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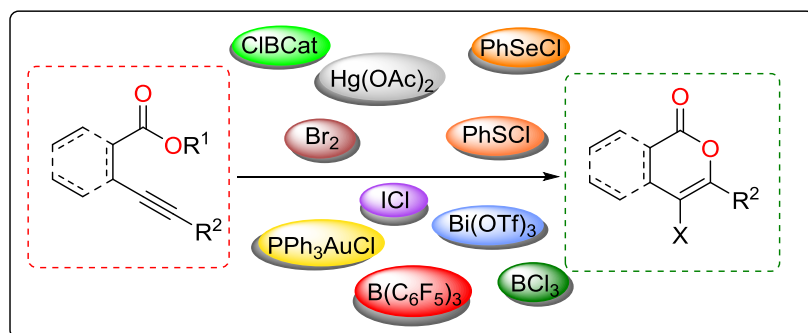
A Comparative Assessment of Modern Cyclization Methods of Substituted Alkynyl Esters, Ethers and Acids.

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Abstract Naturally occurring heterocycles such as pyrones, dihydropyrones and isocoumarins have proven to be highly active biological agents with a vast plethora of applications. Therefore, their synthesis has attracted mentionable notice in recent decades. Of particular synthetic use is the cyclization of substituted alkynyl esters. More recently main group compounds have been studied to affect this synthetic pathway giving access to a large family of heterocyclic derivatives.

Key words 2-pyrone, isocoumarin, dihydropyrone, tris(pentafluorophenyl)borane, electrophiles, tandem, dual catalysis, cyclization

Pyrones and their lactone substructures (Figure 1), especially isocoumarins and dihydropyrones are an important class of naturally occurring lactones which possess a wide range of physicochemical properties.^[1] Derivatives of such compounds have proven to be effective antimicrobial agents,^[2] with additional applications as antibiotic,^[3] anti-inflammatory,^[4] antiviral,^[5] antispasmodic,^[6] and purgative properties.^[7] In addition to these, they are also considered in many cases to be a non-steroidal antagonist to a variety of receptors like the androgen receptor (AR)^[8] or the pregnane X receptor (PXR).^[9] Some 2-pyrones have also qualified as inhibitors for enzymes like the HIV-1^[10] and serine proteases.^[11]

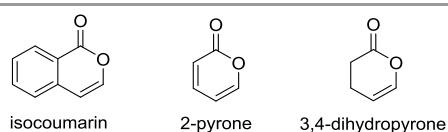
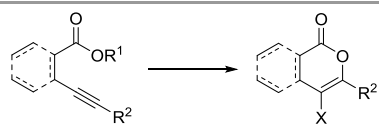


Figure 1 Three biologically active lactone structural motifs.



Rebecca L. Melen studied Natural Sciences at Cambridge University, majoring in Chemistry. Rebecca then continued at Cambridge, completing her PhD in 2012 under the guidance of Prof. Dominic Wright with work focusing on research into catalytic and stoichiometric dehydrocoupling reactions using main group compounds. After two postdoctoral positions at the University of Toronto (Canada) and the University of Heidelberg (Germany), Rebecca took up a lectureship at Cardiff University in 2014 where she has recently been promoted to Senior Lecturer. Rebecca has been the recipient of several award including the RSC Dalton Young Researcher Award (2013), the European Researcher Award (2014) and the Clara Immerwahr Award (2016). Her research themes involve synthesis and catalysis using main group reagents.

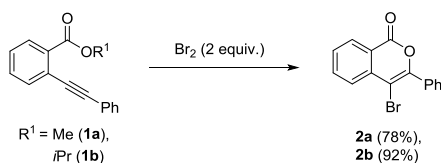
Unsurprisingly the production of these heterocyclic lactone derivatives has been extensively studied with many elegant syntheses being present in the literature using various intermolecular processes such as cascade reactions of propiolic acids or esters with alkynes using gold/silver bimetallic couplings^[12] or ruthenium catalysts.^[13] Alternative methods involve ring expansion of β -lactones as well as inverse Diels-Alder-type chemistry based on reports by Boger and Mullican,^[14] which were subsequently expanded by Yamashita *et al.*^[15] Another approach to form these compounds is the intramolecular cyclization of alkynyl esters (Scheme 1).



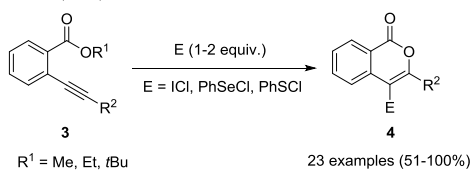
Scheme 1 Generalized intramolecular cyclization of alkynyl esters to generate heterocyclic products.

In 1984, notable work by Gandour *et al.* exhibited how an *in situ* generated electrophilic bromonium ion can promote a 6-*endo-dig* cyclization yielding the 4-bromo isocoumarin **2** with concomitant dealkylation of the ester functional group (Scheme 2, top).^[16] Larock *et al.* then widened this scope by using other main group electrophiles such as iodine (I) chloride, phenylselenenylchloride or phenylsulfenylchloride observing similar reactivity to that discussed by Gandour, with the alkyl ester group being eliminated as an alkyl halide (Scheme 2, bottom).^[17]

Gandour (1984)

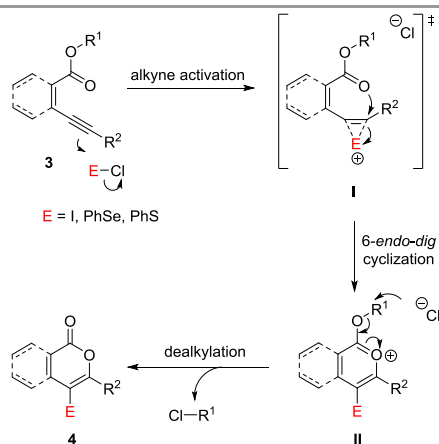


Larock (2003)



Scheme 2 Electrophilic cyclization by Gandour and Larock.

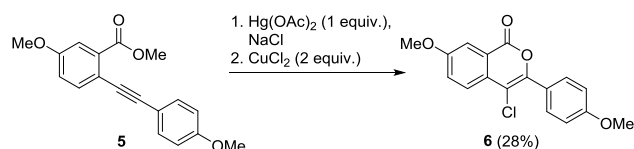
Mechanistically, it is thought that this reaction proceeds *via* three main steps; 1) the electrophile activates the alkyne **3** forming the cationic selenonium or iodonium η -2 intermediate **I** which then undergoes; 2) a 6-*endo-dig* cyclization whereby the carbonyl oxygen acts as the nucleophile to generate the pyrylium intermediate **II** followed by; 3) dealkylation through alkyl group abstraction to liberate the alkyl halide and the γ -substituted cyclized isocoumarin **4** (Scheme 3).



Scheme 3 Proposed mechanism of the electrophilic cyclization.

In a similar fashion, Katzenellenbogen *et al.* used stoichiometric amounts of mercury (II) acetate to conduct the initial cyclization with the subsequent addition of two equivalents of copper (II) chloride to replace the mercury in the γ -position with a chloride to generate **6** (Scheme 4).^[18] While this is conceptually an interesting route to form such lactone products, the use of superstoichiometric amounts of reagent, in addition to the inherent toxicity of mercury, make this process much less desirable than other catalytic methodologies.

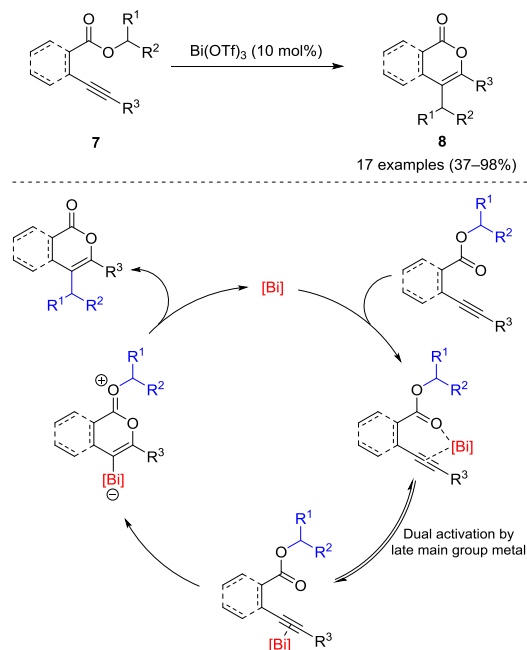
Katzenellenbogen (2005)



Scheme 4 Stoichiometric cyclization using sequential transition metal mediated rearrangements.

In a bid to utilize late *p*-block elements in similar *intramolecular* cyclizations, and move away from transition metals, Takaki *et al.* showcased the dual-activation of alkynyl esters using bismuth (III) triflate.^[19] In this work Takaki defined bismuth as a main group metal capable of both σ -activation of the carbonyl oxygen as well as a π -activation of the unsaturated carbon-carbon bond of **7** bringing the reaction sites (ester and alkyne) within proximity of one another. The cycle is continued with an *intramolecular* 1,5-migration of the ester substituent, in this case a phenylethyl or benzhydrol moiety. This results in the liberation of the cyclized product **8** in generally good yields between 37-98% with a range of substituents on both the pyrone backbone as well as the alkyne terminus (Scheme 5).

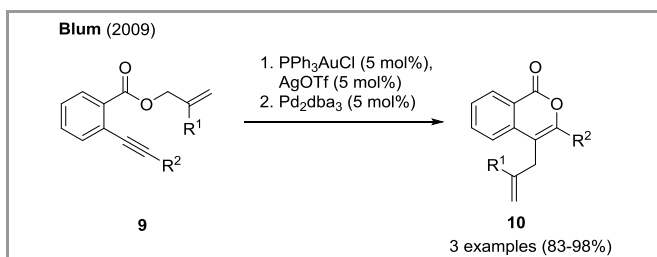
Takaki (2008)



Scheme 5 Catalytic cyclization *via* dual activation by a late main group metal and proposed mechanism.

Deviating away from main group centered catalysts again, Blum *et al.* set forth an approach using a cooperative bimetallic

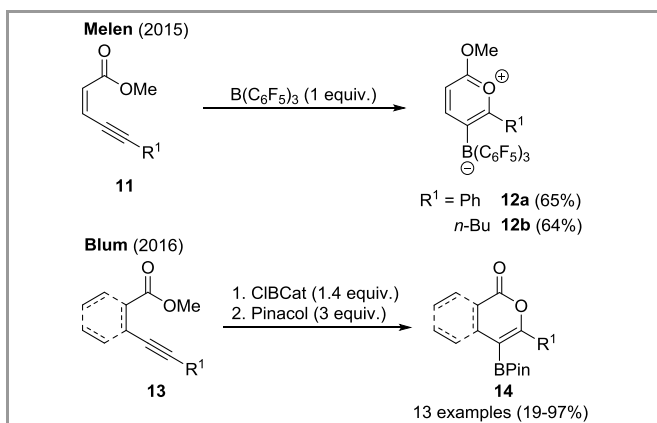
gold/palladium catalytic system (Scheme 6).^[20] Expectedly, the gold (I) chloride catalyst readily undergoes the initial cyclization with **9** to form the oxoauration intermediate in the form of oxonium triflate ion pair, reminiscent of pyrylium borates synthesized within our group (*vide infra*)^[21] and the mercurial isocoumarin intermediate proposed by Katzenellenbogen.^[18] This activated allyl moiety then undergoes a palladium shuttling mechanism to affect a carbodeauration process, thus generating the isocoumarin products **10** in excellent yields of 83-98% using as little as 5 mol% catalyst loading.



Scheme 6 Blum *et al.* using a dual catalytic system to cyclize and migrate the ester substituent.

As stated above, some of the most common applications of pyrones and isocoumarins stem from the pharmaceutical and agrochemical sector,^[22] therefore the use of potentially toxic heavy metals is heavily regulated by international bodies with their removal having a significant impact on total production costs. To combat this, in addition to methods mentioned earlier, an alternative metal-free pathway to complex substituted pyrone subunits is currently a field that is under intense development.^[23]

Early work within our group using the bulky Lewis acid $\text{B}(\text{C}_6\text{F}_5)_3$ in conjunction with alkynyl methyl esters **11** furnished the pyrylium borate products **12** as an isolable crystalline solid,^[21] presumed to proceed *via* a similar *trans*-oxyboration mechanism observed previously (Scheme 7, top).^[24] Using this route we could isolate these zwitterionic products in good yields of 65% and 64% for the phenyl and *n*-butyl substituted moieties respectively. In contrast, when including a *tert*-butyl group in the terminal position of the alkyne, all reactivity was quenched with the carbonyl-borane Lewis adduct prevailing, presumably due to the steric obstruction of the alkyne preventing successful activation by the encumbered borane.

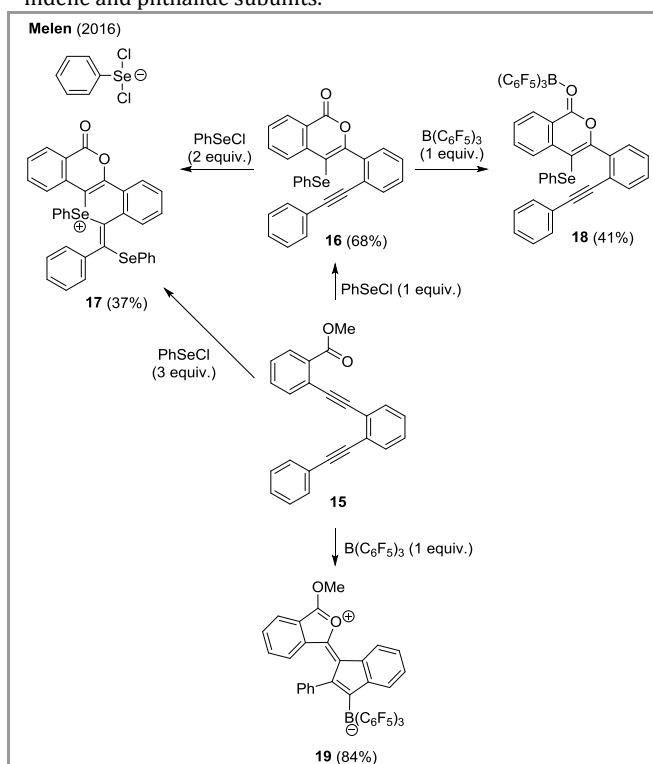


Scheme 7 Metal-free electrophilic cyclization using various boranes.

Building on this, and their own previous findings, Blum and co-workers presented a similar stoichiometric metal-free

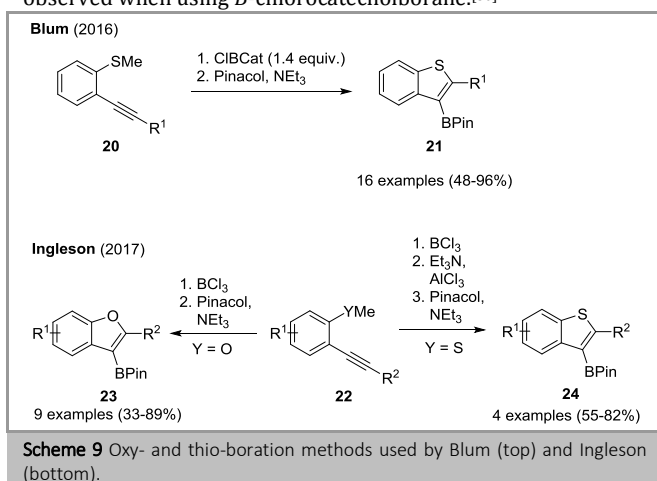
reaction of *B*-chlorocatecholborane with methyl pent-4-ynoates **13**.^[25] This reaction mimics the electrophilic 1,2-*trans*-oxyboration cyclization reaction seen in the formation of the pyrylium borates. In this case however, the generation of the borate intermediate provides a convenient nucleophile in the form a chloride ion that is used as a methyl abstraction agent to yield the catechol boronic ester which was subsequently functionalized, through pinacolation, to give the stable isocoumarin **14** (Scheme 7, bottom). Compounds that incorporate these BPin fragments are of great synthetic importance to organic chemists as they make excellent candidates for further Suzuki-Miyaura cross-coupling reactions.

In extension to this, work conducted within our group using the diyne methyl ester **15** in conjunction with the soft Lewis acid PhSeCl resulted in sequential cyclization reactions.^[26] The addition of one equivalent of the selenane leads to the formation of the isocoumarin selenylether **16** in 68% yield, with concomitant loss of MeCl . This is a common meme within organic chemistry with a number of similar selenolactonizations being carried out using this method.^[27] Upon exposure to two more equivalents of PhSeCl , this selenylether undergoes a second 6-*exo-dig* cyclization, furnishing the extensively conjugated tetracyclic structure **17** containing selenium in three isolated electronic environments, the selenonium cation, neutral selenylether and the selenate anion with single-crystal X-ray crystallography unambiguously confirming the molecular structure (Scheme 8). In an attempt to prompt a second cyclization, one equivalent of $\text{B}(\text{C}_6\text{F}_5)_3$ was added to the selenylether intermediate **16**. Unfortunately, the O-B adduct **18** prevailed with no indication of alkyne activation. Conversely, if the diyne reagent **15** is subjected to the borane alone, then a tandem reaction is observed whereby the distal alkyne unit is activated leading to a cascade reaction of the proximal alkyne and ester unit to give the zwitterionic conjugated biaromatic system **19** consisting of indene and phthalide subunits.



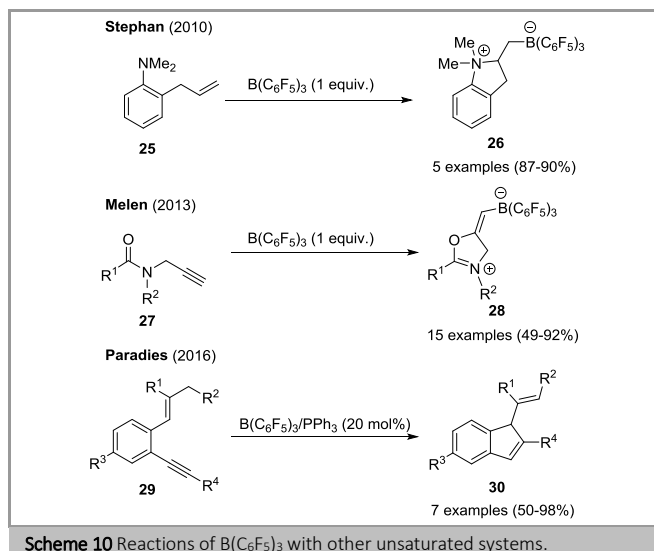
Scheme 8 Cyclizations of diyne methyl esters with differing Lewis acids.

Further work in this field by Blum *et al.* used *B*-chlorocatecholborane as the electrophile in the cyclization of alkynyl methylethers (Scheme 9, top).^[28] In this case the demethylation of the alkynylmethylethers **20** occurred spontaneously as before, with the catecholboronate ester being transformed to the pinacol derivative **21** in good to excellent yields (48-96%). Further work conducted by Ingleson and co-workers shows the successful cyclization of alkynylethers and thioethers to generate benzofurans and benzothiophenes using BCl₃ as the Lewis acid.^[29] The addition of this borane to alkynylmethylethers **22** (where Y = O) undergoes rapid cyclization in as little as 5 minutes, to generate the borylated benzofuran with concomitant loss of MeCl, a similar trope observed in this type of reactivity (Scheme 9, bottom). While the vinylchloroborane that is generated presents certain issues of stability, the facile conversion to the pinacol boronic ester **23** not only generates a bench stable boron compound, but the ideal candidate as a cross-coupling partner for further derivatization. Indeed, the one-pot conversion from the alkynylether to the arylated benzofuran was undertaken, with an isolated yield of 72%. This transformation could then be extended to thioethers with equal success yielding the benzothiophenes **24** in 55-82% yield however, to undergo the demethylation step, a combination of NEt₃ and AlCl₃ had to be incorporated into the synthetic methodology. The above thio-boration reactions were then assessed in further work by Blum *et al.* using a gamut of kinetic and computational studies. It was proposed that two possible mechanisms are in competition; 1) the formation of a vinyl cation after alkyne activation using a strong electrophile or 2) alkyne activation by a weak electrophile with concomitant nucleophilic attack of the sulfur atom to form the cyclized intermediate. Kinetic studies indicate the latter pathway is favored by the less electrophilic *B*-chlorocatecholborane which then generates the convenient chloride nucleophile. To contrast, when using stronger electrophiles such as BCl₃, the loss of a chloride ion from the zwitterionic intermediate is associated with a high dissociation barrier precluding the same bifunctionality that is observed when using *B*-chlorocatecholborane.^[30]



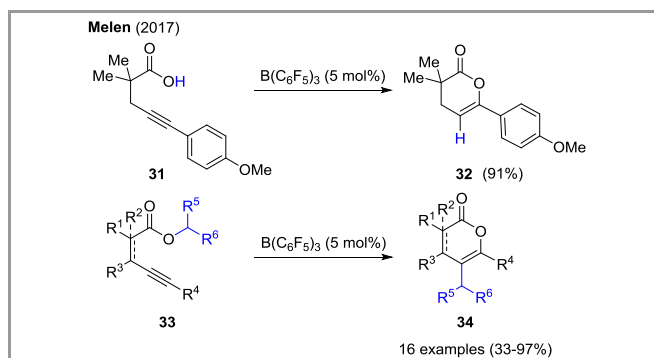
Our group, amongst others, have also used the strong Lewis acid B(C₆F₅)₃ as a π-Lewis acid similar to those described earlier as well as other related transformations such as cycloaminations,^[31] *trans*-oxyborations,^[32] annulations^[33] amongst many others (Scheme 10).^[34] Due to the strong oxophilic character of the hard Lewis acid, it is perhaps interesting to see

such high reactivity with softer π-Lewis bases. This behavior is reminiscent of work by Takaki described earlier through the bifunctionality of the bismuth center, which was capable of activating both the carbonyl oxygen and alkyne together however, boron with its orbital availability being limited to its vacant *p_z* orbital, it only undergoes one activation mode at a given time.



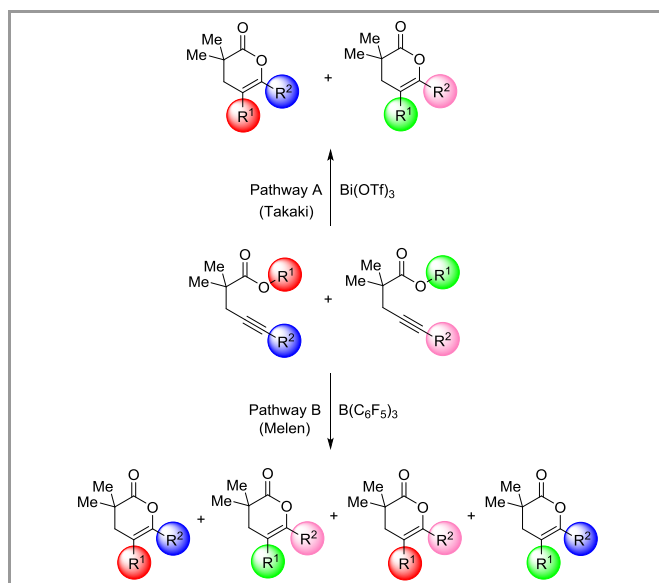
Scheme 10 Reactions of B(C₆F₅)₃ with other unsaturated systems.

Expanding on this, our group used B(C₆F₅)₃ to affect similar rearrangements as observed with Takaki, with stoichiometric experiments generating the pyrone and isocoumarin products in excellent yields (generally >95%) in as little as 10 minutes.^[35] This holds true for a number of substituents on the ether linkage such as benzyl, ethylphenyl and benzhydrol moieties. We then attempted the corresponding carboxylic acid which interestingly did produce the unsaturated 2-pyrone with selective transfer of the proton to the γ-position. This is notable as carboxylic acids are generally not tolerated within borane chemistry, particularly the strong Lewis acid B(C₆F₅)₃, as decomposition pathways prevail such as autoprotolysis of the perfluorophenyl groups. When these reactions were attempted catalytically, the electron rich alkynyl carboxylic acid **31** could be successfully cyclized to give **32** with a number of other alkynyl esters reagents **33** giving generally good to excellent isolated yields of the cyclized products **34** (Scheme 11). The broad spectrum of products, tandem reactivity, low catalyst loading and mild conditions seen here is indeed comparable to similar transition metal and heavy *p*-block centered systems, showcasing the applicability of light group 13 catalysts.



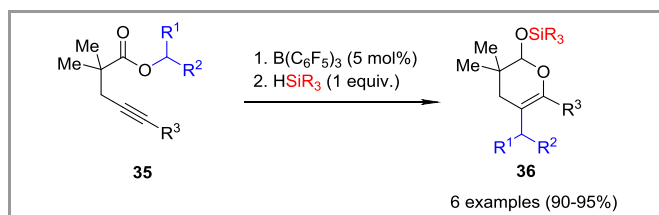
Scheme 11 Cyclization and 1,5-shift of alkynyl carboxylic acids (top) and alkynyl esters (bottom)

An important point to note is the differing reactivity between the bismuthane and borane catalysts in terms of their mechanism when transferring the ester substituent. Crossover experiments using two pyrone variants in conjunction with the bismuth catalyst shows no mixing of substituents indicating an *intramolecular* process (Scheme 12, Pathway A). Conversely, when $B(C_6F_5)_3$ was utilized, a mixture of four distinct products was observed which was designated as the *intermolecular* scrambling of R^1 and R^2 substituents (Scheme 12, Pathway B). It is believed that in this latter case, a carbocationic intermediate is formed which can then add to the alkyne of either substrate whereas the former shuttles the ester substituent directly to the activated alkyne.^{17,26}



Scheme 12 Comparison between Takaki and Melen crossover experiments.

We were then able to conduct a tandem one-pot hydrosilylation of the resultant substituted pyrones to furnish the respective cyclic silylactal products **36** (Scheme 13). This could all be accomplished through simple addition of the silane with gentle heating for 6 h to reduce the lactone carbonyl quantitatively by *in situ* NMR spectroscopy with excellent isolated yields. This particular reaction champions an atom-efficient approach using metal-free catalysts to provide highly complex and structurally diverse heterocyclic compounds. Other derivatizations that could be accomplished were the Suzuki-Miyaura cross-coupling of a *para*-bromophenyl group in the R^2 position.



Scheme 13 Tandem catalytic one-pot cyclization/hydrosilylation.

In summary, pyrones and isocoumarins have extensive uses in the pharmaceutical industry, therefore robust methods to synthesis such structures are of great importance. Indeed, while intermolecular pathways exist, perhaps simpler alternatives

exist through intramolecular cyclization reactions. A number of *p*-block centered catalysts as well as certain coinage and platinum group metals are incredibly effective in this regard, with some never-before-seen reactivity of certain main group compounds. Indeed, in many instances the use of early group 13 centered catalysts effectively mimic the reactivity of their heavier *d*- and *p*-block counterparts ushering in a new era for abundant group 13 compounds in catalysis. This area continues to make great strides toward evermore structurally diverse and complex heterocycles, overcoming obstacles to drive this research forward in increasingly interesting ways.

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