Introduction

Six-membered carbocycles, which include cyclohexane, benzene, and their derivatives, occur as structural cores in a variety of biologically and pharmacologically active products. Examples of such products include (+)-pancratistatin,1 (-)-tetrodotoxin,2 and other nitrogen-containing polyhydroxylated cyclohexane derivatives, which display a range of biological antitumor, anti-ulcer, and anti-infective properties. The benzene derivative hydragenol shows cytotoxic activity against human gastric cancer cell lines,3 while the benzene derivatives thunberginols C, D, and E promote adipogenesis in murine 3T3-L1 cells.4

The importance of six-membered carbocycles in synthetic chemistry makes them attractive synthetic targets. Particularly noteworthy synthetic strategies involve Diels–Alder reaction ([4+2] fashion),5 Robinson annulation reaction,6 double Michael cyclization ([4+2]),7,8 and [5+1]9c), and [2+2+2] cycloaddition.6 Although [3+3] annulation is widely used to construct heteroatom-containing six-membered rings,10a–d the carbo [3+3] reaction has rarely been reported in the literature. In 1979, Chan et al., applied the [3+3] reaction to arene synthesis,10a and much

[References and notes]

later Langer achieved TiCl₄-catalyzed annulation of 1,3-bis(silyl enol ethers) with 1,3-dielectrophiles using a variety of substrates and reaction conditions.¹⁰ Cyclohexane derivatives can be obtained via α,α’-annulation of enamines with bis-electrophiles such as ethyl α-(bromomethyl)acrylate¹¹ and the substrate scope and efficiency of this reaction has been promoted rapidly along with the prosperity of organocatalysis.¹²

These classic approaches to the carbo [3+3] reaction are increasingly inadequate for meeting the needs of modern chemistry. As a result, a wide array of organocatalytic, metal-catalyzed, and even co-catalyzed asymmetric [3+3] annulations have been developed. These methodologies can be classified according to the electronic properties of the two, three-carbon synthons that participate in the reaction (Fig. 1). Type I carbo [3+3] annulations involve the one-step or stepwise coupling of 1,3-dianions with 1,3-dielectrophiles. Type II reactions involve the addition of anions to electrophiles, followed by free radical cyclization.

**Type I: 1,3-Dianion/1,3-dielectrophile strategy**

α,α’-Annulation of ketones

In 1959, Jung reported his discovery of [3+3] annulation of cyclohexanone 1 with enone 2 in KOH/EtOH (Scheme 1).¹³ Subsequently esterification with diazomethane generated the more complex bicyclo[3,3,1] 3. The mechanism was postulated to involve tandem Michael/aldol addition of the α and α’ carbons of 1 to enone 2.

In 1997, Katritzky discovered that benzotriazole acts as an efficient neutral leaving group. This helped them generate heteroaromatized pyridine derivatives from 2-(benzotriazol-1-yl)acetamide and 2-(benzotriazol-1-yl)acetonitrile.¹⁴ It also allowed them to synthesize 3,5-diarylated substituted phenols (Scheme 2).¹⁵ In this procedure, 1-(benzotriazol-1-yl)propan-2-one 5 was first prepared from bromoacetone with benzaltriazol, and then it was subjected to tandem Michael addition/intramolecular aldol condensation with 1,3-dialyprop-2-enones 4a-g under basic conditions. Subsequent leaving of benzotriazole gave the intermediates 6a-g. After rearrangement, the 3,5-diarylated substituted phenols 7a-g were obtained in moderate to good yields. Electron-deficient Ar₁ or Ar₂ facilitated this reaction (7c–7f), while 2-substituted Ar₂ hindered it (7g).

In 2000, Sharma et al. reported their progress toward synthesizing the C–C linked pseudo-saccharide precursors 11–13 (Scheme 3).¹⁶ These reactions serve their larger goal of transforming sugars into C-glycosides, C-C linked disaccharides, and C-linked spiro saccharides. In their [3+3] approach, those authors used the more delocalized ylide 9 instead of the more nucleophilic phosphonate 9a, ensuring that Michael addition would precede Wittig olefination.¹⁶b During 3-oxo-4-(triphenyl-phosphorylidene)-but-
anoate 9 underwent the Michael addition/intramolecular Wittig sequence with sugar-derived enal 8. 2 equiv of NaH was added and most importantly two drops of water were added to promote annulation.\(^{16}\) Because of the chirality of substrate, the tandem reaction produced 10a, 10b, and 10c as a 6:1:5:2.5 mixture.\(^{17}\) Four-step transformation converted the mixture of major compounds 10a/b into the respective isolable six-membered rings 11, 12, and 13.

Diphenylprolinol silyl ethers have attracted the interest of many chemists after being independently developed by Hayashi's group\(^ {18}\) and Jørgensen's group.\(^ {19}\) In 2009, Hayashi et al. reported using tert-butyldimethylsilyl ether of diphenylprolinol 18 in the \(3+3\) annulation of \(\alpha,\beta\)-unsaturated aldehyde 14 with dimethyl 3-oxopentanedioate 15 (Scheme 4).\(^ {20}\) In this reaction, 15 undergoes enantioselective Michael addition to enaminium salts, produced in situ from 14 and 18, followed by hydration of enamines to give the aldehyde. Subsequent intramolecular Knoevenagel condensation produced \(\alpha,\beta\)-unsaturated ketones 16, and reduction by NaBH\(_4\) afforded 17 in up to 99% ee. These results demonstrate the excellent stereocontrol of Michael addition. Various aromatic aldehydes proved compatible with the reaction. Neither electron-deficient nor electron-rich aromatic substituents significantly influenced the reaction. Interestingly, when 1.5 equiv of dimethyl 3-oxopentanedioate 15 was added, the product 16 did not form but instead a single isomer with a structure similar to that of 24 was obtained in 51% yield.

Subsequently 16a was transformed into 19–21, demonstrating the usefulness of this reaction pathway for natural product synthesis (Scheme 5).

Several months earlier than the Hayashi group, Jørgensen and co-workers reported a similar catalytic reaction in 2008 (Scheme 6). They found that when 2 equiv of 15 reacted with 14 in the presence of \((S)-(\_\_\_\_\_\_)\) \(\alpha,\alpha\)-diphenyl-2-pyrrolidinemethanol trimethylsilyl ether 22 and piperidine, the bicyclic[3,3,1] 24 was obtained instead of Hayashi's adduct 16.\(^ {21}\) Jørgensen's strategy was to achieve in one pot via a relay Michael/aldol reaction using 1.0 excess equiv of 15 with Hayashi's adduct 16 in the presence of piperidine. This approach generated the bicyclic [3,3,1] 24 in up to 93% yield with good enantioselectivity and diastereoselectivity.

\(\alpha,\alpha\)-Annulation of enamines

The \(\alpha,\alpha\)-annulation of enamines with 1,3-dielectrophiles plays an important role in the construction of bicyclo[n.3.1] frameworks.

Many chemists like Lawton\(^ {11a}\) and Stetter\(^ {11b}\) devoted a lot of attention to this chemistry and made substantial progress. Scheme 7 shows the steps in Lawton's \(\alpha,\alpha\)-annulation of enamines.

In 2010, Grainger and co-workers exploited this chemistry to construct the highly substituted cyclohexane framework of phyllamic acid and glochidicins B and D (Scheme 8).\(^ {22}\) They used protected dihydroxyacetone in this procedure as well as a cyclic acetal protecting group, which ensured the desired relative chirality for the two oxygen substituents. The procedure involved the reaction of 1,3-dioxan-5–ones 25 with pyrrolidine to form enamines, which underwent Michael addition to ethyl \(\alpha\)-(bromo-\(\alpha\)-methyl)acrylate. The newly generated iminium tautomized into enamine, which underwent a second Michael addition intramolecularly to the in situ generated \(\alpha,\beta\)-unsaturated ester, affording the bicyclo[3.3.1] framework 27. Ketals 27a and benzylidene acetal 27b were obtained in nearly identical yield around 40%, while the ortho acetal 27c was obtained in 61% yield. The chirality of the acetal can

\begin{center}

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Yield (%)</th>
<th>Dr</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(p)-MeO(\text{Ph})</td>
<td>93</td>
<td>92.8</td>
<td>91</td>
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<tr>
<td>2</td>
<td>2-Furyl</td>
<td>86</td>
<td>94.6</td>
<td>90</td>
</tr>
<tr>
<td>3</td>
<td>(\alpha)-Br(\text{Ph})</td>
<td>86 &gt; 99.1</td>
<td>&gt; 99.1</td>
<td>96</td>
</tr>
</tbody>
</table>

\end{center}
be explained in terms of the chair–boat transition state 26: the phenyl group thermodynamically prefers to be farther from the pyrrolidine ring, while the methoxy group prefers to be closer because it creates an additional anomic stabilizing interaction. The relative chirality of the ester group reflects the kinetic protonation of the reaction.

Given that ethyl α-(bromomethyl)acrylate works well as the 1,3-dielectrophile in these annulation reactions, researchers have also screened enones as possible alternative 1,3-dielectrophiles. In 2007, Movassaghi and Chen reported the framework synthesis of galbulimima alkaloid and himandrine,23 in which formal [3+3] annulation of cyclic enamines with enones played a vital role (Scheme 9). Iminium chloride 28 was transformed into cuprate reagent24 using n-BuLi and CuBr, and this underwent conjugate addition to enone 29, followed by tautomerization from imine to enamine. Intramolecular trapping of enamine 30 generated imine 31a, which was reduced by NaBH₄ to the tricyclic amino alcohol 32. This compound contains the same tricyclic amino alcohol framework as galbulimima alkaloid and himandrine, prompting the authors to propose that modifying the initial reagents slightly could lead to these natural products.

The same research group also reported the catalytic asymmetric synthesis of 31. Imine 33, rather than iminium chloride 28, underwent asymmetric Michael addition with enone 29 in the presence of L-proline catalyst. Subsequent treatment with DBU afforded (−)-31b with 52% ee. After recrystallization, (−)-31b was obtained with 90% ee, meeting the significant requirements of total synthesis (Scheme 10).

In addition to a polycyclic architecture similar to those of other lycopodium alkaloids, (+)-fastigiatine contains an unprecedented pentacyclic core with a C4–C10 bond. In 2010, Shair and co-workers reported the first synthesis of the lycopodium alkaloid (+)-fastigiatine, for which they used a similar [3+3] strategy (Scheme 11) to the one above (Scheme 9).25 Deprotecting 34 using hydrochloric acid generated the α,β-unsaturated ketone 35 in situ. The C6 of the enamine underwent 7-endo-trig Michael addition, and aldol addition of the enamine (generated in situ from imine) to C13 formed product 36. After a straightforward four-step transformation, (+)-fastigiatine was accomplished in 15 steps with nearly 30% overall yield. The Michael addition was highly diastereoselective, probably due to its axial addition onto the C16 methyl group.

Inspired by Jung’s work15 (Scheme 1), Tang and his co-workers changed the 1,3-dielectrophiles of Lawton’s work into enone esters, and invented the asymmetric version by using N-(pyrrolidin-2-ylmethyl)-trifluoromethanesulfonyl amide 39 as the catalyst (Table 1).26 Various cyclic ketones 37 and enone esters 38 were examined. The ester group exerted little influence on yield or enantioselectivity (Table 1, entries 1–3), whereas the X group of cyclic ketones and the R₁ group of enone esters substantially influenced the reaction.

Cyclopentanone and acyclic acetone were also tested with enone ester 41. Unfortunately, the ee value of 42 declined signifi-
significantly, while acetone only gave the 1,2-addition product (Scheme 12).

In 2009, Tang extended the scope of enone esters in this reaction to include (E)-2-nitroallylic acetates, which have properties similar to those of ethyl α-(bromomethyl)acrylate (Scheme 13).²⁹

Pyrrrolidine-thiourea 45 proved to be more efficient than catalyst 39 (Table 1), giving the bicyclic[3,2,1] 46 in up to 98% ee. As in previous work (42 in Scheme 12 vs entry 1 in Table 1), the bicyclic[3,2,1] 46b was obtained in higher yields than 46a but with

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**Table 1**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Product</th>
<th>Yield (%)</th>
<th>ee (%)</th>
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<tr>
<td>1</td>
<td>X = CH₂, R¹ = Ph, R² = Me</td>
<td>80</td>
<td>90</td>
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<td>2</td>
<td>X = CH₂, R¹ = Ph, R² = Et</td>
<td>74</td>
<td>91</td>
</tr>
<tr>
<td>3</td>
<td>X = CH₂, R¹ = Ph, R² = Bn</td>
<td>76</td>
<td>91</td>
</tr>
<tr>
<td>4</td>
<td>X = CH₂, R¹ = p-MeO-Ph, R² = Me</td>
<td>77</td>
<td>87</td>
</tr>
<tr>
<td>5</td>
<td>X = CH₂, R¹ = p-Ph-Ph, R² = Me</td>
<td>80</td>
<td>90</td>
</tr>
<tr>
<td>6</td>
<td>X = CH₂, R¹ = Ph, R² = Me</td>
<td>77</td>
<td>90</td>
</tr>
<tr>
<td>7</td>
<td>X = CH₂, R¹ = Me, R² = Et</td>
<td>56</td>
<td>94</td>
</tr>
<tr>
<td>8</td>
<td>X = O, R¹ = Ph, R² = Me</td>
<td>66</td>
<td>90</td>
</tr>
<tr>
<td>9</td>
<td>X = N(Me), R¹ = Ph, R² = Me</td>
<td>92</td>
<td>80</td>
</tr>
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</table>

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**Table 2**

<table>
<thead>
<tr>
<th>Entry</th>
<th>X</th>
<th>Yield (%)</th>
<th>endo/exo</th>
<th>ee of endo product (%)</th>
</tr>
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<tr>
<td>1</td>
<td>X = O</td>
<td>78</td>
<td>&gt;98:2</td>
<td>93</td>
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<tr>
<td>2</td>
<td>X = CH(CH₃)</td>
<td>84</td>
<td>&gt;98:2</td>
<td>89</td>
</tr>
<tr>
<td>3</td>
<td>X = CH(O-Me)</td>
<td>60</td>
<td>&gt;98:2</td>
<td>95</td>
</tr>
<tr>
<td>4</td>
<td>X = CH(²Bu)</td>
<td>74</td>
<td>&gt;98:2</td>
<td>81</td>
</tr>
<tr>
<td>5</td>
<td>X = -OCH₂CH₂O⁻</td>
<td>76</td>
<td>&gt;98:2</td>
<td>98</td>
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</tbody>
</table>

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**Scheme 12.** Tang’s organocatalytic [3+3] annulation of cyclopentanone and acetone.

**Scheme 13.** Tang’s organocatalytic [3+3] annulation involving pyrrolidine-thiourea.

**Scheme 14.** Hu’s metal-catalyzed [3+3] annulation of 50.
slightly lower enantioselectivity. Similar to the low levels of 43 (Scheme 12), 46c was not even detected. These results suggest that these asymmetric [3+3] annihilations are more likely to form bicyclo[3.3.1] (Table 1, entries 1–9 and Scheme 13, 46a) than bicyclo[3,2,1] (Scheme 12 and 42 and Scheme 13, 46b) or a six-membered ring (Scheme 12 and 43 and Scheme 13, 46c), making this approach potentially powerful for constructing nitrogen-substituted six-membered rings.

It may be possible to use metal–allylidenes generated from propargyl alcohols or their derivatives as 1,3-dielectrophiles in this reaction. Theoretical and experimental studies indicate that these compounds have electrophilic centers on Cx and Cy.

In 2012, Hu and co-workers exploited this possibility to make substantial progress toward constructing the bicyclo[2.3.1], bicyclo[3.3.1] and bicyclo[4.3.1] skeleton via an asymmetric [3+3] strategy (Table 2, Schemes 14 and 15).28 This procedure involved a,γ-annulation of enamines via a metal–allylidenic intermediate generated from propargyl alcohol derivative 47. As the mechanism (Scheme 15) showed, nucleophilic attack of enamines 48 affords Cu-acetylide complex 50b, which underwent a H shift to give the Cu-vinyldiene complex 50c. Further intramolecular nucleophilic attack finished the [3+3] annulation. And the combination of Cu(OAc)₂·H₂O and chiral tridentate ferrocenyl-P,N,N ligand 51 gave the endo-adduct 49a in moderate to good yields with good enantioselectivity and excellent endo-selectivity. These standard conditions need to be modified slightly when using enamines 52a and 52b in the reaction. More reactive 51 should be used instead of propargyl alcohol acetate 47, and the base, temperature, and solvent need to be adjusted (Scheme 14).

Nitro-enals also show promise as 1,3-dielectrophiles for this reaction. Alonso and co-workers reported a general method to synthesize β-(hetero)aryl-α-nitro-α,β-enals in 2008.29 In 2006, Alonso and co-workers used α,γ-annelation of enamines to construct the polyhydroxylated cyclohexane ring of the potential antitumor agent (+)-pancratistatin (Fig. 2).30 They utilized the β-(hetero)aryl-α-nitro-α,β-enal 56 as biselectrophile, while commercially available 2,2-dimethyl-1,3-dioxan-5-one 57 reacted with pyrrolidine to form the enamine. Fortunately, nitro-enals 56 reacted with enamine in the presence of PPTS, creating five stereocenters in one step (Scheme 16). This method led to 58b in 42% yield. After further six-step transformations, (−)-7-deoxy-2-epi-pancratistatin tetracetate (Fig. 2) was prepared on gram scale from 56c and 57 in seven steps with 10% overall yield.

Alonso’s group later resorted to enantioselective [3+3] annulation.31 After screening various catalysts, such as proline and its
derivatives, (R)-2-(methoxymethyl)-pyrrolidine was found to be the best, giving 58c in 75% ee and up to 99% ee after crystallization (Scheme 17). After further eight-step transformations, (+)-pancratistatin was produced from (–)-7-deoxypancratistatins can be synthesized in the same way. It is assumed that (+)-7-deoxypancratistatin can be synthesized in nine steps. Since the enamines generated by ketones can undergo [3+3] self-condensation of crotonaldehyde (Scheme 18). Since the enamines generated by ketones can undergo [3+3] self-condensation of crotonaldehyde (Scheme 18). Since the enamines generated by ketones can undergo [3+3] self-condensation of crotonaldehyde (Scheme 18).


\[ \text{Method A: catalyst, CH}_3\text{CN, 25 }^\circ\text{C, }25\text{ min.} \]  
\[ \text{Method B: catalyst, } \text{TiCl}_4, \text{DCM, -78 to } 20^\circ\text{C.} \]  
\[ \text{Method C: catalyst, CH}_3\text{CN, 25 }^\circ\text{C, 25 min.} \]

Using this methodology, Alonso and co-workers completed the total synthesis of (±)-tetrodotoxin (Fig. 2) in 2010\(^\text{32}\) and developed a concise pathway to the dioxaadamantane core (55 and 6-epi-55) (Fig. 2) of (±)-tetrodotoxin in 2014\(^\text{31}\).

**α,α’-Annulation of enamines**

Since the enamines generated by ketones can undergo α,α’-annulation with 1,3-dielectrophiles, the enamines made from α,β-unsaturated aldehydes should also act as 1,3-dianions at Cα and Cγ.

In 2006, Hong and co-workers reported the first asymmetric [3+3] self-condensation of crotonaldehyde (Scheme 19).\(^\text{34}\) The enamine reacted with the iminium through the (E)-TS instead of the (Z)-TS (Fig. 3), forming the chiral methyl center in the (s)-adduct. This mechanism may reflect high energy due to steric hindrance in (Z)-TS. Subsequent intramolecular aldol addition of enamine to carbonyl gave aldehyde 59/60 (50:44) along with little aromatic product 61 through dehydroxylation and aromatization. Aldehydes 59 and 60 are important intermediates in the total synthesis of (−)-isopulegol hydrate and (−)-cubebaol, respectively.

### Table 3

Hong’s comparison of [3+3] and [4+2] annulations

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Method</th>
<th>Cat. I yield (%)</th>
<th>Cat. II yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>R1 = R2 = H, R3 = CH3</td>
<td>Method A</td>
<td>81 (96:4)</td>
<td>20 (100:0)</td>
</tr>
<tr>
<td>2</td>
<td>R1 = R2 = H, R3 = Ph</td>
<td>Method A</td>
<td>78 (100:0)</td>
<td>23 (100:0)</td>
</tr>
<tr>
<td>3</td>
<td>R1 = R2 = H, R3 = Ph</td>
<td>Method C</td>
<td>80 (100:0)</td>
<td>48 (48:52)</td>
</tr>
<tr>
<td>4</td>
<td>R1 = H, R2 = CH3</td>
<td>Method C</td>
<td>75 (82:18)</td>
<td>80 (16:74)</td>
</tr>
<tr>
<td>5</td>
<td>R1 = H, R2 = Pr, R3 = Bu</td>
<td>Method B</td>
<td>71 (10:90)</td>
<td>75 (1:99)</td>
</tr>
<tr>
<td>6</td>
<td>R1 = CH3, R2 = H, R3 = Ph</td>
<td>Method B</td>
<td>80 (100:0)</td>
<td>ND</td>
</tr>
</tbody>
</table>

Reagents and conditions: Method A: catalyst, CH3CN, 25 °C. Method B: catalyst, MnO2, MeCN, reflux. Method C: (1) catalyst, CH3CN, 25 °C and (2) DDQ, C6H6, reflux.

### Table 4

Molander’s [3+3] annulations

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product</th>
<th>Yield (%)</th>
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<tr>
<td>1</td>
<td>75</td>
<td>78</td>
<td>50</td>
<td>4.9:1</td>
</tr>
<tr>
<td>2</td>
<td>76</td>
<td>77</td>
<td>52</td>
<td>9:1</td>
</tr>
<tr>
<td>3</td>
<td>77</td>
<td>78</td>
<td>60</td>
<td>9:1</td>
</tr>
</tbody>
</table>


Scheme 20. Langer’s [3+3] annulation strategy to framework synthesis of hydrangenol and thunberginol.

α,α’-Annulation of enamines

Since the enamines generated by ketones can undergo α,α’-annulation with 1,3-dielectrophiles, the enamines made from α,β-unsaturated aldehydes should also act as 1,3-dianions at Cα and Cγ.

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In 2007, Hong and co-workers systematically studied [3+3] and [4+2] approaches to synthesizing aromatic aldehydes (Table 4). In that study, two catalyst systems were tested on various α,β-unsaturated aldehydes; the combination of pyrrolidine with acetic acid gave much higher yields and selectivity of the [3+3] annulation reaction than proline did. Results also showed that the R3 group exerts little influence on selectivity (Table 3, entries 1–3), whereas R1 and R2 groups play a decisive role (Table 4, entries 4–6).

**Annulations of 1,3-bis(silyl enol ethers)**

Langer and co-workers capitalized on Chan’s [3+3] annulation involving 1,3-bis(silyl enol ethers) 67 with 1,3-dielectrophile 66 to form arenes (Scheme 19). They used this approach to construct various highly functionalized arenes, which they reported in 2006.11

Utilizing this [3+3] strategy, Langer and his colleagues synthesized the framework of hydrangenol and thunberginol C and D in 2008. They used 1,3-bis(silyl enol ether) 67 with 1,3-dielectrophile 69, which was obtained from acetylacetone and benzaldehyde in two steps (Scheme 20). In the same year, the same research group synthesized the framework of the dye Alizarin Yellow R using diazene 73 as the 1,3-dielectrophile (Scheme 21). Diazene 73 was prepared from aniline in two steps.

A possible mechanism for the formation of 71 is outlined in Scheme 20. The more reactive terminal carbon atom of 67 undergoes conjugate addition to 69, followed by cyclization to give intermediate 72c. The Sn2 reaction of the chloride anion with the carbon atom which attached to the phenyl group generates the product 71.

**Annulations of other 1,3-dianionic synthons**

In 1987, Molander and co-workers reported a stereo-controlled [3+3] approach to six-membered carbocycles. They first prepared epoxy aldehyde 75 by Sharpless asymmetric epoxidation/Swern oxidation of allylic alcohol, then treated it with 3-iodo-2-[(trimethylsilyl)methyl]propene 76 in the presence of SnF2 (Scheme 22). The allyltin trihalide generated from 76 and SnF2, underwent an aldol reaction with the carbonyl in the Felkin–Anh fashion with good diastereoselectivity. Then Sn2 co-catalyzed the nucleophilic addition of allylsilane to the epoxide ring. The six-membered annihilation product was generated in moderate yields with moderate to good selectivity. Consistent with the fact that the reaction proceeds through intermediate 77, stereo-controlling on the annulation reaction was easier using E oxides (entries 2 and 3) than Z oxides (entry 1), which display lower diastereoselectivity due to steric hindrance.

**Figure 4. Cid’s [3+3] annulation strategy to cyclohexenylamines.**

In 2001, Ila and Junjappa wrote a mini-review on the synthesis of naphthalenes and other condensed aromatic rings via treatment of α-oxoketene dithioacetals 79 with allyl anions and Lewis acid (Scheme 22). In this approach, allyl metal anions (Grignard and lithium reagents) underwent 1,2-addition or sequential 1,4- and 1,2-addition to form carbinols 80a and 80b. After cycloaromatization in the presence of BF3.Et2O, carbinols 80a/b were transformed into the corresponding arenes. The regioselectivity of the allyl anions may be attributed to the hard–soft match principle as well as to steric effects. Organocuprate reagents promoted a one-pot addition–cycloaromatization reaction in the presence of TMSCl and TMEDA. In contrast, the stabilized benzyl carbanions derived...
from arylacetonitriles or benzyl phenyl sulfones underwent only 1,4-addition to give carbinols 80c, which cycloaromatized in the presence of H3PO4. In the case of β-oxoketene dithioacetals 81, obtained by reducing α-oxoketene dithioacetals 80, only 1,2-addition occurred and the corresponding carbinol 80d was transformed into naphthalene via the same Lewis acid-catalyzed cycloaromatization.

Cyclohexenylamine moieties are important synthons in the preparation of various natural products. While [4+2] annulations of non-activated dienes with nitroalkenes require harsh conditions,22 introducing an electron-withdrawing group allows the reaction to proceed efficiently under mild conditions.23,24 However, this group must subsequently be removed, so identifying mild, efficient ways to do so should be a priority for future investigation. In 2013, Cid and co-workers reported their investigations into a new asymmetric [3+3] procedure to generate this moiety (Fig. 4).23a

Pre-bis(nucleophile) 83 was prepared from sulfone 82 in 90% yield, and it underwent asymmetric Michael addition with α,β-unsaturated aldehyde 84 via iminium activation in the presence of diphosphinolyl silylethoxymethyl ether 85 (Scheme 23). Subsequent intramolecular Julia–Kocienski olefination in the presence of Cs2CO3 generated olefin 87. Using DBU and low temperature significantly increased the diastereoselectivity. Reduction by H2 afforded amine 88 in 98% ee and 90:10 de, demonstrating absolute stereocontrol of Michael addition and the importance of DBU. This stepwise Michael addition/intramolecular Julia–Kocienski olefination generated the cyclohexenylamine moieties 88 from 82 in five steps with perfect enantioselectivity, satisfying the requirements of the enantioselective synthesis of trandolapril (Scheme 23). This approach is more efficient than the low-yield Diels–Alder reaction and subsequent enzymatic resolution of the racemate.23b

In 2013, Li and co-workers accomplished the total synthesis of (+)-hirsutene and (+)-capnellene via [3+2] annulations (Scheme 24).24 In this approach, the key intermediate 89 acted as both anion synthon and electrophile synthon at different stages. In the [3+3] approach, it can also serve as 1,3-dianionic synthon to react with methyl acrylate and construct the framework 94a of eudesmane sesquiterpene.

Allylsilane 91, which is easily prepared from readily available (+)-carvone derivative 90, underwent coupling with methyl acrylate in the presence of Ni(0)–pyridine catalyst to afford ester 92 in 80% yield. Subsequent reduction by Dibal-H generated aldehyde 93, which underwent SnCl4-catalyzed aldol reaction with allylsilane to form 94a/94b. Interestingly, solvent and temperature played a vital role in this transformation: 94a was produced in 61% yield only if 1,2-dichloroethane was used as the solvent and the temperature was −20°C; 94a/94b (1:3) was produced in 52% yield with dichloromethane solvent at −90°C (Scheme 25).

Type II: Allylation/radical cyclization strategy

While Type I approaches to [3+3] annulation involve 1,3-dianions and 1,3-dielectrophiles, an alternative strategy is a sequence of
Lewis acid-catalyzed allylation and free radical mediated annulation. In 1991, Ward et al. reported the application of the conjunction reagent 3-phenylthio-2-(trimethylsilylmethyl)-propene 96. This compound underwent TiCl4-mediated allylation with acetal 95 in a so-called 'two electron' process that formed 97. Subsequent free radical-mediated cyclization, as a so-called 'one electron' process, ultimately afforded 98 (Scheme 26). These two steps generated a six-membered ring. The regioselectivity (6-endo-dig vs 5-exo-trig) may reflect the importance of the phenylthiomethyl substituent on the olefin and chairlike transition states. Attempts to alter the substituents on 95 and the reaction temperature gave disappointing results, particularly because of the low selectivity.

In 1994, Ward et al. applied this method to the synthesis of (+)-actinobolin and bactobolin (Scheme 27). Aldehyde 99 underwent the 'two electron' process with 3-phenylthio-2-(trimethylsilylmethyl)-propene 96 to give alcohol 100 with chelation-controlled selectivity. Several subsequent transformations led to 101a. The 'one electron' process under hv generated the cyclization product 102 in 40% yield with excellent diastereoselectivity. A further three-step transformation afforded 103, which is the key precursor of (+)-actinobolin and bactobolin. One year later, the group announced a modification to this synthetic route: sulfide of (+)-actinobolin and bactobolin. This modification lead to intermediate 104 with allenylsilanes 105 (Scheme 28). One possible mechanism occurs as follows (Scheme 29): the Michael addition of allenylsilane 105 to α,β-unsaturated acylsilane 104 gives vinyl cation 108, and the subsequent 1,2-TMS shift and intramolecular cyclization lead to intermediate 110. Ring expansion occurs via vinyl shift to the carbonyl, and the newly generated cation 111 undergoes the second TMS shift, followed by desilylation to give the [3+3] products 106 and 107.

Interestingly, the vinyl shift from 110 to 111 would be interrupted to give the [3+2] annulation products if changing 104 into t-butylidimethyl acylsilane, minimizing the reaction time (<2 min) and keeping the reaction temperature not exceeding −78 °C. In 2010, Liu and co-workers published their tandem dealkoxylation/[3+3] annulation reaction involving acetalallene. This may prove a powerful approach for constructing the central core of dichroanal B (Scheme 30).

Other annulation strategies

In 1995, Danheiser and Fink discovered that TiCl4 catalyzes the [3+3] cyclization of 2-alkyl-substituted α,β-unsaturated acylsilanes with allenylsilanes 105 (Scheme 28). Another possible mechanism occurs as follows (Scheme 29): the Michael addition of allenylsilane 105 to α,β-unsaturated acylsilane 104 gives vinyl cation 108, and the subsequent 1,2-TMS shift and intramolecular cyclization lead to intermediate 110. Ring expansion occurs via vinyl shift to the carbonyl, and the newly generated cation 111 undergoes the second TMS shift, followed by desilylation to give the [3+3] products 106 and 107.

Interestingly, the vinyl shift from 110 to 111 would be interrupted to give the [3+2] annulation products if changing 104 into t-butylidimethyl acylsilane, minimizing the reaction time (<2 min) and keeping the reaction temperature not exceeding −78 °C. In 2010, Liu and co-workers published their tandem dealkoxylation/[3+3] annulation reaction involving acetalallene. This may prove a powerful approach for constructing the central core of dichroanal B (Scheme 30). After screening numerous catalysts like [Au], [Ag], [Cu], [Pt], and Lewis acid, the authors identified PPh3AuSbF6 as the most powerful catalyst. Reacting the acetalallene 112 with 1.0 equiv of 2-phenyllallylsilane 113 gave 104 with allenylsilanes 105 (Scheme 28). Another possible mechanism occurs as follows (Scheme 29): the Michael addition of allenylsilane 105 to α,β-unsaturated acylsilane 104 gives vinyl cation 108, and the subsequent 1,2-TMS shift and intramolecular cyclization lead to intermediate 110. Ring expansion occurs via vinyl shift to the carbonyl, and the newly generated cation 111 undergoes the second TMS shift, followed by desilylation to give the [3+3] products 106 and 107.

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the annulation product 114 as the major product in 76% yield, along with 115 in 9% yield. Using 2.0 equiv of 113 afforded 115 as the major product in up to 82% yield. These results can be explained by proposing the following mechanism: initial Prins cyclization \(^\text{116}\) turns 112 into allylic cation 116, which undergoes [3+3] annulation with one molecule of 113 to give intermediate 117. After deprotonation, 114 is obtained. If one more equiv of 113 is added, 117 can capture another molecule 113 to form 115. The innate chirality of 117 seems the most likely reason for the diastereoselectivity of 115. Using 2-siloxymethylallylsilane \(^\text{118}\) instead of 113 gave the aldehyde 120a/120b in the presence of TEA after standard [3+3] reaction conditions (Scheme 31). Even more complex and novel structures have been obtained in a similar manner.

Benzo[\(\alpha\)]fluorene and its derivatives, which contain a tetracyclic skeleton, occur in numerous natural products. Some polyhydrobenzo[\(\alpha\)]fluorenes act as bone loss inhibitors or estrogen receptors, making them attractive targets for synthetic chemists. In 2012, Sanz and co-workers reported the gold(I)-catalyzed intramolecular [3+3] annulation of \(\alpha\)-alkynylstyrenes to prepare benzo[\(\alpha\)]fluorene derivatives (Scheme 32). \(^\text{52}\) First, \(\alpha\)-alkynylstyrenes 121 underwent intramolecular cyclization to give intermediate 123 in the presence of [Au], which underwent a H-shift to give cation 124. Intramolecular nucleophilic attack generated 6,6α,6α'-dihydro-5H-benzo[\(\alpha\)]fluorenes 122, which subsequent heating transformed into 6,11-dihydro-5H-benzo[\(\alpha\)]fluorenes 122. Asymmetric catalysis was thought to require 122 in order to form the chiral intermediate 123. This approach has ultimately led to good yield, but enantioselectivity remains low.

Like benzo[\(\alpha\)]fluorenes, carbazoles are also widespread in various biological natural products, such as tubingensin A, clausenine, clausenol, and P7C3 (Fig. 5). \(^\text{52}\) They also play an important role in photorefractive materials and organic dyes. In 2014, Wang and co-workers reported a novel Yb(OTf)3-catalyzed [3+3] strategy to generate these structures. \(^\text{53}\) Propargylic alcohol 124 was transformed into allenic carbocation in situ by dehydroxylation in the presence of Yb(OTf)3, which underwent a Friedel–Crafts reaction to form intermediate 126. Subsequent 1,5-H shift, electrocyclic reaction, and 1,2-aryl shift generated intermediate 130, which underwent deprotonation to give product 131 (Scheme 33). Studies with deuterium-labeling have corroborated this mechanism.

When electron-rich benzylic alcohol 133 was used instead of indole-2-methanol 125 (Scheme 34), the [3+3] product 134 was generated in 74% yield. The mechanism may be similar to that described above. Various propargylic alcohols were screened in the reaction with 125 or 133, and moderate to good yields were obtained.

**Conclusions**

This review gives an overview of the formal carbo [3+3] strategy to form six-membered carbocycles. The \(\alpha,\alpha'\)-annulations of ketones...
The biological usefulness of the annulation products ensures the power of this tool in organic chemistry.

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References and notes


7. Acknowledgment

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