bonds effectively in one reaction vessel clearly represents an extremely severe challenge due to the multiplicity of reaction pathways available to reactive polyfunctional molecules and to several monofunctional molecules in the same reaction vessel; success, however, would provide rapid and efficient means for transforming simpler molecules into structurally much more complex, nonpolymeric, useful compounds. Over the years, various different procedures have been developed for constructing three to six bonds in one-pot annulation reactions. It is difficult, however, to search the chemical literature comprehensively for examples of such three-to-six bond-forming one-pot annulations because they usually do not appear in the titles of articles or in the key words.

This review, although not exhaustive, is intended as a survey of the most prominent examples known to this author of multicomponent one-pot annulations involving formation of three-to-six bonds. Such an overview will put into perspective what has been accomplished

† No reprints available.

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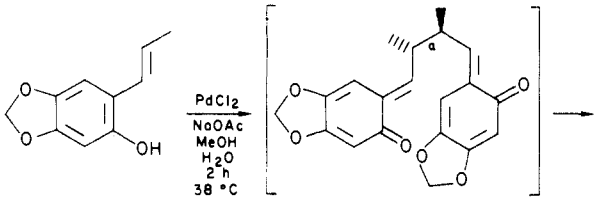
in this area through mid-1986 and thus, it is hoped, will provide impetus for further insights into, and design of, annulation reactions for forming 3 or more bonds in one reaction vessel.

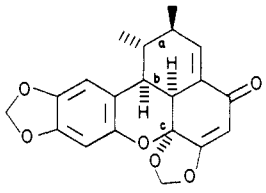
This review is organized from a synthetic (in contrast to a mechanistic) viewpoint around the following questions: (1) How many reacting components are involved (e.g., two, three, four) and, of these, how many are different (e.g., A + B + B vs. A + B + C)? (2) What is the size of the new ring, and what is the number of atoms involved in each of the separate units coming together to form this new ring (e.g., 1 + 2 → three-membered ring, 1 + 2 + 2 → five-membered ring, 2 + 2 + 2 → six-membered ring)? When more than one ring is formed, the annulation is discussed under the section dealing with the *first-formed* ring [e.g., (2 + 2 + 2) + (1 + 2) is discussed under six-membered rings]. (3) How many new bonds are formed (e.g., three, four, five)? (4) What kinds of reactions (i.e., what mechanisms) are involved in forming the new bonds (e.g., Michael–Michael-1,6-aldol)?

One-component (e.g., polyketide,[7a] polyolefin[7b]) cyclizations[7c-i] are outside the scope of this review.

II. Two-Component Coupling (A + B)

One elegant example of a two-component A + A coupling (all of the other couplings in this section use two *different* components, A + B) involves regiocontrolled oxidative dimerization of an *o*-propenylphenol followed, in situ, by an intramolecular 2 + 4 cyclization to form three new bonds (a–c) and two new six-membered rings (eq 1).[8] This process involves effective





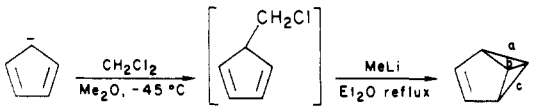
(1)

46%

formation of five contiguous chiral centers with the relative stereochemical configurations found in the natural product carpanone, a lignan in the bark of the carpano tree; this impressive one-pot two-component annulation is now used as a reliable and exciting undergraduate laboratory experiment![8b]

A. Three-Membered Rings

Based on the work of Katz,[9a] several examples by different research groups have been reported in which non-benzenoid 4*n* + 2 aromatic anions react with methylene chloride to give tricyclc products having three new bonds (a–c) and a new bicyclobutane ring.[9] Formally this process involves connecting (1 + 2) + (1 + 3) atoms in what has been shown to be a sequential S_N2-carbenoid cyclopropanation reaction (eq 2).[9c] For



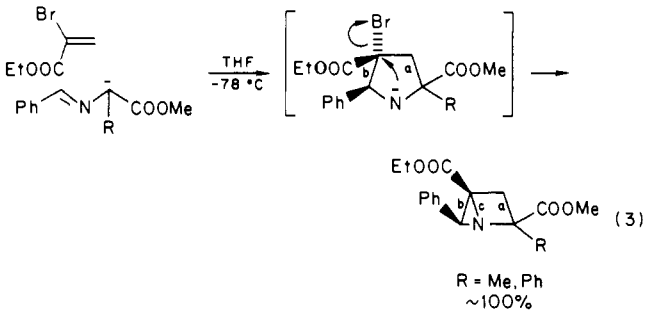
(2)

29%

other mechanistically unrelated cyclopropanations, see eq 3, 4, 15–17, 21, 33, 50.

B. Five-Membered Rings

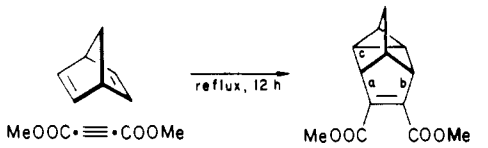
One-pot annulations occur in excellent yield and with high stereoselectivity when 2-azaallylic anions react with ethyl 2-bromoacrylate via sequential (2 + 3) + (1 + 2) Michael–Michael-1,3-S_Ni reactions to form azabicyclopentanes having three new bonds (eq 3).[10]



(3)

R = Me, Ph
~100%

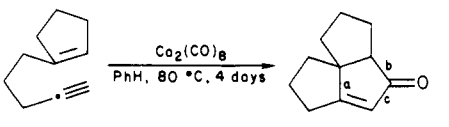
Dimethyl acetylenedicarboxylate reacts with norbornadiene in a (2 + 3) + (0 + 3) Diels–Alder cycloaddition mode to form a polycyclic adduct with three new carbon–carbon bonds, one new five-membered ring, and one new three-membered ring (eq 4).[11]



(4)

50%

Dicobalt octacarbonyl reacts with 1,6-enynes to form polycyclic cyclopentenones via intramolecular cyclization and carbon monoxide insertion reactions (eq 5);

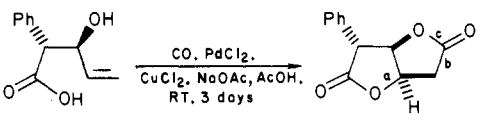


(5)

35%

this one-pot annulation is known as the Pauson–Khand reaction, and it is used to form a large variety of cyclopentenones from acyclic as well as from cyclic alkenes.[12] An excellent review is available.[12a]

A related carbon monoxide insertion involves a (0 + 5) + (1 + 4) annulation producing two fused lactone rings via organopalladium intermediates (eq 6).[13]

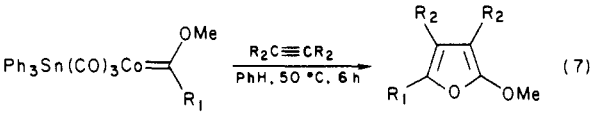


(6)

63%

(Methoxyalkylidene)(triphenylstannyl)tricarbonylcobalt(0) complexes react with alkynes via cycloaddition of the ligands (methoxyalkylidene, alkyne, carbon

monoxide) on the cobalt center to produce 2-alkoxyfurans exclusively in moderate to excellent yields (eq 7).[14]



(7)

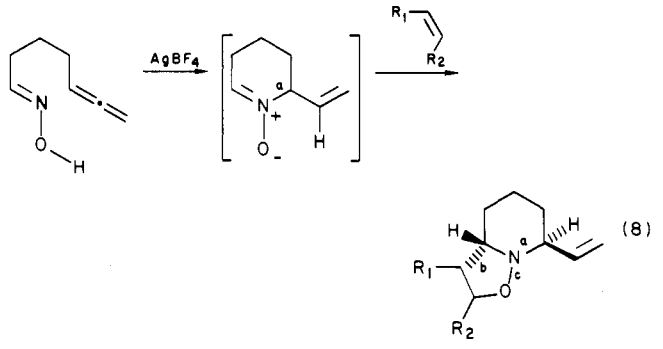
R_1 = *n*-Bu, Ph
R_2 = Me, Et, Ph

39-93%

C. Six-Membered Rings

1. (0+6)+(2+3)

Certain allenic oximes undergo a silver(I)-catalyzed ene-type cyclization to give nitrones which are trapped in situ by various 1,3-dipolarophiles producing overall three new bonds and new six- and five-membered rings (eq 8).[15]

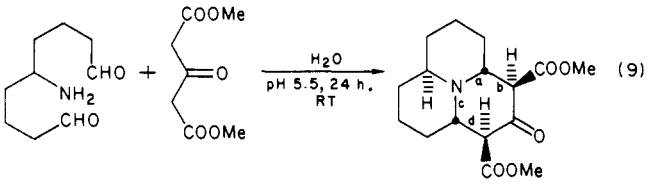


(8)

25-43%

2. 1+1+1+3

The Stevens alkaloid synthesis shown in eq 9 represents combining two components via an *inter*molecular and then an *intra*molecular Mannich condensation; four new bonds (a–d), five new chiral centers, and three new rings are formed in 75% yield![16] The substantial increase in structural and stereochemical complexity in going from reactants to product in eq 9 very nicely



(9)

75%

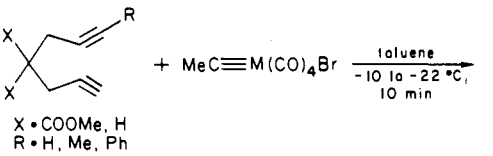
illustrates the great synthetic potential of such one-pot annulations. For comparison see eq 53.

3. 1+1+2+2

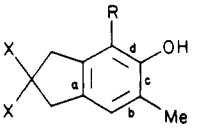
Chromium and tungsten carbyne complexes react with α,ω-diacetylenes to produce phenols in which four new bonds and two new rings are formed via sequential carbon–metal insertion reactions (eq 10).[17] This appears to be a general process.

4. 1+2+3

Pentacarbonylchromium alkenylmethoxycarbene complexes react with alkynes via cycloaddition of the ligands (alkene, alkyne, carbon monoxide) associated with the chromium center to produce 1,4-hydroquinone



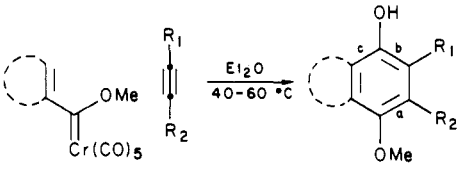
X = COOMe, H
R = H, Me, Ph



(10)

M = W, 42-60%
M = Cr, 31-50%

ring systems having 3 new bonds (eq 11).[18] Such 1,4-hydroquinones are key structural units in many physiologically active anthracyclines.

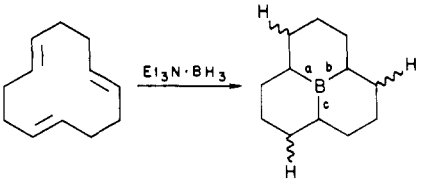


(11)

60-90%

5. 1+5

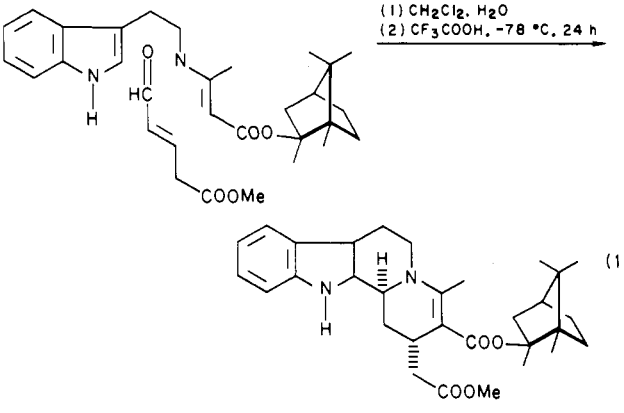
Hydroboration of 1,5,9-cyclododecatriene leads to formation of three new carbon–boron bonds and three new carbon–hydrogen bonds in the form of perhydro-9b-boraphenalene (eq 12).[19] Subsequent replacement



(12)

of the boron atom by a tertiary carbinol unit can be achieved.

Stitching together the skeleton of an indole alkaloid has been accomplished via a two-component (1 + 5) + (3 + 3) coupling in which three new bonds and two new rings are formed in one pot with high absolute stereochemical control under the influence of a temporarily attached chiral auxiliary group (eq 13).[20]



(13)

59% (76% diastereomeric excess)

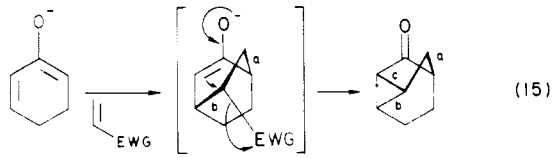
Reaction of *cis*-1,3,5-cyclohexanetriol with glyoxylic acid involves a (1 + 5) + (2 + 5) ring-forming process (eq 14) which is a key step in the elegant Woodward synthesis of prostaglandin $F_{2\alpha}$.[21]

85%

(14)

6. 2+2+2

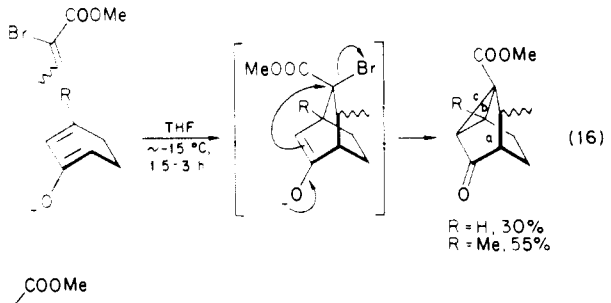
(a) +(1 + 2). Kinetic deprotonation of 2-cyclohexenones produces cross-conjugated dienolates which can add to various 2-carbon Michael acceptors; a second intramolecular Michael addition produces a new enolate which consummates the 2 + 2 + 2-annulation with an *irreversible* 1,3-S_Ni cyclization (eq 15). In this *Mi-*



(15)

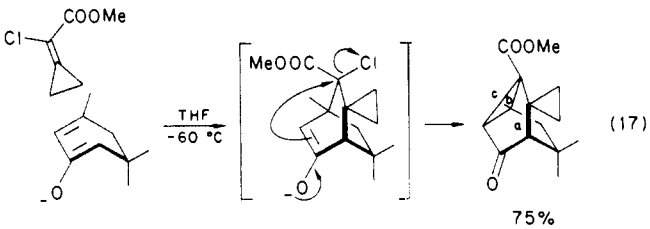
EWG = $^+PPh_3$, SO_2Ph, NO_2

chael-Michael-ring closure (MIMIRC) sequence, three new bonds, one new six-membered ring, and one new three-membered ring are formed. Cory and co-workers have developed this bicycloannulation procedure very nicely into a reliable and useful synthetic method, and they have applied this protocol to syntheses of some terpenes.[22] Similar 2-component (2 + 2 + 2) + (1 + 2) bicycloannulations forming three new bonds and involving more complex Michael acceptors are shown in eq 16 and 17 leading ultimately to some sesquiterpenes and diterpenes, respectively.[23,24]



R = H, 30%
R = Me, 55%

(16)

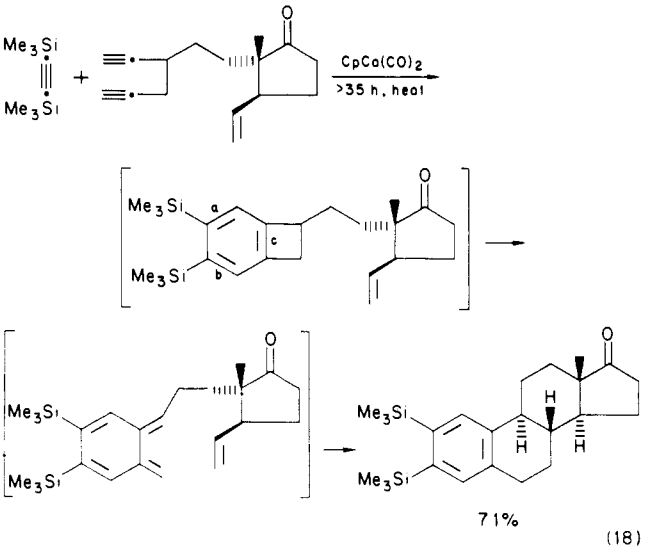


75%

(17)

In this review, enolate and dienolate anions are discussed without consideration of the corresponding metal counterions (which are almost always lithium cations for the examples recorded here). Obviously this is an oversimplification because the nature of these metal counterions probably has an important effect on the course of these multiple coupling reactions[25] and especially on the equilibrium position of such reversible reactions as 1,6-aldol condensations (e.g., possible chelation driving the aldol in the forward direction).[5a]

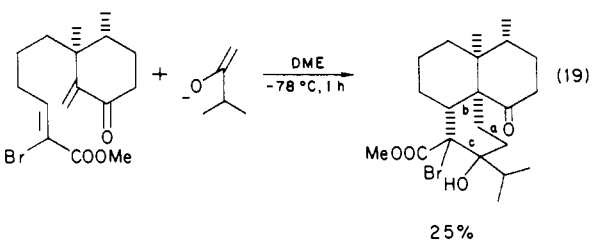
(b) +(0 + 4). Based in part on the work of Wakatsuki and Yamazaki,[26] Vollhardt has pioneered the use of cobalt templates to organize α,ω-diynes and acetylenes in order to promote their 2 + 2 + 2 annulation leading to regiospecifically substituted aromatic compounds having three new bonds; such systems have been used as the key components in various short, intramolecular Diels–Alder total syntheses of estrone steroids involving (2 + 2 + 2) + (0 + 4) formation of crucial benzocyclobutene intermediates (eq 18).[27]



71%

(18)

(c) +(0 + 6). Combining a structurally appropriate bis Michael acceptor with the kinetic enolate of 3-methyl-2-butanone has led to the one-pot 2 + 2 + 2 annulation shown in eq 19 forming three new bonds and



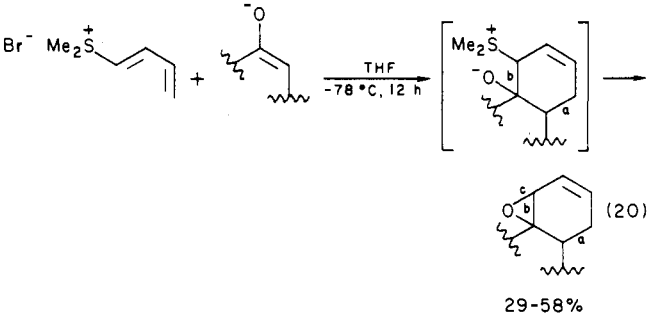
25%

(19)

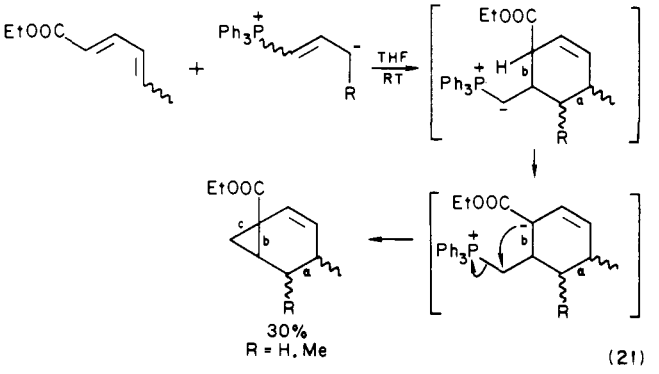
two new six-membered rings via two sequential Michael additions and a final, *reversible*, 1,6-aldol cyclization.[28] Despite the strongly basic aprotic conditions, this 2 + 2 + 2 MIMIRC [or 2 + 2 + 2 *sequential Michael-ring closure* ("SMIRC")][29] reaction proceeds in a controlled fashion, and the final aldol cyclocondensation is favored over the retroaldol process. This multiple annulation sequence is the key step in a total synthesis of some indolic diterpenes, and Danishefsky and co-workers have studied in detail the influence of various factors on the structural and stereochemical outcome of this process.[28]

7. 2+4

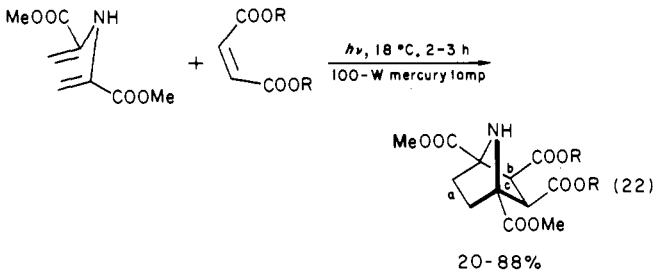
(a) +(1 + 2). Two types of annulation procedures fall into the category of (2 + 4) + (1 + 2) reactions forming first a new six-membered ring and then a new three-membered ring. In the first, a vinylogous Michael addition of a ketone enolate to a butadienyl sulfonium salt is followed in situ by an intramolecular 1,6-cyclization and then an irreversible intramolecular 1,3-Darzens cyclization leading to a general synthesis of dihydroarene oxides having three new bonds (eq 20).[30] In the second, a vinylogous Michael addition to ethyl 2,4-pentadienoate (sorbate) is followed in situ by an intramolecular 1,6-cyclization, a 1,3-proton shift, and then an irreversible intramolecular 1,3-cyclization leading to a general 2 + 4 MIMIRC synthesis of nor-



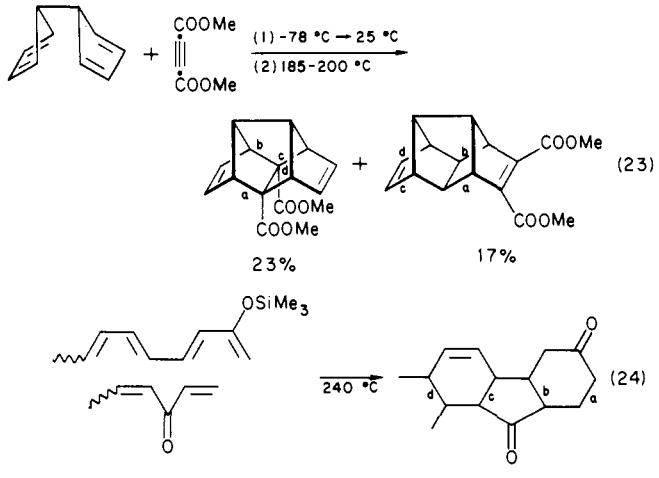
caranes [i.e., bicyclo[4.1.0]heptanes, eq 21] with 3 new bonds.[31]



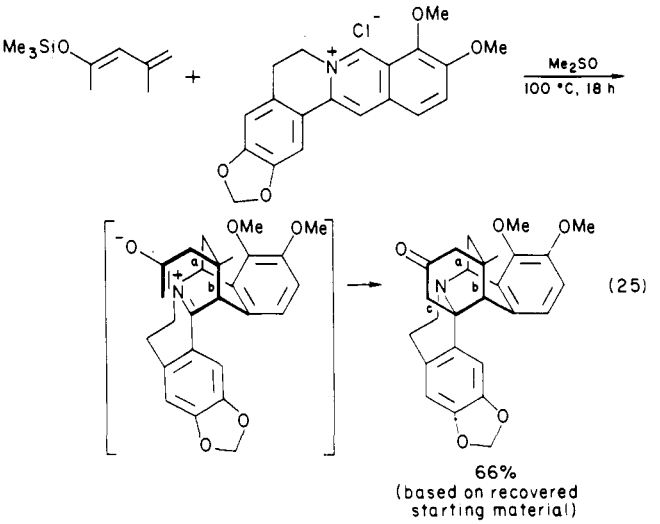
(b) +(0 + 5). One 2-component photochemical bicycloannulation of unestablished mechanism involves forming three new bonds and three new rings (one six-membered and two five-membered, eq 22).[32]



(c) +(2 + 4). Tandem *inter*molecular and then *intra*molecular 2 + 4 cycloadditions have been used in "domino" and in "timed" Diels–Alder reactions to form four new bonds (a–d) and two new six-membered rings in the form of several polycyclic adducts (eq 23 and 24).[33,34] Equation 24 gives much better results, however, when performed in two stages (i.e., a two-pot sequence).

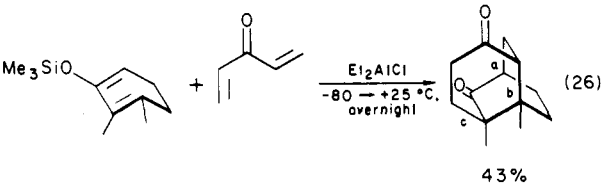


One short and efficient entry into the protoberberine alkaloid class involves a one-pot, stepwise, (2 + 4) + (2 + 4) multiple annulation as shown in eq 25 in which



three new bonds (a-c) and two new six-membered rings are formed via sequential Mannich–Michael–1,6-Mannich condensations.[35]

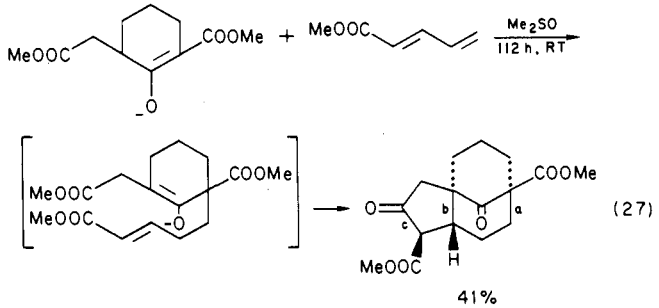
A similar two-component 2 + 2 + 2 annulation involves three sequential Michael additions under aprotic, Lewis acid-promoted conditions; the terminal step occurs via a *reversible* 1,6-Michael ring closure (eq 26).[36]



Three new bonds and two new six-membered rings are formed from (2 + 4) + (2 + 4) fragments. This 2 + 4 MIMIRC process, which was shown to be general for a series of differently substituted cyclohexadienol silyl ether Michael donors, was applied to synthesis of the sesquiterpene seychellene.[36]

8. 3+3

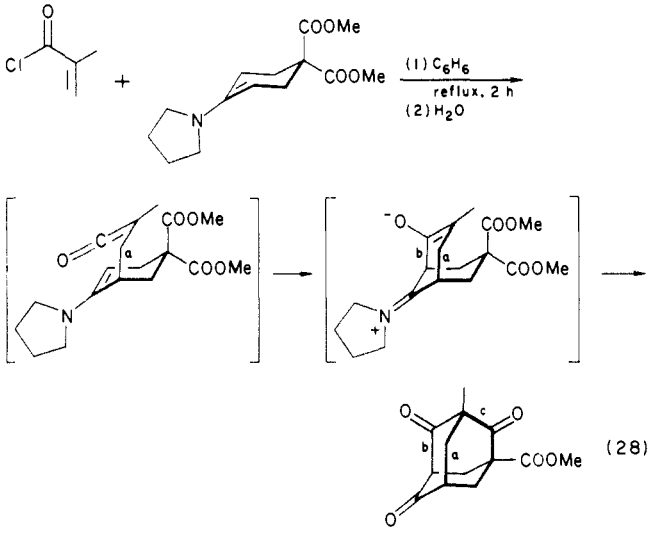
(a) +(2 + 3). A MIMIRC sequence occurs in one reaction vessel via 1,6-conjugate addition of a highly functionalized cyclohexanone enolate to methyl 2,4-pentadienoate, then intramolecular conjugate addition, and finally 1,5-Dieckmann cyclization forming three new bonds and new six- and five-membered rings via a (3 + 3) + (2 + 3) sequence as in eq 27.[37] The tricyclic



skeleton produced in eq 27 belongs to the clovane sesquiterpene class.

(b) +(2 + 4). Capping a 4-carboxycyclohexanone system with four carbon atoms to form an adamantane

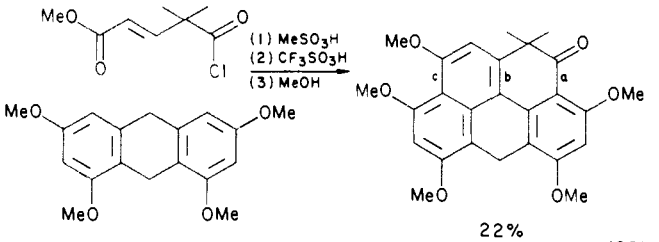
unit has been achieved via a two-component (3 + 3) + (2 + 4) one-pot annulation involving the sequential Michael addition, 1,6-ketene addition, and then 1,6-Dieckmann condensation shown in eq 28, in which three



(28)

new bonds (a–c) are formed.[38a] For a closely related example, see ref 38b.

(c) +(3 + 3). Kelly has recently used a two-component, one-pot, (3 + 3) + (3 + 3) annulation involving probably sequential Friedel–Crafts reactions for construction of the fourth and fifth six-membered rings of the antibiotic resistomycin containing the benzo[*cd*]-pyrene ring system (eq 29).[39]



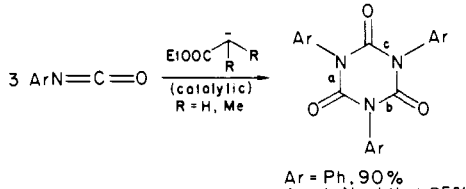
(29)

III. Three-Component Coupling

A. A + A + A

1. Six-Membered Rings

Trimerization of formaldehyde and of acetone leads to 1,3,5-trioxane and to 1,3,5-trimethylbenzene, respectively. Electrochemically generated ester enolates catalyze 2 + 2 + 2 cyclotrimerization of aryl isocyanates into 1,3,5-triazinetriones with three new bonds in excellent yields (eq 30).[40] Titanium oxide on silica–alumina promotes 2 + 2 + 2 cyclotrimerization of phenylacetylene into 1,3,5-triphenylbenzene.[41] Zinc metal promotes cyclotrimerization of some α-bromocyclopropanecarboxylic acid chlorides presumably via organozinc intermediates rather than via free carbene intermediates (eq 31).[42]



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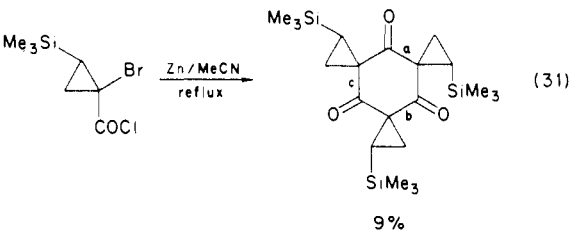
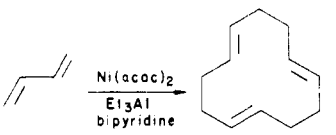


(31)

2. Twelve-Membered Rings

A milestone in the modern history of organometallic chemistry involves use of transition metals to promote oligomerization of small monomer units in a controlled and selective fashion, as exemplified by Wilke's A + A + A cyclotrimerization of 1,3-butadiene to give all *trans*-1,5,9-cyclododecatriene (eq 32).[43]

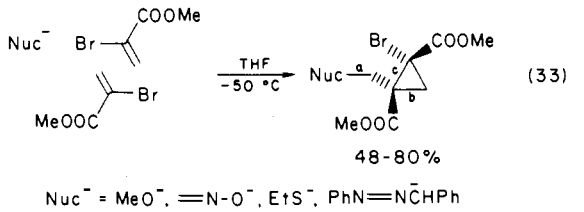


(32)

B. A + B + B

1. Three-Membered Rings

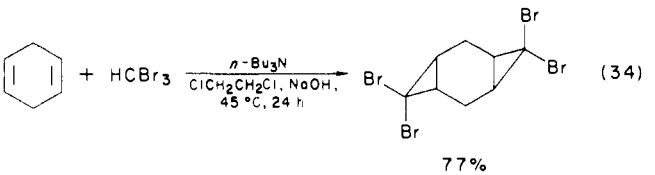
Conjugate addition of methoxide, of oxime anions, of sulfur anions, and of hydrazone anions to methyl α-bromoacrylate generates ester enolate ions which themselves undergo conjugate addition to another molecule of the bromoacrylate; this 3-component, 1 + (1 + 2) MIMIRC sequence terminates with an irreversible S_Ni displacement of a bromide ion with formation of vicinally and stereospecifically tetrasubstituted cyclopropane rings (eq 33).[44]



(33)

$Nuc^- = MeO^-, =N\text{-}O^-, EtS^-, PhN{=}N\bar{C}HPh$

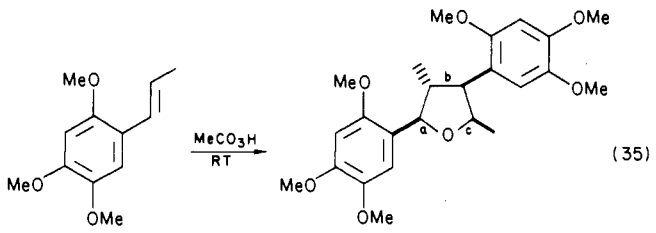
Double carbene addition under phase transfer conditions to the two ethylenic linkages in 1,4-cyclohexadiene produces two new three-membered rings via (1 + 2) + (1 + 2) cycloadditions even on a 100-g scale (eq 34); this is a key step in a total synthesis of the neurotoxic alkaloid anatoxin a.[45]



(34)

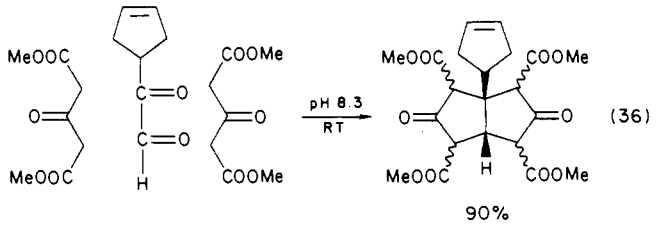
2. Five-Membered Rings

2,3,4,5-Tetrasubstituted tetrahydrofuran rings are formed stereospecifically when some arylpropenes are treated with peracetic acid; equation 35 represents a biogenetic-type synthesis of magnosalicin, a neolignan with antiallergy activity, from α-ascarone via a one-pot, A + B + B, 1 + 2 + 2 annulation with formation of



three new bonds (a–c) in 15.6% yield.[46]

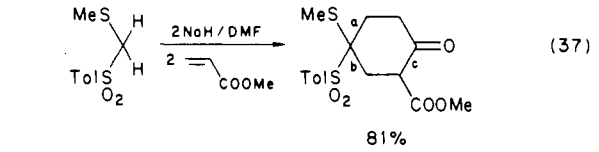
A mild, efficient, one-pot protocol for forming four bonds and two five-membered rings from three different components involves a repeating series of aldol and Michael additions as shown in eq 36.[47] Note that the



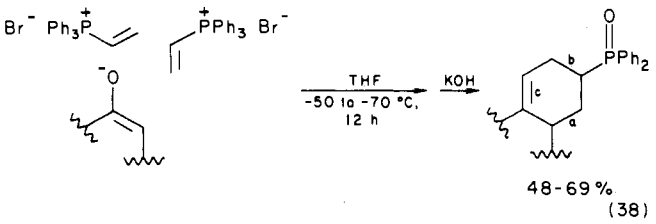
overall yield is 90% (i.e., an average yield of 97.4% for each of the four new carbon–carbon bonds)! This sequence has recently been termed the Weiss reaction, and it is one of the most dramatic examples of efficient syntheses possible using multiple-component one-pot annulations.

3. Six-Membered Rings

(a) 1 + 2 + 3. A doubly sulfur-stabilized carbanion adds in a Michael fashion to 2 equiv of methyl acrylate via a 1 + 2 + 3 MIMIRC sequence, in which the culminating 1,6-ring closure is a Dieckmann cyclization, to give a new six-membered ring with three new bonds (a–c) in 81% yield (eq 37)![48]

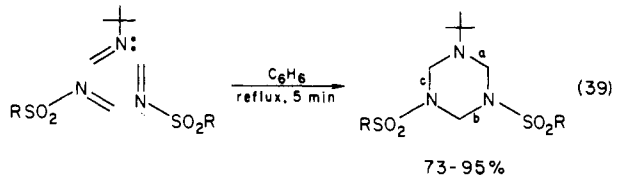


(b) 2 + 2 + 2. (1) **1,6-Wittig.** In 1980, based in part on Schweizer's work with vinyltriphenylphosphonium bromide (VTB),[49] Cory published a bicycloannulation paper which included the first example of an enolate Michael addition to 2 equiv of VTB leading via sequential Michael–Michael–1,6-Wittig reactions to one phosphorus-substituted cyclohexene.[50] In 1985, we demonstrated the generality and practicality of this three-component MIMIRC procedure forming three new bonds by preparing under high-dilution conditions seven different phosphorus-substituted cyclohexenes including some bicyclic and spirocyclic systems in 48–69% overall yields (eq 38).[51] In some cases, tri-

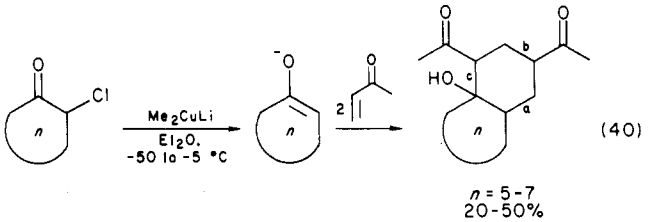


ethylboron was used to moderate enolate reactivity and thus to improve overall yields.

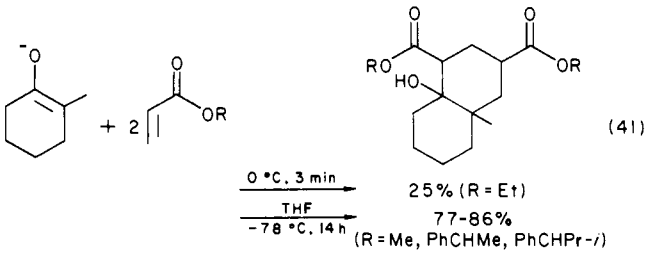
(2) 1,6-Mannich. The nucleophilic nitrogen atom of *N*-methylene-*tert*-butylamine adds in a Michael fashion to an electrophilic *N*-methylenesulfonamide to produce a sulfonamide anion which itself undergoes a Michael addition to another molecule of the original *N*-methylenesulfonamide; this three-component 2 + 2 + 2 annulation forming three new bonds ends with a 1,6-Mannich-type condensation leading to *N,N,N*-trisubstituted 1,3,5-triazines (eq 39).[52]



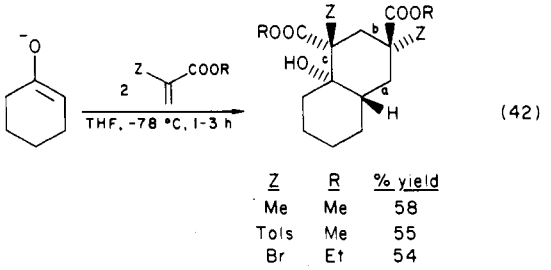
(3) 1,6-Aldol. In 1973, Wakselman and Mondon reported that enolates of 5–7-membered cycloalkanones undergo Michael addition to only two molecules of methyl vinyl ketone and then in situ chain-terminating intramolecular 1,6-aldol cyclization (eq 40); these au-



thors attributed this reaction pathway (rather than the classical Robinson annulation pathway) to the presence of copper(I) ions.[53] In 1978, Dionne and Engel recorded that the more highly substituted enolate of 2-methylcyclohexanone likewise undergoes Michael addition to only two molecules of ethyl acrylate and then chain-terminating intramolecular 1,6-aldol cyclization (eq 41,

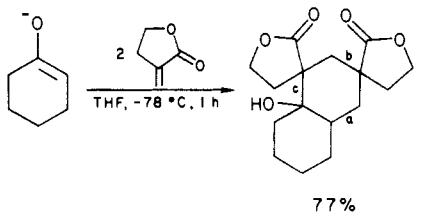


upper pathway).[54] By performing the same reaction under substantially milder conditions (–78 °C instead of 0 °C) and in THF (rather than DME) solvent, we have been able to make this three-component, one-pot, 2 + 2 + 2 MIMIRC process into a general, high-yield synthetic method of substantial utility for preparation of regiospecifically polysubstituted decalin systems (eq 41, lower pathway[55] and eq 42)[56] as well as bis spiro adducts containing three new bonds as shown in eq 43.[56]



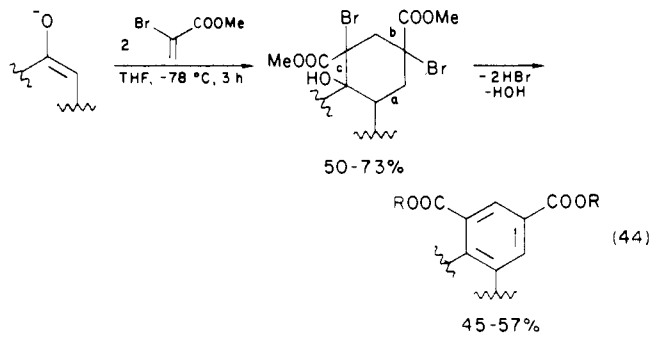
Z	R	% yield
Me	Me	58
Tols	Me	55
Br	Et	54

Note that in eq 42, the examples shown involve formation of *only one diastereomer*; this stereoselectivity



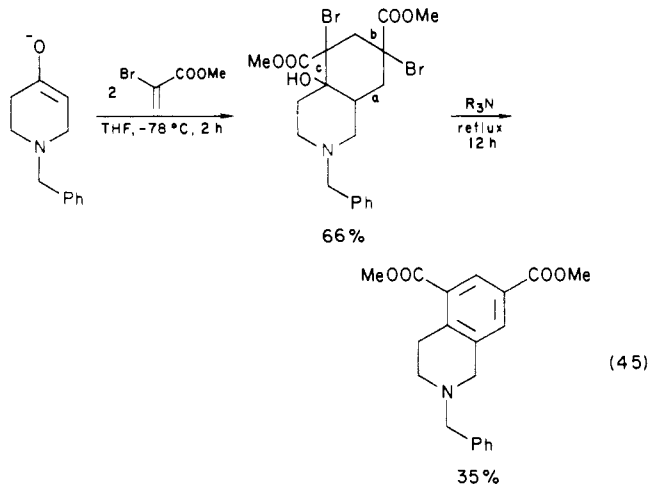
(43)

adds to the synthetic value of this one-pot annulation. The enolates derived from cycloheptanone, acyclic 3-pentanone, and aromatic *p*-anisyl methyl ketone and 1-tetralone also undergo Michael addition with methyl 2-bromoacrylate in this type of easy, one-pot, A + B + B, 2 + 2 + 2 annulation sequence (eq 44).[39,40] High-



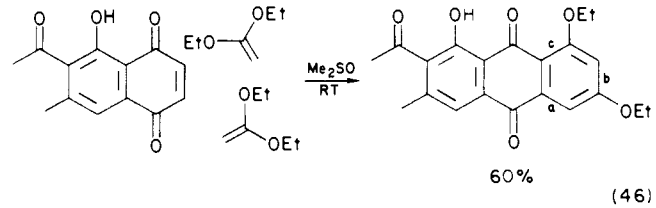
(44)

dilution conditions are *not* required in these cyclohex-annulations. One-pot dehydration and double dehydrobromination then constitute overall a direct, two-step procedure for annulating a *m*-dicarboxylated benzene ring onto the $-COCH_2-$ group of a ketone (eq 44); unsymmetrical biaryls, 9,10-dihydrophenanthrenes, and tetrahydroisoquinolines (eq 45) can be prepared in



(45)

this way.[56] A related 1,6-aldol-type closure terminates a three-component coupling between *p*-quinones and 2 equiv of 1,1-diethoxyethylene to produce regiospecifically *m*-dioxygenated benzoquinones (eq 46),[57] with

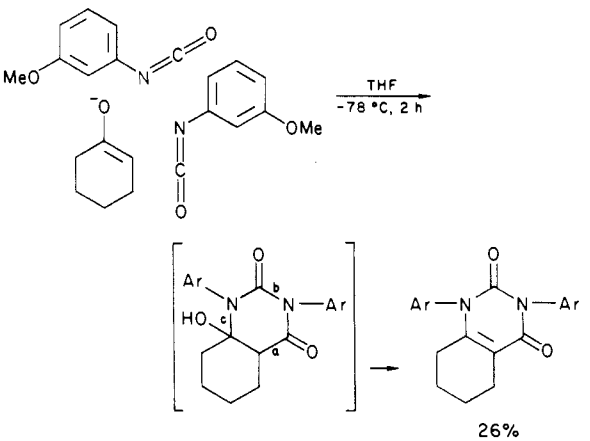


(46)

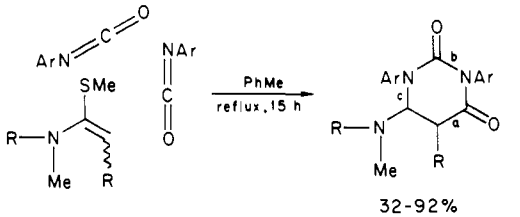
successful applications to synthesis of some anthraquinone insect pigments.[57b]

It is noteworthy that the *reversible* Michael–Michael–1,6-aldol condensations in eq 40–43 under highly basic *aprotic* conditions proceed to give annulated adducts. If one were to consider only the thermodynamic stability of the reactant ketone ($pK_a \sim 20$) enolate ion vs. that of the considerably less stable ester ($pK_a \sim 24$–25) enolate ion produced by the first Michael addition,[58] then one might expect no Michael reaction at all. Approximate thermodynamic considerations indicate very clearly, however, that the overall Michael–Michael–1,6-aldol process represented in eq 40–43 is very favorable; the energy liberated (enthalpy factor) by forming the three new carbon–carbon σ bonds a–c very heavily outweighs the energy required to bring the three reactants together in a stepwise fashion (entropy factor) and to sacrifice their π bonds. The chain-terminating intramolecular aldol condensation involves a thermodynamically very favorable conversion of the enolate of an ester ($pK_a \sim 24$–25) into the alkoxide of a tertiary alcohol ($pK_a \sim 17$).[58] 1,6-Aldol condensation (i.e., cyclohexanol formation) obviously is thermodynamically more favorable than 1,4-aldol condensation (i.e., ring-strained cyclobutanol formation).

We have begun to find that this type of one-pot annulation using isocyanates as electrophiles can be applied successfully to direct synthesis of such heterocyclic compounds as uracil pyrimidines (eq 47).[59] Similar results using ketene *S,N*-acetals have been recorded (eq 48)[60] as have reactions using iso*thio*cyanates and leading initially to pyrimidinedithiones.[61]



(47)



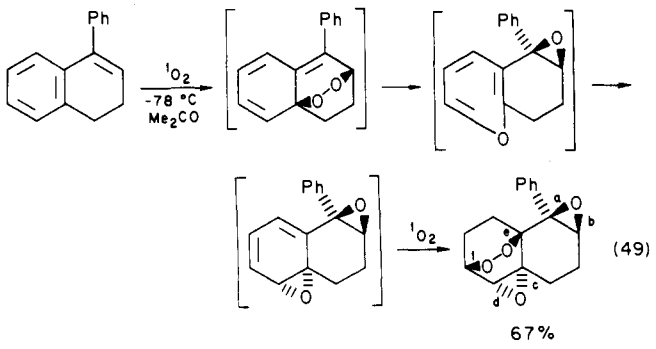
(48)

(c) **2 + 4.** Singlet molecular oxygen ($^1O_2$) reacts with many conjugated arylalkenes mainly via a 2 + 4 cycloaddition pathway creating in situ a cyclohexadiene unit which then also undergoes a 2 + 4 cycloaddition with $^1O_2$ (eq 49).[62] The extraordinary three-component coupling shown in eq 49 involves formation of no fewer than six new carbon–oxygen bonds, six new chiral centers, and three new rings!

C. A + B + C

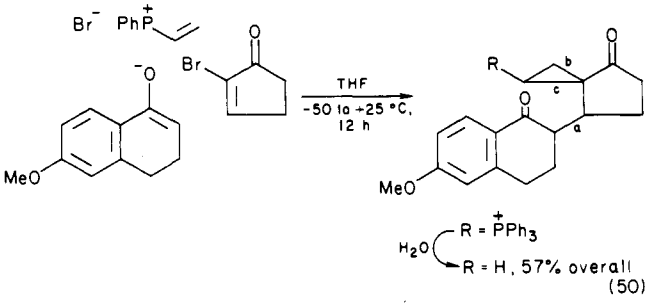
1. Three-Membered Rings

Conjugate addition of a ketone enolate to 2-bromo-2-cyclopentenone generates a bromoenolate which un-



(49)

dergoes Michael addition to vinyltriphenylphosphonium bromide (VTB); this A + B + C, 2 + 2 + 2 MIMIRC sequence ends with an *irreversible* S_Ni-displacement of a bromide ion with formation of a cyclopropylphosphonium salt (eq 50). After exposure to water, loss

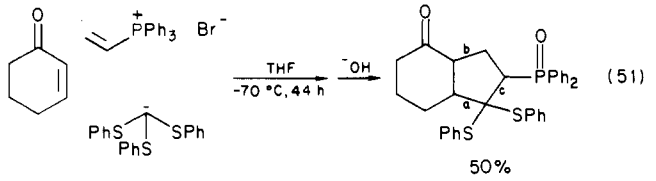


(50)

of triphenylphosphine oxide liberates a spirocyclopropylcyclopentanone in 57% yield overall.[63]

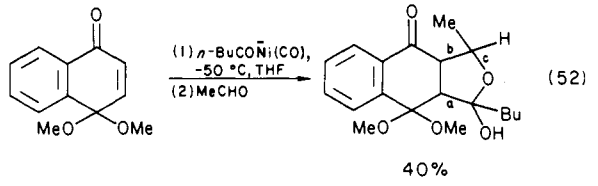
2. Five-Membered Rings

We have begun to develop a 1 + 2 + 2 MIMIRC procedure for one-pot construction of cyclopentanes containing three new bonds. This stitching together of A + B + C units occurs via Michael addition of a nucleophile, stabilized by groups which can serve later as leaving groups, followed by a second Michael addition and then an irreversible 1,3-S_Ni cyclization (eq 51).[64]



(51)

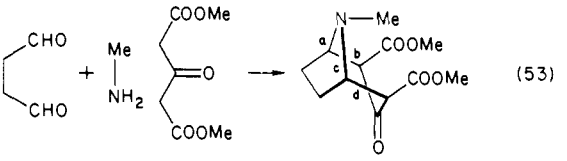
Such an approach represents a conceptually new multicomponent process in cyclopentannulation chemistry, and it requires use of initial Michael donors which do not undergo 1,3-S_Ni *cyclopropane* formation before the second Michael acceptor has reacted. A report of a somewhat similar three-component 1 + 2 + 2 annulation leading to a tetrahydrofuran system (eq 52) has just appeared.[65]



(52)

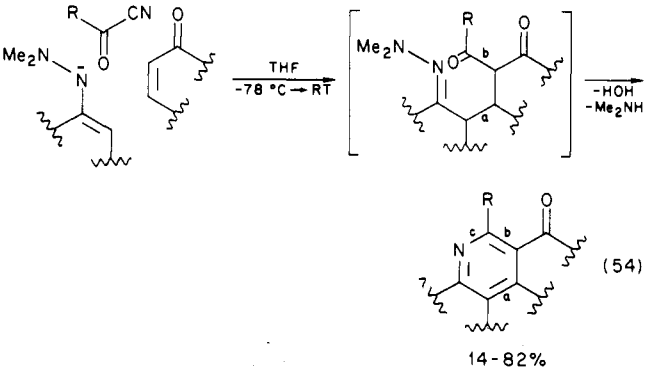
3. Six-Membered Rings

(a) 1 + 1 + 1 + 3. Probably the most famous example of one-pot annulations forming several bonds is the now classical Robinson–Schöpf synthesis of tropane alkaloids, as developed in the first half of this century.[66] Such a process under physiological-type conditions involves three different components being joined together with four new bonds via double Mannich condensations, the first *inter*molecular and the second *intra*molecular (for example, see eq 53). For comparison, see eq 9.



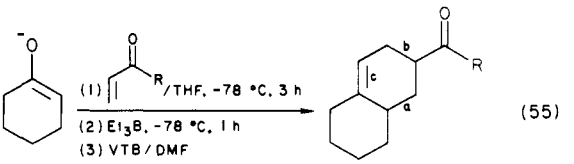
(53)

(b) 1 + 2 + 3. Kelly and Liu have developed a new, general pyridine synthesis involving sequential one-pot, three-bond-forming, 1 + 2 + 3 annulations of *N,N*-dimethylhydrazone anions, α,β-unsaturated ketones, and acyl cyanides. The first *new* bond is formed via a Michael addition, the second via a Claisen condensation, and the third via an intramolecular 1,6-carbonyl addition; elimination of water and dimethylamine leads in a conceptually new approach to variously substituted pyridine heterocycles (eq 54).[67]



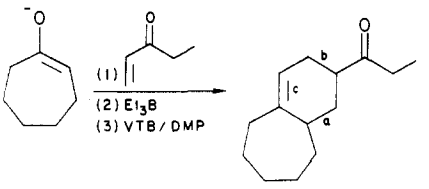
(54)

(c) 2 + 2 + 2. (1) 1,6-Wittig. In section III.B.3.b.1., A + B + B Michael–Michael–1,6-Wittig annulations were discussed. Now, we turn to the much more difficult three-*different* (A + B + C) component cases in which the first Michael addition has to be essentially complete before the next Michael acceptor is introduced into the reaction vessel. By using sustained low-temperature (e.g., −78 °C) for several hours and by using boron derivatives to stabilize some of the enolate intermediates, we have succeeded in limiting Michael addition to only 1 equiv of several different ketone Michael acceptors reacting with several different ketone enolate Michael donors. Then motor-driven syringe high-dilution conditions allow the next vinylphosphonium Michael acceptor to be placed in the reaction vessel so as to consummate the annulation with an irreversible 1,6-Wittig cyclization (eq 55–58).[68] In most of these 2 + 2 + 2 MIMIRC cases, a small amount (<10%) of the undesired A + B + B annulation product is observed. The average yield for each of the three new bonds a–c in eq 55–58 ranges from 60–83%. This A +



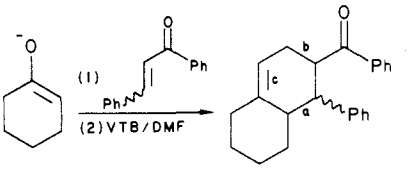
(55)

R	% Yield
Me	21
Et	57
Ph	44



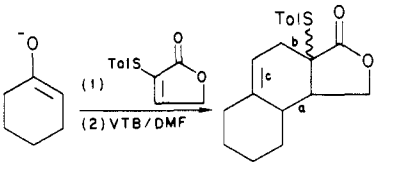
(56)

35%



(57)

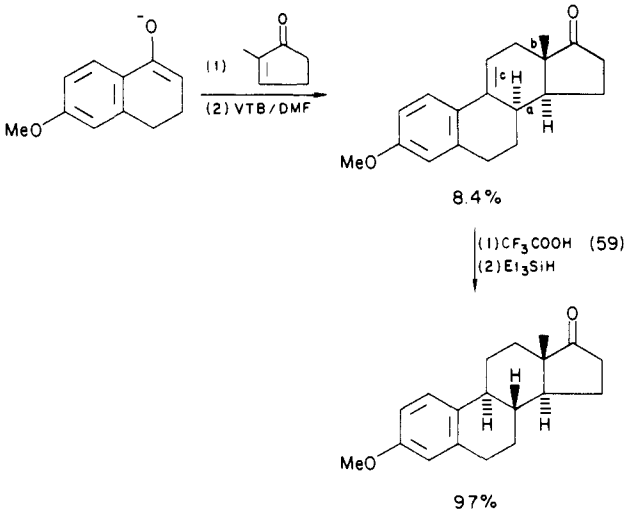
35%



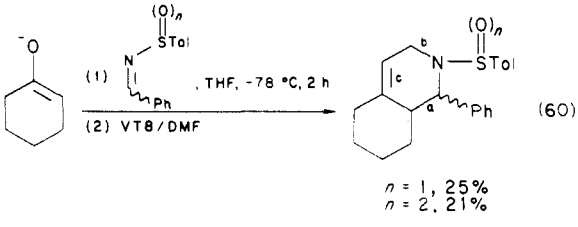
(58)

26%

B + C 2 + 2 + 2 cyclohexannulation protocol, in which the terminal 1,6-Wittig condensation was inspired by Schweizer's publications using VTB,[49] has been used in a *one-pot* total synthesis of the estrone steroid skeleton (eq 59).[63]



We have begun to find that this type of one-pot, three-*different*-component, 2 + 2 + 2 MIMIRC concept can be applied successfully also to synthesis of heterocyclic tetrahydropyridines (eq 60).[59] Further

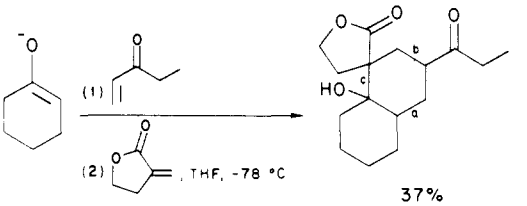


(60)

straightforward elimination and oxidation reactions should lead to a conceptually new pyridine synthesis.

Although the *overall* yields in eq 55–58 and 60 are only moderate, the global transformations represent formation of new bonds by linking together three *different* units in one reaction vessel. Substantial flexibility is possible in choice of reactants of diverse structures and substitution patterns. A potential problem concerns the stereochemical mixtures of products that can be, and in some cases are, produced.

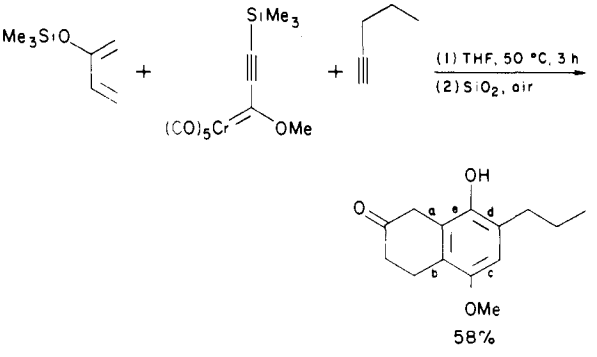
(2) 1,6-Aldol. Final 1,6-cyclization involving a *reversible* ring closure is an even more challenging goal. We have succeeded in performing such a one-pot, three-*different*-component, 2 + 2 + 2 annulation by combining the enolate of cyclohexanone with 1 equiv of the Michael acceptor ethyl vinyl ketone and, after TLC analysis has indicated completion of the first Michael addition, then with the second (different) Michael acceptor α-methylene-γ-butyrolactone under dilute conditions; final intramolecular aldol condensation (which should be reversible under these basic aprotic conditions) culminates this sequence to produce a richly functionalized cyclohexannulation product having three new bonds in 37% overall yield (72% average yield for each of the three new bonds a–c, eq 61).[68]



(61)

37%

(d) 2 + 4. Placing a 1,3-diene, a chromium alkynylcarbene complex, and an acetylene together in one reaction vessel leads under neutral conditions to a (2 + 4) + (1 + 2 + 3) cycloaddition-annulation sequence in which five new bonds and two carbocyclic rings are formed (eq 62)! Several interesting and useful examples of this protocol have been reported.[69]



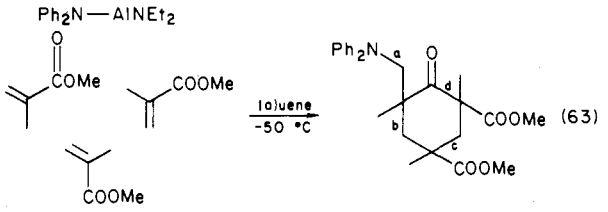
(62)

IV. Four-Component Coupling. Six-Membered Rings

A. A + B + B + B

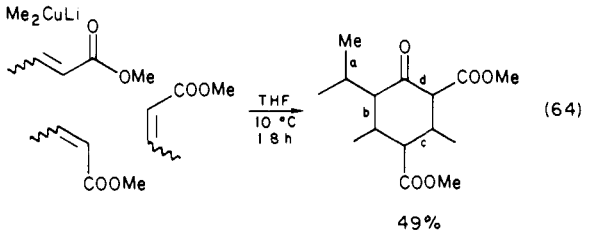
Although 3–5 *ring* bonds are *not* formed in the Ugi four-component condensation process[70] or in Joullié's modification of that process,[71] we refer to these two procedures here because they do represent important multicomponent coupling processes of preparative value in peptide synthesis.

In 1967, a Japanese group studying anion-initiated polymerization of acrylate esters reported an unusual result: mixing equimolar amounts of methyl methacrylate and Et_2NAlPh_2 in toluene at –50 °C produced the cyclic trimer shown in eq 63 (no yield reported).[72] Evidently polymerization was interrupted by a 1,6-Claisen condensation.



(63)

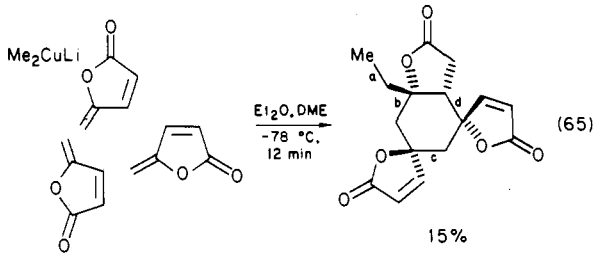
In 1977, Ullenius and co-workers reported a similar observation: excess dimethylcopperlithium in THF at 10 °C initiated a cyclotrimerization of methyl crotonate. Once again, polymerization was interrupted by a 1,6-Claisen condensation (eq 64).[73]



49%

(64)

In 1985, Font and co-workers in Spain published a similar observation: malonate and diorganocopperlithium reagents initiated a cyclotrimerization of protoanemonin, a γ-methylenebutenolide, which terminated with an intramolecular 1,6-Michael addition (eq 65).[74]



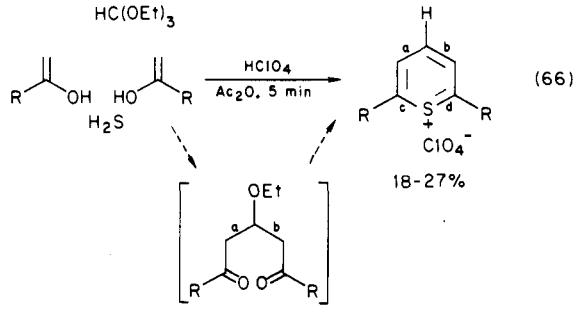
15%

(65)

These three results of sequential *Mi*chael–*Mi*chael–*Mi*chael *r*ing *c*losure (MIMI–MIRC) reactions demonstrate forcefully that anion-initiated polymerization of Michael acceptors[75] can, under appropriate conditions, be regulated to stop when a 1,6-ring closure can occur. That 1,6-ring closure need *not* be an *irreversible* step; we have already seen several examples of 1,6-ring closures involving a *reversible* last step (e.g., eq 19, 40–45, 61).

B. A + B + B + C

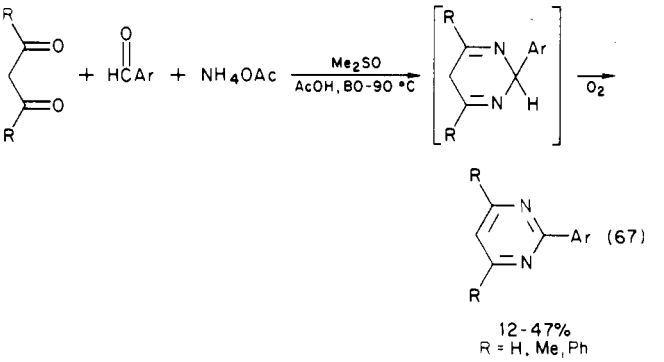
Ethyl orthoformate reacts with 2 equiv of a methyl ketone and with hydrogen sulfide to produce some 2,6-disubstituted thiopyrylium salts; in this one-pot reaction four of the six bonds (a–d) in the thiopyrylium ring are formed (eq 66).[76]



18-27%

(66)

Weis has developed a one-pot four-component coupling process leading initially to 1,4-dihydropyrimidines which are oxidized in situ into the corresponding pyrimidines (eq 67).[77]



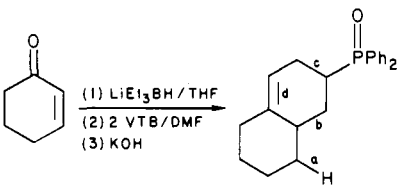
12-47%
R = H, Me, Ph

(67)

C. A + B + C + C

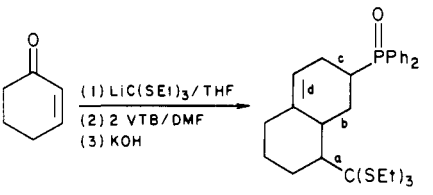
1. 1,6-Wittig

We have shown that, at low temperature (–78 °C), the enolate ion formed by conjugate addition of hydride[53] and of a stabilized carbon nucleophile[78] to 2-cyclohexenone can react under dilute conditions (motor-driven syringe) with only 2 equiv of VTB to produce a new cyclohexene ring via a MIMI–MIRC sequence with a terminal, *irreversible* 1,6-Wittig condensation (eq 68,69).[78]



70%

(68)

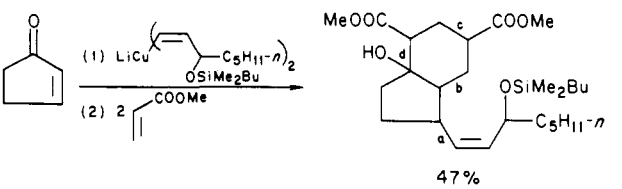


57%

(69)

2. 1,6-Aldol

In a 1979 report from the Syntex laboratories,[79] a single example is given of a one-pot, four-component annulation terminating in a 1,6-aldol ring closure; despite the general reversibility of such intramolecular aldol condensations under aprotic basic conditions, the cyclohexanol adduct was isolated in 47% yield (eq 70).

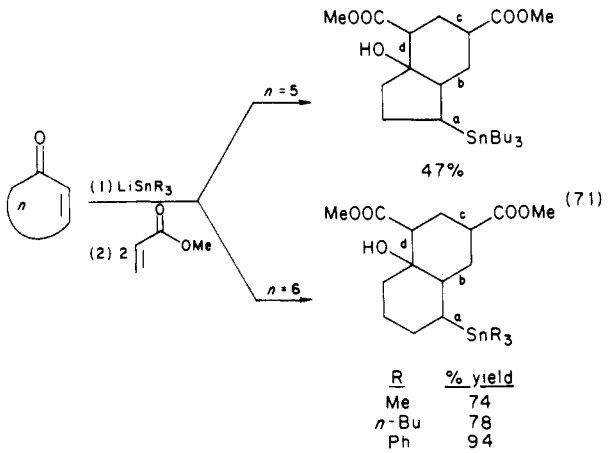


47%

(70)

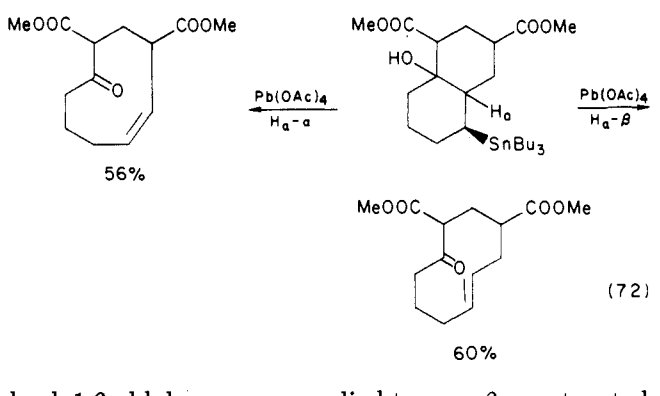
We are developing such quadruply-convergent MIMI–MIRC reactions into a useful, high-yield, one-pot cyclohexannulation synthetic method which does *not* re-

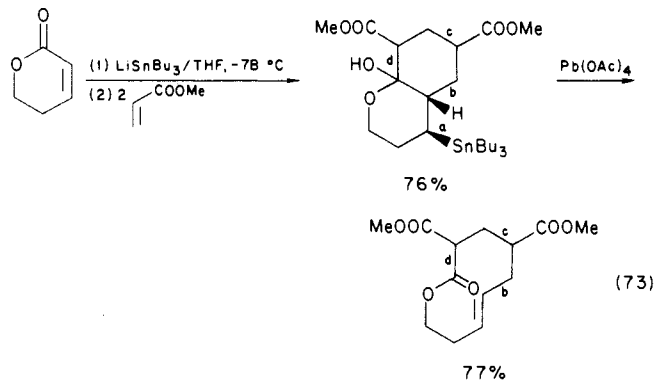
quire high-dilution conditions. Some of our results are shown in eq 71, 73–76.[78] For other 1,6-aldol ring-closures, see eq 40–45 and 61.



R	% yield
Me	74
n-Bu	78
Ph	94

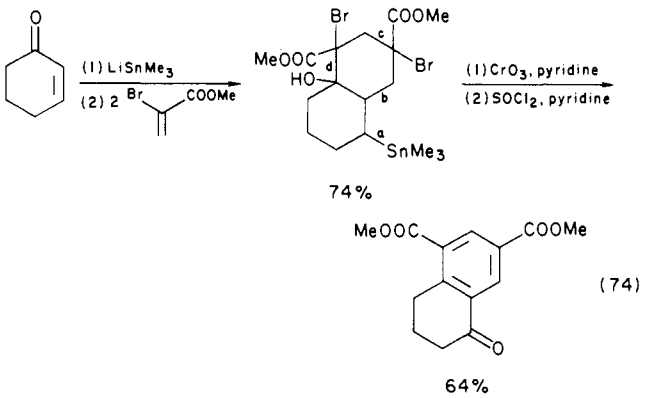
The utility of the γ-hydroxystannanes[80] produced in this annulation process is shown by oxidative fragmentation of the initial cyclohexanol adducts into *n* + 4 ring-expanded cyclic *trans*- or *cis*-ethylenic ketones (eq 72);[78] the same one-pot Michael–Michael–Michael–1,6-aldol sequence applied to an α,β-unsaturated lactone leads to a cyclohexannulation product and then via oxidative scission to an n + 4 ring-expanded, unsaturated macrolide (eq 73).[64] Finally, using 2 equiv

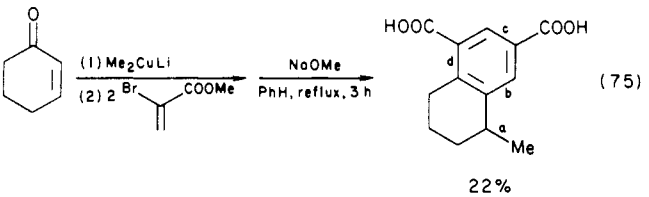




of a 2-bromoacrylate as the third and fourth components in this quadruple coupling process leads to a richly polysubstituted cyclohexanol which undergoes oxidation and then triple elimination to form a *m*-disubstituted benzannulated product (eq 74).[78]

A four-component one-pot annulation followed by aromatization is shown in eq 75 leading to a regiospecifically trisubstituted cyclohexane ring and a regiospecifically tetrasubstituted benzene ring (eq 75).[81]

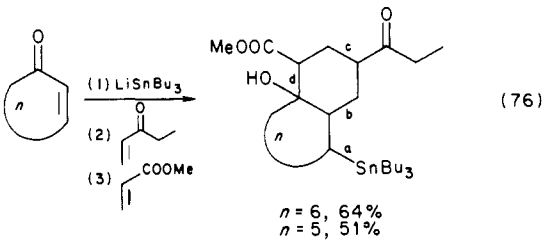




D. A + B + C + D

1. 1+(2+2+2)

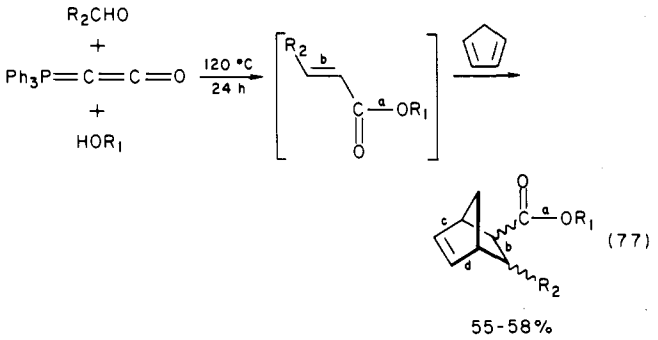
A severe test of just how well one-pot multiple Michael additions under strongly basic aprotic conditions can be controlled involves sequential coupling of three *different* electrophilic Michael acceptors initiated by one nucleophilic Michael donor. Because so many different electrophiles are being used, there exist numerous possible undesirable reaction pathways involving linking of two molecules of the *same* Michael acceptor. By operating in THF at −78 °C and by monitoring the progress of the reaction at each step (by TLC analysis of small aliquots), we have been able to accomplish the four-*different* (A + B + C + D) component 1 + (2 + 2 + 2) MIMI–MIRC reactions shown in eq 76 in which two different α,β-unsaturated ketones



and one α,β-unsaturated ester are joined with a terminal 1,6-aldol cyclization in 51–64% overall yields.[78]

2. 1+2+(2+4)

Bestmann and Schobert have provided two examples of what appears to be a general process for one-pot formation of four new bonds via the consecutive ketene addition, Wittig, Diels–Alder reactions shown in eq 77.[82] The key component in this process is an easily accessible ketenylidenetriphenylphosphorane, and all four components are mixed together at the start of the reaction, thereby demonstrating an extraordinary selectivity of each reagent for its appropriate partner as shown in eq 77.



V. Conclusions

The many structurally diverse and highly successful examples cited in this review demonstrate that one-pot annulations forming three to six bonds in new three to six-membered rings is a ripe area, and this the right time, for vigorous research activity. Design and execution of new one-pot annulations forming three to six bonds will certainly continue to increase the already important preparative value of these multicomponent, multi-bond-forming cyclization reactions. It is hoped that this review will stimulate such activity and will provide an appropriate perspective with which to evaluate the significance of new results. Readers of this review are encouraged to send to the author other examples of multicomponent one-pot annulations forming three to six bonds.

VI. Acknowledgments

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