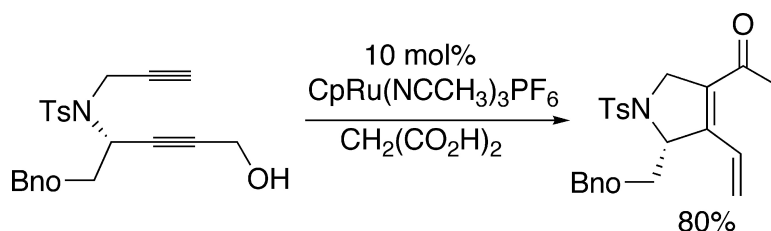


## Ruthenium-Catalyzed Cycloisomerizations of Diynols

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## Ruthenium-Catalyzed Cycloisomerizations of Diynols

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**Abstract:** A wide variety of diynols containing tertiary, secondary, and primary propargylic alcohols undergo a cycloisomerization reaction to form dienones and dienals in the presence of a catalytic amount of [CpRu-(CH<sub>3</sub>CN)<sub>3</sub>]PF<sub>6</sub>. The formation of five- and six-membered rings is possible using this methodology. Secondary diynols react to form single geometrical isomeric dienones and -als. Primary diynols undergo a cycloisomerization as well as a hydrative cyclization process. The utility of primary diynol cycloisomerization is demonstrated in a synthesis of (+)- $\alpha$ -kainic acid.

## Introduction

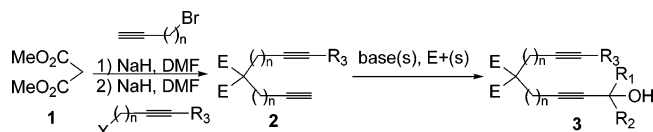
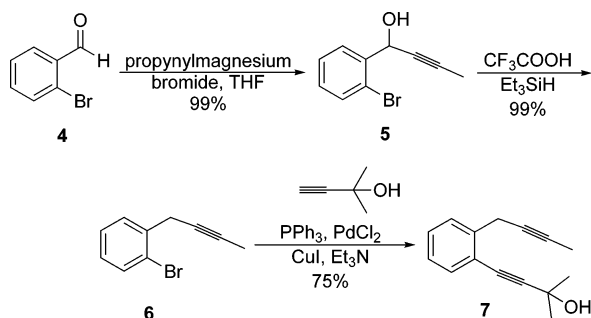
Utilization of easily accessible starting materials to create highly functionalized ring structures through addition reactions allows the creation of molecular complexity<sup>1,2</sup> while preserving atom economy.<sup>3–5</sup> The use of transition metal-catalyzed cyclization reactions often allows one to achieve synthetic efficiency in ways not normally attainable through traditional means. The intramolecular aldol condensation<sup>6–11</sup> is a classic method to construct 1-acyl-cyclopentenes and 1-acyl-cyclohexenes. However, some of the disadvantages of this reaction are the difficult or lengthy synthesis of the keto-aldehyde starting materials and the potential complications inherent when more than a single enolate can be formed.<sup>11</sup> While some methods have been developed to carry out chemoselective aldol condensations,<sup>6,7</sup> there is not a general solution to this problem. Additionally, the inherent reactivity of ketones and aldehydes makes the use of protecting groups frequently necessary in the total synthesis of complex molecular targets. We have recently developed a series of ruthenium-catalyzed propargylic alcohol dimerization<sup>12</sup> and diynol cycloisomerization reactions which form dienones and dienals with excellent chemoselectivity.<sup>13–15</sup> The products of these reactions formally result from a chemoselective intramolecular aldol condensation of aldehydes or ketones with enals.

In contrast to the sometimes-difficult synthesis and protection of carbonyls, alkynes are known to be synthetically robust, and the synthesis of substituted alkynes and propargylic alcohols can be quite simple. A wide variety of methods are known for the construction of propargylic and homopropargylic alcohols and amines.<sup>16–27</sup> Unfunctionalized alkynes are less readily accessible than ones containing proximal heteroatoms, but there are still many straightforward methods of synthesis, including various isomerization,<sup>28–32</sup> homologation,<sup>33–38</sup> and metal-catalyzed cross-coupling<sup>39</sup> methods.

**Preparation of Diyne Substrates.** The most readily available diynols can be made starting from the commercially available 1,7-octadiyne and 1,6-heptadiyne. Mono- and bis-deprotonation followed by trapping of the anion(s) with aldehydes and ketones leads to various diynols. More functionalized diynols **3** can be

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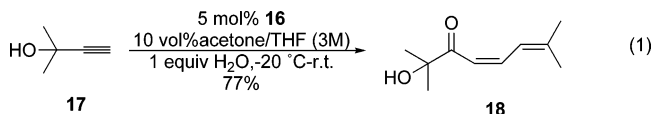
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**Scheme 1.** Synthesis of Diynols Based on Dimethylmalonate**Scheme 2**

prepared through sequential alkylation of dimethylmalonate with various propargylic and homopropargylic halides (Scheme 1). Subsequent deprotonation and trapping with various electrophiles leads to a wide variety of diynol substrates in a few simple steps. Oxygen- and nitrogen-containing diynols can also be constructed in a related manner starting from propargylic alcohols and protected amines. More complex diynols can also be synthesized in a facile manner. A Sonogashira coupling is the key reaction in the three-step synthesis which leads to diynol **7** (Scheme 2). Starting from cyclohexanone, the functionalized tertiary diynol **12** is prepared in four simple steps via a sequence of enolate alkylation, addition of propynylmagnesium bromide, acetate formation, and alkylation with acetone (Scheme 3). Acyclic diynols are also available via similar steps. An ester-tethered diynol can be prepared in a direct fashion starting from butynoic acid (Scheme 4). DCC-mediated ester formation followed by alkylation with acetone yields diynol **15** in two steps.

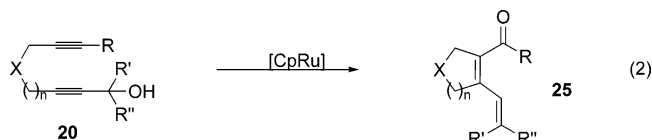
**Cycloisomerization of Tertiary Diynols.** The utility of the ruthenium precatalyst  $[\text{CpRu}(\text{CH}_3\text{CN})_3]\text{PF}_6$  (**16**) in various alkene–alkyne coupling reactions has been reported extensively in the literature.<sup>40–49</sup> This and related  $[\text{CpRu}]$  complexes are also known to promote several alkyne–alkyne coupling reactions, notably including alkyne trimerization<sup>50–52</sup> and diyne cycloadditions with 1,3-dienes,<sup>53</sup> allylic ethers,<sup>54</sup> other alkenes,<sup>55</sup> nitriles,<sup>56,57</sup> isocyanates,<sup>58</sup> isothiocyanates,<sup>59</sup> carbon disulfide,<sup>59</sup>

and tricarbonyl compounds.<sup>60</sup> Several alkyne–alkyne dimerizations, other than the one described by us (eq 1),<sup>12</sup> using related catalyst systems have also been described.<sup>61–65</sup>

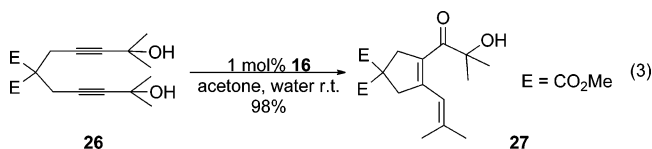


We proposed a mechanism for this (eq 1) dimerization based upon ruthenacyclopentadiene formation, elimination of a water molecule, re-addition of water to the other side of the ruthenacycle,  $\beta$ -H elimination, and reductive elimination. It appeared to us that only a single molecule of propargylic alcohol should be required, and thus a cross-coupling of alkynes and propargylic alcohols should be possible (Scheme 5).

Initially, using the optimized conditions developed for the intermolecular dimerization of propargylic alcohols (eq 1), the cycloisomerization (eq 2) of diynols proceeded in good yields ( $\sim 70\%$ ). However, it was quickly discovered that the high



concentration/mixed-solvent system required for the dimerization (eq 1) to yield a single product was not required for the cycloisomerization. The catalyst loadings could also be lowered in many of the cases. For example, the substrate which is a direct conjugate to a propargylic alcohol dimerization, diynol substrate **26**, cycloisomerized in nearly quantitative yield with only 1 mol % ruthenium complex **16** (eq 3).



The success of this reaction led us to explore the scope of the cycloisomerization reaction with various tertiary diynols (Table 1). Terminal alkynes (entries 1 and 3) as well as internal alkynes (entries 2 and 4) are well tolerated. Geminal diester groups in the tether are not required, as the substitution of ether and sulfonamide functionality does not result in any decrease in yield (entries 2 and 3). Bicyclic unsaturated ketones can be

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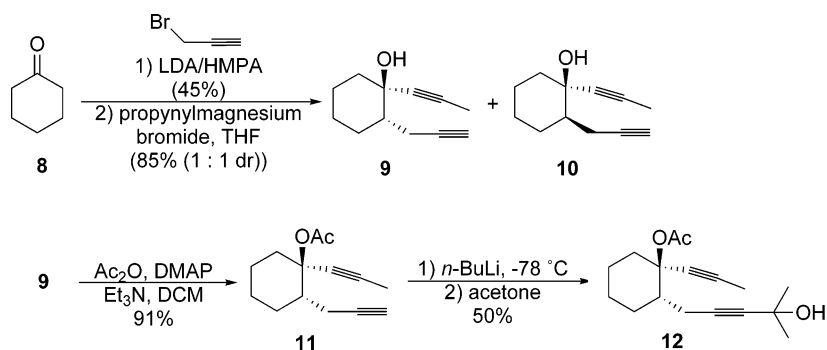
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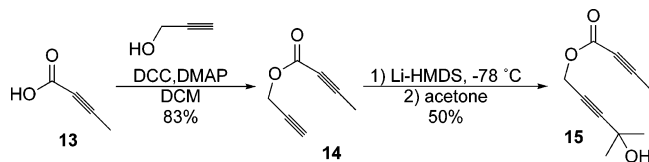
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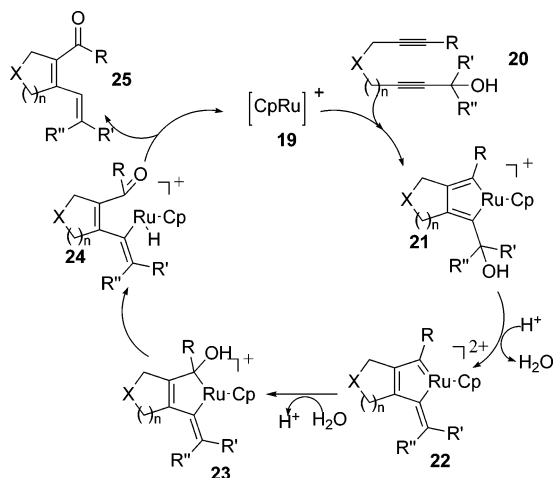
Scheme 3



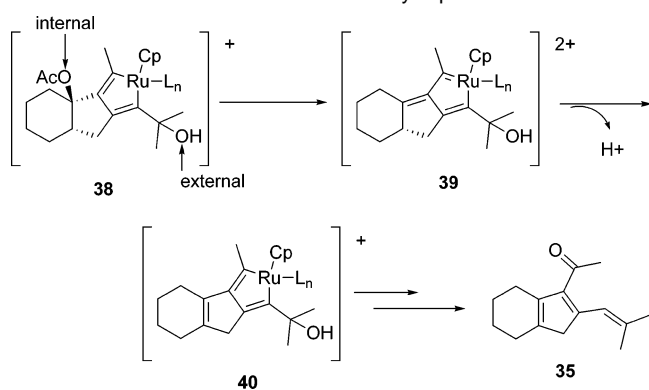
Scheme 4. Synthesis of Ester-Tethered Diynol



Scheme 5. Mechanistic Proposal for Diynol Cycloisomerization



Scheme 6. Rationale for Formation of Cyclopentadiene



formed easily as well (entry 4). This example also demonstrates compatibility with aromatic alkynes. In general, 1–5 mol % catalyst is all that is required to achieve complete conversion of this class of substrates. In entries 5 and 6, not only is the cycloisomerization taking place, but the tertiary propargylic leaving groups on the inside of the forming rings are eliminated as well, thus realizing a synthesis of functionalized cyclopentadienes. The corresponding free alcohol of **12** also cyclizes, although in slightly diminished yield. The crude NMR revealed

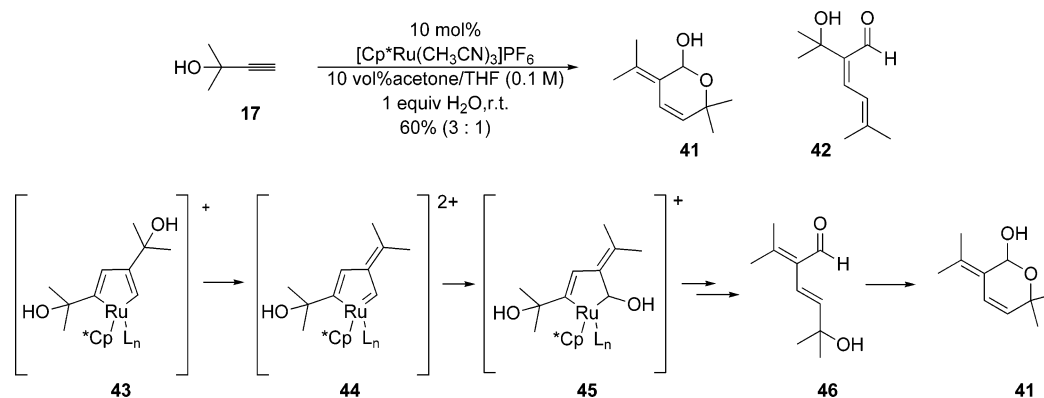
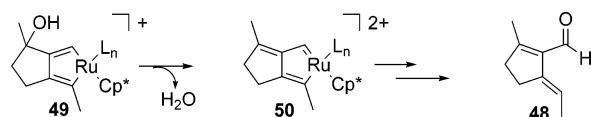
Table 1. Ruthenium-Catalyzed Cycloisomerization of Tertiary 1,6-Diynols

Entry	Substrate	Conditions <sup>a</sup>	Product	Isolated Yield
1		1 mol% <b>16</b>		98%
2		2 mol% <b>16</b>		90%
3		3 mol% <b>16</b>		99%
4		5 mol% <b>16</b>		89%
5		10 mol% <b>16</b>		63%
6		10 mol% <b>16</b>		40%

<sup>a</sup> All reactions at 0.1 M concentration in acetone with ~1 equiv of H<sub>2</sub>O at room temperature for 1 h. E = CO<sub>2</sub>Me.

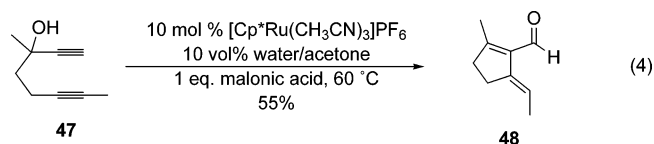
complete disappearance of the acetate group; no side products contained an acetate residue either. A mechanistic rationale for the formation of these unexpected products is given in Scheme 6.

It is envisioned that elimination of the “internal” leaving group on **38** would form **39**, which following a proton abstraction gives **40**. Functionalized cyclopentadiene **35** is then produced following the previously discussed sequence of events (Scheme 5). The difficulty of acetate elimination after cycloisomerization likely precludes this possibility. Additionally, the elimination of an “internal” hydroxyl group has precedence in the dimerization of propargylic alcohols using [Cp\**Ru*(CH<sub>3</sub>CN)<sub>3</sub>]PF<sub>6</sub> as

**Scheme 7.** [Cp\*Ru(CH<sub>3</sub>CN)<sub>3</sub>]PF<sub>6</sub>-Catalyzed Dimerization of Propargylic Alcohols**Scheme 8.** Rationale for Observed Isomer of **69**

the catalyst (Scheme 7)<sup>12</sup> and with substituted cyclobutylpropargylic alcohols.<sup>65</sup>

Substrates containing only internal propargylic alcohol functionality can undergo cycloisomerization as well (eq 4).



Cyclization of **47** was accomplished under slightly modified conditions with the more sterically hindered [Cp\*Ru(CH<sub>3</sub>CN)<sub>3</sub>]PF<sub>6</sub> to produce a single geometrical isomeric cross-conjugated aldehyde (**48**) whose configuration was assigned on the basis of a 2% NOE between the allylic methyl group and the cyclopentene methylene. The somewhat low yield may be attributable to the volatility of the product. The isolation of **48** as the only isomer supports the proposed ruthenacyclopentadiene mechanism, as the observed olefin geometry agrees with the prediction of a  $\beta$ -hydride elimination from an intermediate like **50** (Scheme 8).

Heating of the reaction mixture was required to obtain significant conversion with either the [CpRu] or the [Cp\*Ru] complex, and addition of malonic acid resulted in an increase in yield from 20% to 55%. The standard ruthenium complex **16** does indeed promote the cyclization, but the [Cp\*Ru] catalyst carries out the transformation more efficiently. This is in agreement with the fact that the “internal” elimination was also seen with this catalyst in the dimerization of propargylic alcohols to form hemiacetal products (Scheme 7). This again demonstrates that elimination of the “internal” hydroxyl group requires more bulky, donating ligands. This may indicate that coordination of the alcohol to ruthenium (not feasible with “internal” alcohols) is important to achieve a rapid and high-yielding reaction with the [CpRu] catalyst **16**.

While all the previous examples utilized electronically neutral alkynes, electron-poor alkynes can also participate quite satisfactorily in the cyclization. When alkynoate **51**, with an ester group external to the forming ring, is submitted to the cyclo-

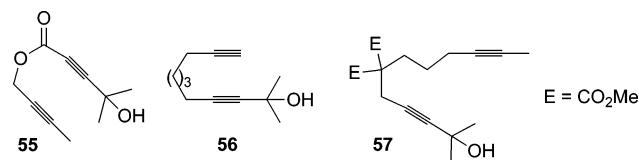
isomerization conditions, the product isolated is not the expected unsaturated ketone **52**, but instead is the isomeric [6H]-pyran **53** (Scheme 9).

It is assumed that the initial product is **52** and pyran **53** is the isolated product on the basis of the instability of the initial  $\alpha$ -keto ester relative to the pyran. This type of isomerization is well known<sup>66</sup> for  $\alpha,\beta,\gamma,\delta$ -unsaturated ketones, and the presence of electron-withdrawing groups is known to stabilize the pyran isomer. On the other hand, an internal carbonyl group (**15**) does not affect the product outcome, and the expected dienone **54** is isolated in excellent yield (Scheme 9). While **15** readily participates in the cycloisomerization, changing the location of the carbonyl group such that the leaving group is in conjugation with the carbonyl (**55**) results in a very poor cycloisomerization substrate (Figure 1). Having demonstrated a range of tertiary propargylic alcohol 1,6-diyne in the cycloisomerization reaction, we sought to test the feasibility of 1,7-diyne to function in this reaction (Table 2).

While the yields shown in Table 2 are good, some optimization was required for each compound. It was found that 7 mol % of catalyst **16** was required to achieve full conversion of geminal diester compound **62**. The terminal alkyne 1,7-diyne **58** needed to be heated to 60 °C in 10 vol % water/acetone with 1 equiv of malonic acid in order to reach full conversion with 10 mol % **16**. To realize good yield in the cyclization of the more sterically hindered internal diyne **60**, raising the concentration to 1 M was required. However, with these modifications, 1,7-diyne can participate in the ruthenium-catalyzed cycloisomerization to yield cyclic unsaturated ketones and aldehydes. Submitting two 1,8-diyne (**56**, **57**) to the cycloisomerization conditions led to very low conversion, and thus this was not further pursued (Figure 1). Other larger ring systems were not explored.

**Cycloisomerization of Secondary Diynols.** Attempts to utilize secondary propargylic alcohols in the simple dimerization reaction (eq 1) led to very low conversions and yields of the corresponding dimeric products. It is assumed that the ease with which tertiary propargylic alcohol diynes cyclize is indicative of the increased rate of formation and stability of the proposed ruthenacyclopentadiene intermediates, and that this might enable secondary propargylic alcohols to participate in the cycloisomerization as well. Gratifyingly, submitting these compounds

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**Figure 1.** Poor substrates for cycloisomerization.

**Table 2.** Ruthenium-Catalyzed Cycloisomerization of Tertiary 1,7-Diynols

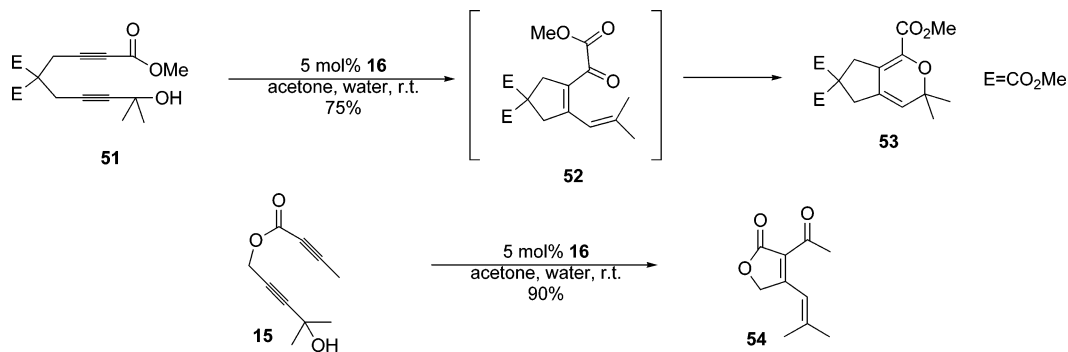
Entry	Substrate	Conditions	Product	Isolated Yield
1		10 mol% <b>16</b> <sup>b</sup>		90%
2		10 mol% <b>16</b> <sup>c</sup>		73%
3		7 mol% <b>16</b> <sup>a</sup>		91%

<sup>a</sup> 0.1 M concentration in acetone with  $\sim 1$  equiv of H<sub>2</sub>O at room temperature. <sup>b</sup> 0.1 M concentration in 10 vol % water/acetone at 60 °C, 1 equiv of malonic acid. <sup>c</sup> 1 M concentration in acetone with  $\sim 1$  equiv of H<sub>2</sub>O at room temperature. E = CO<sub>2</sub>Me

to the standard cyclization conditions led to formation of the expected products as single geometrical isomers in good yields (Table 3).

The cyclizations of secondary propargylic alcohols to form five- and six-membered rings are possible; however, the six-membered-ring formation is somewhat lower yielding, and various other decomposition products are formed as well. In general, these reactions are not as clean as the tertiary alcohol examples, but good yields can still be obtained with alkyl (entries 1 and 3) and aromatic (entry 2) secondary propargylic alcohol diynes. Also, the only isolable products have the *E*-olefin configuration at the  $\gamma,\delta$ -double bond. This olefin geometry could be the result of the thermodynamic stability of this isomer as compared the corresponding *Z*-olefin. It was demonstrated in the context of propargylic alcohol dimerization<sup>12</sup> that the  $\alpha,\beta$ -alkene can isomerize under the reaction conditions (**16** and aqueous acetone), and thus it is reasonable that the  $\gamma,\delta$ -alkene may as well.

**Scheme 9.** Cycloisomerization of Electron-Poor Diynols

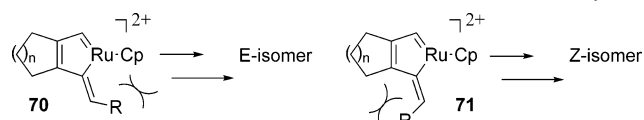


**Table 3.** Ruthenium-Catalyzed Cycloisomerization of Secondary Diynols

Entry	Substrate	Conditions <sup>a</sup>	Product	Isolated Yield
1		2 mol% <b>16</b>		70%
2		5 mol% <b>16</b>		70%
3		10 mol% <b>16</b>		60%

<sup>a</sup> Reactions at 0.1 M concentration in acetone with  $\sim 1$  equiv of H<sub>2</sub>O at room temperature for 1 h. E = CO<sub>2</sub>Me.

**Scheme 10.** Steric Effect in Determination of Olefin Geometry



Another possibility is that the elimination/1,2 shift of the hydroxyl group occurs in a stereoselective fashion based upon a preference to minimize steric interaction between the R group and the cyclopentane ring (**70** vs **71**, Scheme 10).

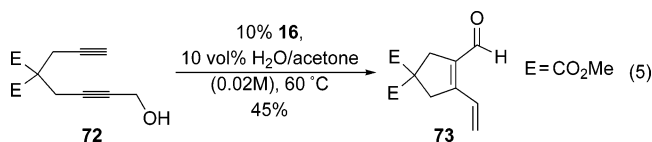
**Cycloisomerization of Primary Diynols.** Even though the dimerization of primary propargylic alcohols does not proceed at all,<sup>12</sup> on the basis of the success of secondary propargylic alcohols in the cycloisomerization reaction, primary propargylic alcohol diynes were prepared and examined in the ruthenium-catalyzed cycloisomerization as well. When **72** was submitted to the standard cycloisomerization conditions (10 mol % **16**, acetone,  $\sim 1$  equiv of H<sub>2</sub>O, room temperature), we were gratified to see that some cycloisomerized product **73** was formed. However, the conversion was very low. Addition of malonic acid and heating of the reaction to 60 °C led to complete conversion of the starting material, but the isolated yield was only 30% even though the reaction was nearly spot-to-spot. The crude mass recovery was also only a little over 30%, and it seemed that decomposition to baseline material must have been occurring. Various other conditions were tried in order to

**Table 4.** Temperature, Concentration, and Malonic Acid Effect on Ratio of **75** to **76**

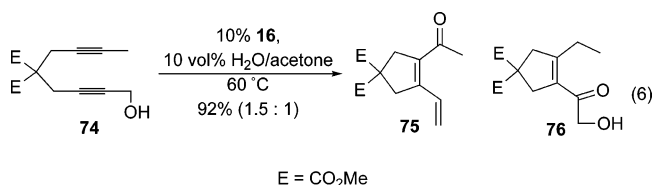
entry <sup>a</sup>	temp (°C)	additive	concn (M)	reaction time (h)	ratio <b>75:76</b>
1	60		0.1	<1	1.5:1
2	60	malonic acid (1 equiv)	0.1	1	2.5:1
3	rt		0.1	15	3:1
4	rt		1	3	2.2:1
5	0–rt		0.1	>30	3.4:1

<sup>a</sup> Reactions with 10 mol % **16**, in 10 vol % water/acetone. Total yield of **75** and **76** is approximately 90%.

optimize the yield, and it was discovered that the addition of more (up to 10 vol %) water increased the isolated yield of **73** to 45% (eq 5).

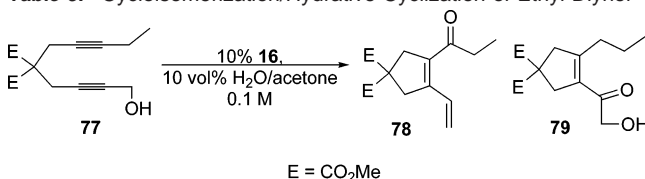


At this point, it was assumed that the low yield and mass recovery were results of the instability of the product because the reaction appeared very “clean” by TLC, and that ketone products, resulting from internal alkynes, should be more stable. In fact, when **74** was treated with 10 mol % **16** in 10 vol % water/acetone (0.1 M) at 60 °C, nearly a quantitative amount of the expected mass was recovered. Unexpectedly, two different products (**75** and **76**), in a ratio of 1.5:1, were isolated (eq 6).



While **75** is the expected methyl ketone product, **76** is a formally hydrated form of this compound (the molecular weight is that of **75** plus water). The mechanism of this transformation is clearly not a simple hydration of either **74** or **75**, but for convenience, **76** and related products will be referred to as hydrated products. It is also noteworthy that the carbons in **75** and **76** are pictured in the same orientation; the methyl alkyne is transformed into the ethyl group. It is not obvious that this is the case at this juncture, but this will become clear with the next example. The ratio of the two products was then found to be quite sensitive to temperature, concentration, and malonic acid (Table 4).

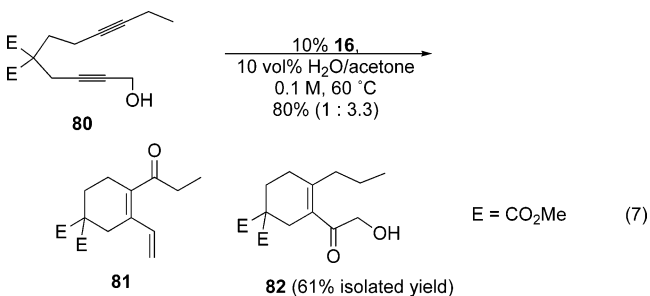
Basically, the longer amount of time required for full conversion of the starting material, the higher percentage of “normal” product **75** that was obtained. Inclusion of malonic acid (entry 2) or lower temperatures (entries 2–5) reduced the reaction rate, thus leading to more **75**. Higher concentration (entry 4) increased the rate of reaction, and thus the 3:1 ratio obtained at room temperature was reduced to 2.2:1. The reaction conducted at 0 °C (entry 5) did not go to completion even after 30 h, but upon raising the temperature to room temperature, the remaining starting material was consumed in a few hours. All these conditions resulted in a combined yield of ~90%. If a small amount of water (~1 equiv) was used in any of these

**Table 5.** Cycloisomerization/Hydrative Cyclization of Ethyl Diynol

entry	temp (°C)	ratio <b>78:79</b>	total yield (%)
1	rt	1:1.5	77
2	60	1:2.0	78
3	100	1:2.0	83

reactions, then conversion to both products was very low. Importantly, it was demonstrated that the two products do not interconvert. Submission of either isolated compound to the reaction conditions did not lead to any formation of the other product. This indicates that the mechanism of this reaction is diverging into two different products or that two different mechanisms are operative. It is unclear whether the rate of reaction is the cause of the change in product ratio, or if the rate is a byproduct of some more fundamental change. The product ratio between the “normal” and the “hydrated” products was also very sensitive to substrate identity.

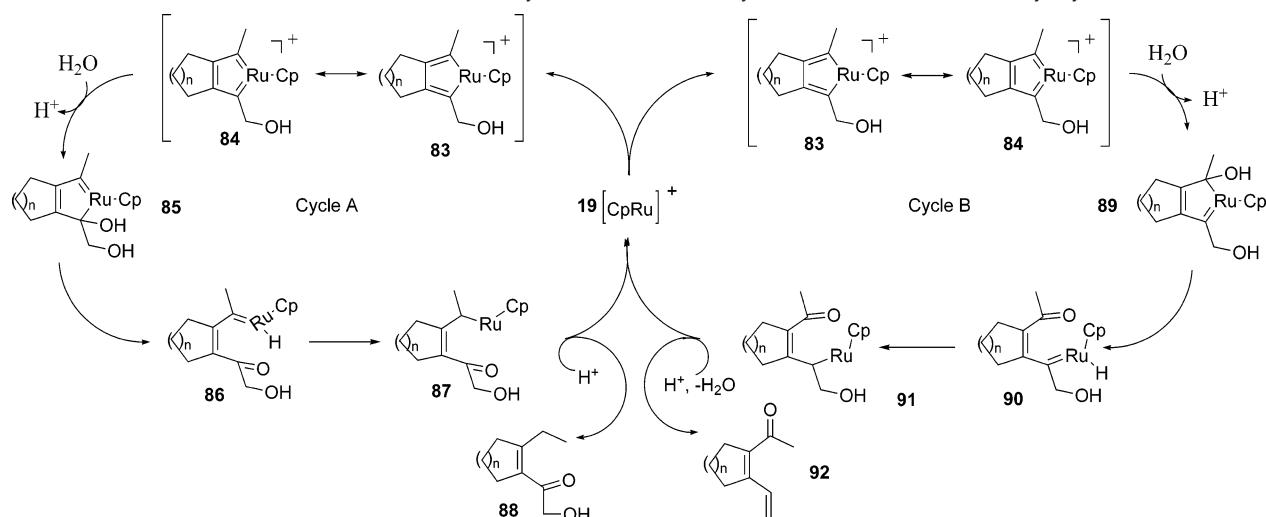
A seemingly minor change to an ethyl alkyne (**77**) leads to a reversal in the major product formed (Table 5). Under conditions where methyl alkyne substrate **74** cyclizes in a 1.5:1 ratio of normal to hydrated products, ethyl alkyne **77** cyclizes in a 1:1.5 ratio (entry 1). Raising the temperature (entries 2 and 3) increases the relative amount of the hydrated product, as was seen in the previous example. In this example, it is quite obvious that the ethyl alkyne becomes the propyl group, while the propargylic alcohol carbons are the  $\alpha$ -hydroxy ketone portion in **79**. If the tether between the two alkyne moieties is lengthened to four atoms, then the product ratio is pushed even further (1:3.3) toward the formation of the hydrated product **82** (eq 7).



Diynol **80** does not cyclize to a significant extent at room temperature and must be heated in order to obtain good conversion. These examples demonstrate that the more steric hindrance present in a cyclization reaction (ethyl alkyne vs methyl alkyne), the more “hydrated” product that is formed.

**Mechanistic Considerations in Primary Diynol Cyclizations.** While the mechanism presented in Scheme 5 nicely accounts for the results with tertiary and secondary propargylic alcohols, to rationalize the formation of both products in the primary alcohols case, the following mechanism is proposed (Scheme 11).

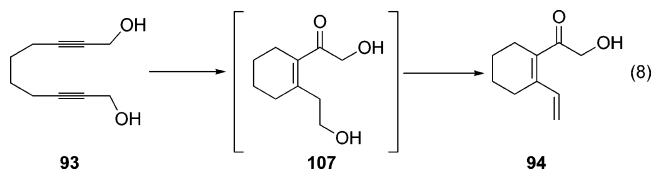
The key component to the proposed catalytic cycles is the invocation of the ruthenacyclopentatriene (**84**) resonance in

**Scheme 11.** Mechanistic Rationale for the Formation of Hydrative and Normal Cyclization Products with Primary Diynols

analogy to Kirchner<sup>88–90</sup> and Dixneuf's<sup>61,63</sup> proposal for phosphine and carboxylate addition to ruthenacyclopentadienes. Metallacyclopentatrienes, which can have a folded or planar geometry, have been isolated for a variety of metals.<sup>91–96</sup> In particular, a [CpRu] fragment has been shown to exist as a ruthenacyclopentadiene or -pentatriene, depending on the ligand environment.<sup>96</sup> In the case of primary propargylic alcohol diynes, addition of water to one of the two carbene carbons would produce either **85** or **89**, depending on the chemoselectivity of the addition. Rearrangement of **85** would lead to **86** and, following hydride shift and protonation, would result in forma-

tion of the “hydrated” product **88**. Rearrangement of **89** would lead to **90**, which results in formation of **92** following hydride shift and  $\beta$ -hydroxide elimination or protonation followed by water elimination. The differences in product ratios may be a result of subtle factors contributing to which carbene carbon is attacked. For example, a hydroxy methylene is slightly larger than a methyl group, and thus water attack is favored at the methyl carbon. Conversely, the use of a larger ethyl group leads to favored attack at the smaller hydroxymethylene. It is also possible that this mechanism and the “elimination first” mechanism presented in Scheme 5 are both operative. It is believed that the reason for this “water addition first” mechanism (Scheme 11) becoming active with primary alcohols is related to the poor leaving group ability of primary propargylic alcohols relative to secondary and tertiary alcohols.

To probe the effect of the free hydroxyl group on the cyclization, several protected tertiary and primary diynols were submitted to the reaction conditions. As Table 6 reveals, the presence of a free propargylic alcohol is not critical for reactivity. Bispropargylic alcohol **93** cyclizes to form a single product **94**, the cycloisomerized “normal” product (entry 1). While it may initially appear that no hydrative product is formed and that something about the substrate must be preventing this pathway, the expected hydrative product has a facile elimination which could take place, and thus both pathways may still be operative (eq 8).



The monoprotected analogue **95** also behaves similarly and generates a 1:1.7 mixture of products, favoring the addition of water to the free propargylic alcohol alkyne (entry 2). Entry 3 demonstrates the exclusive elimination of a tertiary propargylic alcohol under either low water ( $\sim 1$  equiv of  $\text{H}_2\text{O}$ ) or high water (10 vol %  $\text{H}_2\text{O}$ ) conditions. Protection of the primary propargylic alcohol also has no effect (entry 4). Protection of the simple primary propargylic alcohol substrate as a methyl ether or as an acetate does not affect the ratio of products at all (entries 5

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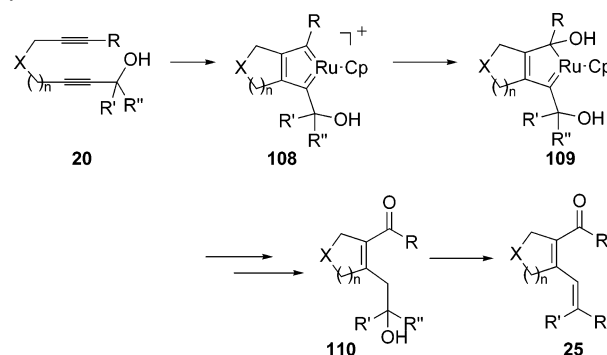
**Table 6.** Effect of Protecting Groups on Cycloisomerization/Hydrative Cyclization

Entry	Substrate	Products	(product ratio) isolated yield
1			(only product) 74%
2			(1 : 1.7) 72%
3			(only product) 80%
4			(only product)
5			(1.5 : 1)
6			(1.5 : 1)
7			(only product)
8		-----	-----

<sup>a</sup> Reactions at 0.1 M concentration in 10 vol % water/acetone at 60 °C for 1 h. <sup>b</sup> Ratio determined by <sup>1</sup>H NMR integration on crude samples. E = CO<sub>2</sub>Me.

and 6; a 1.5:1 ratio is obtained with the free alcohol as well). Entry 7 reveals that a free alcohol is not required for cyclization of tertiary alcohol substrates either. On the other hand, a tertiary acetate does not participate in the cycloisomerization at all. It is possible that the presence of the highly activated tertiary propargylic acetate leads to deactivation of the catalyst (entry 8).

Due to the lack of effect of the propargylic functionality for most substrates, these data seem to indicate that a propargylic alcohol is not required for cyclization of certain substrates. Some understanding of the mechanism of both reactions can be gained from this information along with the data from a reaction carried out with O<sup>18</sup>-water.<sup>97</sup> When the reaction in Table 1, entry 1, was performed in the presence of 3 equiv (relative to **28**) of H<sub>2</sub>O<sup>18</sup>, only 2 times the background level of O<sup>18</sup> was incorpo-

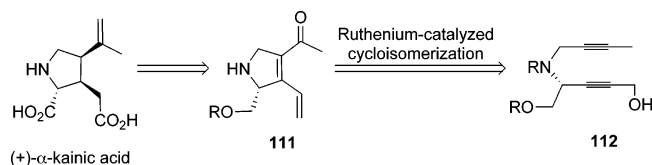
**Scheme 12.** Possible Mechanism of Tertiary Propargylic Alcohol Cycloisomerization

rated into the product **29**. Raising the amount of H<sub>2</sub>O<sup>18</sup> to 100 equiv only resulted in 42% of the product containing O<sup>18</sup> (37 times the background level), even though every attempt was made to exclude adventitious H<sub>2</sub>O.<sup>16</sup> This indicates that the carbonyl oxygen can come from both the propargylic alcohol and exogenous water; the eliminated water from the propargylic alcohol can be transferred to the other alkyne, but in the presence of a large excess of water, exchange may occur as well. While this explanation is reasonable, there is a possibility that O<sup>18</sup> can be incorporated after the aldehyde is formed via a Lewis-acid-catalyzed hydration/elimination process. For primary propargylic alcohol substrates that participate in the hydrative process, clearly exogenous water is being incorporated, although the “normal” products were not checked for O<sup>18</sup> incorporation. At this point, we still believe that for tertiary and secondary propargylic alcohol diynes, the mechanism depicted in Scheme 5 is largely correct. It *can* be proposed that all the reactions presented in this article proceed by water addition followed by a facile  $\delta$ -elimination of water to yield the observed  $\alpha,\beta,\gamma,\delta$ -unsaturated aldehydes and ketones, and that only one product is isolated because addition next to the hindered tetrasubstituted center is disfavored (Scheme 12).

However, the remarkable difference between reactions with tertiary and primary propargylic alcohols suggests otherwise. For example, tertiary alcohol diynes react nearly instantaneously with ~1 equiv of water, while the corresponding primary substrates require excess water and heat to react quickly. While elimination of the tertiary  $\delta$ -hydroxyl may be faster than that of the corresponding primary hydroxyl, if the elimination (**110** to **25**) is the rate-limiting step, then a buildup of the  $\delta$ -hydroxy ketone should be seen. However, if this type of elimination occurs within the catalytic cycle (**91** to **92**, Scheme 11) and is the rate-limiting step, then it is possible that both tertiary and primary propargylic alcohol diynes react via the same mechanism. However, it is unclear why the amount of water present would have such an effect on primary alcohols, but none for tertiary. Therefore, from the data at hand, it seems likely that tertiary/secondary alcohol substrates react by one mechanism, and primary alcohols primarily react by another. Finally, it is important to note that the preceding discussion is based upon empirical examples and not upon kinetic and mechanistic studies.

**Synthesis of  $\alpha$ -Kainic Acid.** The factors which determine the ratio of “normal” to “hydrated” cyclization products were

(97) 75% isotopic purity as measured by mass spectrometric analysis carried out by Dr. David Walthall in the Brauman group at Stanford University on Oct 31, 2001.

**Scheme 13.** Retrosynthesis of  $\alpha$ -Kainic Acid

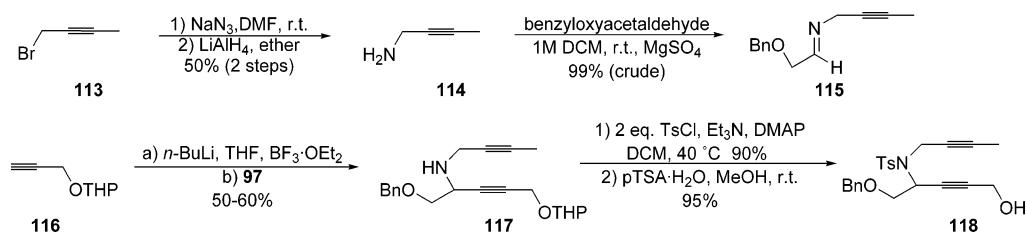
then further explored in the context of a synthesis of  $\alpha$ -kainic acid (Scheme 13).<sup>14</sup>

We planned to introduce the isopropylidene fragment through an olefination of the ketone (**111**). We envisioned hydroxyl-directed hydrogenation would set the required relative stereochemistry present in the natural product. Introduction of a hydroxyl group or oxygen equivalent would immediately follow the ruthenium-catalyzed cycloisomerization of the diyne substrate **112**. Based upon the hypothesis that less of the hydrated product is formed when there is greater steric hindrance near the propargylic alcohol, the cycloisomerization of **112** should be favored over the corresponding hydration/cyclization.

The key cyclization precursor **112** can be made in two distinct ways. First, aldimine **113** can be alkynylated with a protected propargylic alcohol (**116**) to produce diyne **117**. Protection of the free amine with tosyl chloride and removal of the THP group reveals the desired racemic cyclization substrate **118** (Scheme 14). Alternatively, a Mitsunobu reaction of a chiral propargylic alcohol (**-**)-**121** and a protected propargylic amine provides a similar protected amino diyne **124** in a more convergent fashion (Scheme 15). Asymmetric reduction of the ynone **122** using the  $\text{LiAlH}_4/\text{BINOL}/\text{MeOH}$  system developed by Noyori<sup>67,68</sup> provided rapid, high-yielding, and nearly enantiopure access to propargylic alcohol (**-**)-**121**. The sense of chirality of this alcohol eventually leads to the unnatural enantiomer of  $\alpha$ -kainic acid; however, the natural enantiomer is readily available by simply using (*S*)-BINOL in the asymmetric reduction.

Upon submitting diyne **118** to the standard cycloisomerization conditions developed for primary propargylic alcohols (10 mol % ruthenium catalyst **16**, 10 vol % water/acetone, 60 °C), the cycloisomerization product **125** can be isolated in good yield (75%). The ratio of cycloisomerized to “hydrated” products (5:1) was much greater in this case as compared to the simple primary diyne substrate (Table 7). This is in agreement with the observation that the more hindered the propargylic alcohol is, the less hydrated product that is obtained.

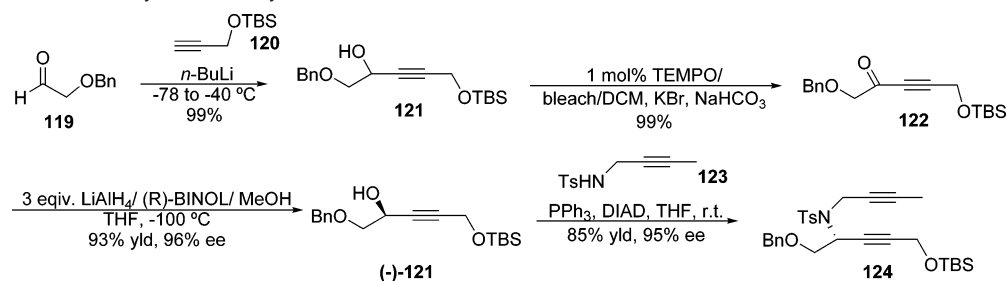
As was observed for simple substrates, lowering the temperature increased the ratio favoring cycloisomerized product **125**. In this example (entries 3 and 4), the formation of the “hydrated” product **126** can be completely eliminated; however, a slightly higher isolated yield of the cycloisomerized product **125** can be obtained if the reaction is performed at 45 °C in the presence of 1 equiv of malonic acid, even though a small amount of **126** is formed as well. These two products are easily separable, and thus the conditions from entry 2 are considered superior.

**Scheme 14.** Synthesis of Racemic Cyclization Precursor

One of the most straightforward methods to introduce oxygenation at the  $\delta$ -carbon is a chemoselective hydroboration–oxidation of the  $\gamma,\delta$ -olefin in the presence of the  $\alpha,\beta$ -olefin and the ketone. While unprecedented in a conjugated system like this, it would seem to be reasonable. Using simple borane reagents ( $\text{BH}_3\text{-SMe}_2$ ), mainly 1,2-reduction products were isolated in low yield along with extensive decomposition under various oxidation conditions. The use of dicyclohexylborane<sup>69</sup> or 9-BBN dimer<sup>70</sup> led to predominantly 1,6-reduction; however, low yields were obtained uniformly. Use of rhodium or nickel catalysts also did not allow any isolation of the desired product. It is believed that the presence of the conjugated ketone was the problem in the reaction, and thus the ketone was masked as an ethylene glycol ketal (Scheme 16).

Chemoselective hydroboration–oxidation to form primary alcohol **128** was then readily accomplished using dicyclohexylborane and a standard basic peroxide workup. The resulting free alcohol was then protected as the nonligating TBS-silyl ether (**129**). The homoallylic benzyl ether then needed to be deprotected in order to carry out the planned directed hydrogenation. Alternatively, the required oxygenation at the  $\delta$ -carbon can be introduced through a 1,6-addition of an oxygen surrogate group ( $-\text{SiPhMe}_2$ ) (Scheme 17). While much work has been done on the 1,4-addition of silyl cuprates,<sup>71,72</sup> the 1,6-addition was unknown. When the phenyldimethylsilyl cuprate<sup>73</sup> was added to (+)-**125** at  $-78$  °C no reaction occurred; however, when the temperature was raised to 0 °C, a mixture of 1,6-addition diastereomers **131** (in a 2.8:1 ratio) was isolated. The olefin could be easily isomerized into conjugation with DBU in refluxing benzene to give the desired product **132** in 87% yield over the two steps. It is also of note that no racemization occurred in the cyclization or conjugate addition steps. The benzyl group was then removed using Pd/C in formic acid/methanol to provide free alcohol **133**.

The relative stereochemistry was then set by a directed hydrogenation of the sterically hindered tetrasubstituted olefin (**130**, **133**). Various functional groups are known to participate in a directed reduction including methyl ethers; however, no reaction occurred with benzyl ether compounds **129** or **132** using Crabtree’s catalyst,<sup>74,75</sup>  $[\text{Ir}(\text{cod})\text{Py}(\text{PCy}_3)]\text{PF}_6$ . On the basis of the hindered nature of the olefin, the most active catalysts used in hydroxyl-directed hydrogenations ( $[\text{Rh}(\text{nbd})\text{dppb}]\text{BF}_4$ <sup>76–78</sup> and  $[\text{Ir}(\text{cod})\text{py}(\text{PCy}_3)]\text{PF}_6$ <sup>74,75,79</sup> (Crabtree’s catalyst)) were tested first with the free alcohol compounds **130** and **133**. Under all conditions attempted, the [Rh] catalyst failed to give any reduction product. Crabtree’s catalyst is known to be even more active, and that proved to be the case here as well. Under 1 atm of hydrogen, no reaction occurred with either substrate, but ketal **130** reacted utilizing a higher pressure of hydrogen (8.2 atm) and 20 mol % [Ir]; reduction occurred to give a quantitative yield of the expected reduced product ( $\pm$ )-**134** as

**Scheme 15.** Enantioselective Synthesis of Cyclization Precursor**Table 7.** Optimization of the Ruthenium-Catalyzed Cycloisomerization

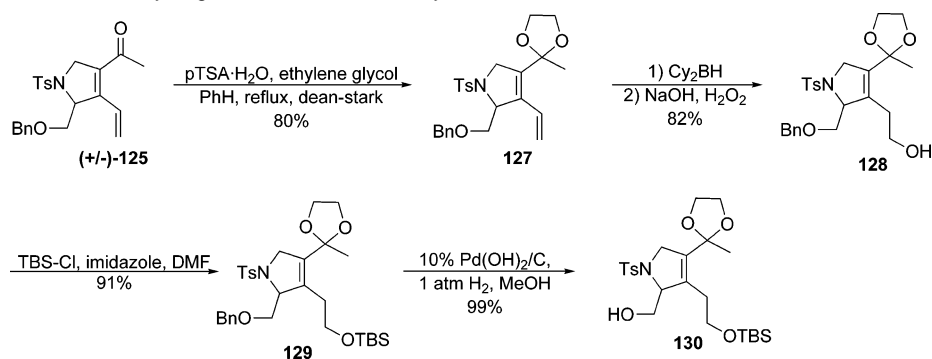
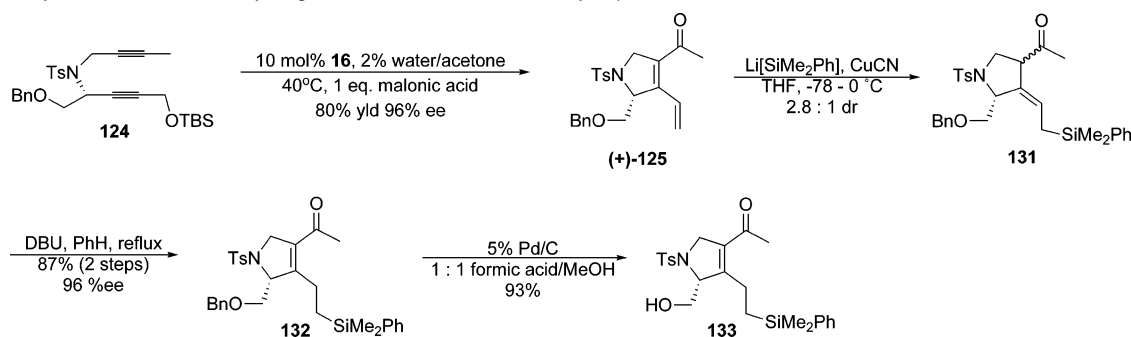
entry	temp (°C)	additive (equiv)	ratio 125:126	isolated yield of 125 (%)
1	60		5:1	75
2	45	malonic acid (1)	10:1	80
3	rt		1:0	75
4	rt	malonic acid (1)	1:0	75

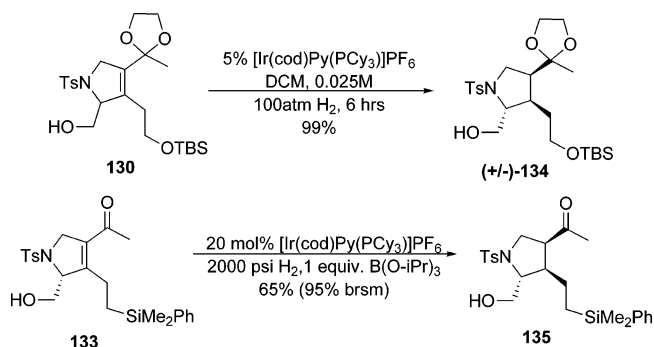
a single diastereomer. It was subsequently found that 5% [Ir] was sufficient (under 100 atm of hydrogen gas) to convert the ketal **130** completely into a single reduced product ( $\pm$ )-**134** in quantitative yield (Scheme 18).

The  $\alpha,\beta$ -unsaturated ketone **133** was even more difficult to reduce than the ketal-protected analogue **130**; with 2000 psi hydrogen and 20% [Ir], a 1:1 ratio of **133** to **135** was isolated after 24 h. Similar to the reduction of **130**, only a single diastereomer resulting from directed hydrogenation was isolated. Tetrasubstituted olefins and  $\alpha,\beta$ -unsaturated alkenes are known to be difficult to reduce with Crabtree's catalyst, and Crabtree

has even demonstrated that a ketone directs hydrogenation more efficiently than a free alcohol, while ethylene glycol ketals function poorly as directing groups.<sup>75</sup> This may indicate that the ketone is coordinating to the iridium catalyst and reducing the rate of the desired hydroxyl-directed hydrogenation. Using lower catalyst loadings, lower conversions were obtained, and at higher catalyst loadings (50%), somewhat higher conversions were obtained (0.7:1 **133** to **135**). Attempts to form the dimethyl ketal in situ with trimethylorthoformate led to no reaction. Even the isolated dimethyl ketal of **133** failed to react to any significant extent. It was envisioned that if another Lewis acid could break up this ketone–iridium coordination, then greater catalyst turnover could be achieved. Use of  $\text{Ti}(\text{OiPr})_4$  led to no reaction, and acetic acid also produced no product. However, use of 1 equiv of  $\text{B}(\text{OiPr})_3$  along with 20 mol % Crabtree's catalyst led to increased catalyst turnover such that the desired hydrogenated product (**135**) was isolated in 65% yield (95% based on recovered **133**) (Scheme 18). Use of excess  $\text{B}(\text{OiPr})_3$  led to decreased yields.

The racemic synthesis of  $\alpha$ -kainic acid was then completed in five steps (Scheme 19). The methyl ketone was olefinated to form diol ( $\pm$ )-**138** following removal of the ketal protecting group and re-protection of the resulting diol as a bis-TBS ether. Oxidation of diol ( $\pm$ )-**138** to bis-acid ( $\pm$ )-**139** was accomplished

**Scheme 16.** Synthesis of Directed Hydrogenation Precursor via Hydroboration**Scheme 17.** Synthesis of Directed Hydrogenation Precursor via 1,6-Silylcuprate Addition

**Scheme 18.** Hydroxyl-Directed Reduction of Tetrasubstituted Olefins

using Jones's reagent, and the tosyl group was removed using Li/NH<sub>3</sub> to yield racemic  $\alpha$ -kainic acid.

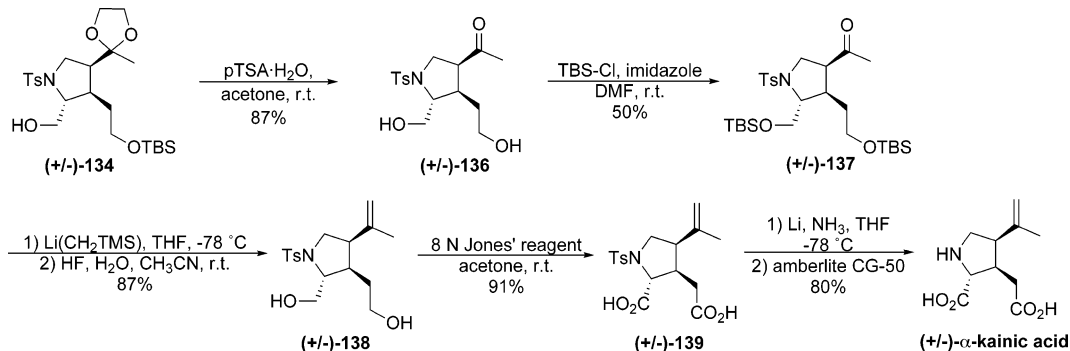
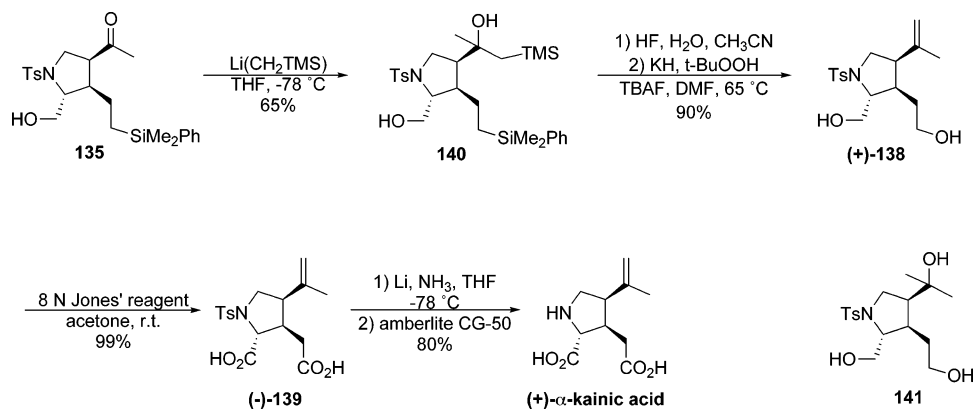
The synthesis of (+)- $\alpha$ -kainic acid was also completed via a related olefination, oxidation, and deprotection sequence. After the initial step of the Peterson olefination,<sup>80,81</sup> it was envisioned that the elimination and the oxidation of the phenyldimethylsilyl group could be carried out simultaneously. This in fact was possible using the Woerpel modification<sup>82</sup> of the Tamao–Fleming oxidation.<sup>83–85</sup> The standard Tamao–Fleming conditions require strong acids or electrophiles to oxidize phenyldimethylsilyl groups, which were expected to be incompatible with the olefin present in the molecule. The addition of (trimethylsilylmethyl)lithium proceeded smoothly to give **140**, which could be directly converted to (+)-**138** using the Woerpel KH/*t*-BuOOH/TBAF conditions (Scheme 20).

However, some amount of a protodesilyated product **141** was also isolated under these conditions, and modifications to minimize this undesired product resulted in lower yields of (+)-

**138**. Higher yields were obtained if the elimination was carried out with HF/acetonitrile first, followed by the Woepel oxidation to diol (+)-**138** without any prior purification (Scheme 20). Both primary alcohols were then oxidized simultaneously with Jones's reagent to give a quantitative yield of the diacid (–)-**139**. The tosyl group was then removed in a known step<sup>86,87</sup> with Li/NH<sub>3</sub> to give the unnatural enantiomer of  $\alpha$ -kainic acid in 80% yield over two steps (Scheme 20).

## Conclusion

In this article, the extension of the propargylic alcohol dimerization to an intramolecular reaction has been detailed. Not only are the yields for the cycloisomerization very high for a range of five- and six-membered ring-forming reactions, but the reaction represents a novel chemoselective alternative to aldol condensation. Tertiary and secondary propargylic alcohol diynes cycloisomerize in the presence of a catalytic amount of ruthenium complex **16** to yield  $\alpha,\beta,\gamma,\delta$ -unsaturated aldehydes and ketones. Secondary propargylic alcohol diynes cyclize to form the more thermodynamically stable *E*-dienone, a single geometrical isomer. Primary propargylic alcohol diynes cyclize as well, but in addition to the expected products, formally hydrated cyclized products are isolated. A mechanistic proposal (Scheme 11) has been put forth which supports the formation of these products. It is reasonable that the primary alcohols react via this alternate pathway because of reduced leaving group ability. The product ratios presented can be explained by proposing that attack of a molecule of water occurs at the least hindered carbene carbon. This proposal was reinforced, and the utility of the methodology was demonstrated, through the synthesis of (+)- $\alpha$ -kainic acid. It is also evident that the presence of a propargylic alcohol is not critical for the hydrative

**Scheme 19.** Completion of Racemic Synthesis of  $\alpha$ -Kainic Acid**Scheme 20.** Completion of (+)- $\alpha$ -Kainic Acid

cyclization pathway to function, and thus the possibility of a hydrative diyne cyclization on simple diynes is raised. This avenue has been explored and was discussed in a previous publication.<sup>98</sup>

## Experimental Section

**3-Formyl-4-(2-methyl-propenyl)-cyclopent-3-ene-1,1-dicarboxylic Acid Dimethyl Ester (29).** To a test tube containing **28** (53 mg, 0.2 mmol) were added acetone (2.0 mL), water (5  $\mu$ L, 0.27 mmol), and catalyst **16** (1 mg, 0.002 mmol) under argon. The resulting yellow-orange solution was then stirred for 1 h, after which it was filtered through a pad of silica gel with Et<sub>2</sub>O as the eluent. The solvent was then removed in vacuo to give the crude product which was further purified by silica gel chromatography (60% Et<sub>2</sub>O/petroleum ether) to yield 52 mg (98%) of **29**.

*R<sub>f</sub>* (80% Et<sub>2</sub>O/petroleum ether): 0.65. Mp = 86–87 °C. IR (neat): 2955, 2848, 1736, 1659, 1629, 1579, 1434, 1268, 1202, 1076 cm<sup>-1</sup>. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): 9.86 (s, 1H), 6.27 (s, 1H), 3.74 (s, 6H), 3.41 (s, 2H), 3.24 (s, 2H), 1.91 (s, 3H), 1.86 (s, 3H). <sup>13</sup>C NMR (75.4 MHz, CDCl<sub>3</sub>): 188.1, 171.8, 155.5, 144.17, 135.0, 117.3, 57.3, 53.2, 45.7, 37.9, 27.7, 20.8. HRMS (EI, [M]<sup>+</sup>): calcd for C<sub>14</sub>H<sub>18</sub>O<sub>5</sub>, 266.1154; found, 266.1164 (0.8), 252.0940 (100), 191.0721 (55.9), 147.0811 (16.3), 119.0859 (10.1).

**1-[3-(2-Methyl-propenyl)-1H-inden-2-yl]-ethanone (34).** To a test tube containing **7** (41 mg, 0.19 mmol) were added acetone (1.9 mL), water (5  $\mu$ L, 0.27 mmol), and catalyst **16** (4 mg, 0.0095 mmol) under argon. The resulting yellow-orange solution was then stirred for 1 h, after which it was filtered through a pad of silica gel with Et<sub>2</sub>O as the eluent. The solvent was then removed in vacuo to give the crude product which was further purified by silica gel chromatography (40% Et<sub>2</sub>O/petroleum ether) to yield 36 mg (89%) of **34**.

*R<sub>f</sub>* (40% Et<sub>2</sub>O/petroleum ether): 0.35. Mp = 57–60 °C. IR (neat): 2967, 2922, 2858, 1649, 1556, 1446, 1370, 1288, 1247, 1184, 1147, 1016, 948 cm<sup>-1</sup>. <sup>1</sup>H NMR (200 MHz, CDCl<sub>3</sub>): 7.51 (m, 1H), 7.33–7.42 (m, 3H), 6.24 (m, 1H), 3.74 (d, *J* = 2.6 Hz, 2H), 2.44 (s, 3H), 2.02 (d, *J* = 1.4 Hz, 3H), 1.61 (d, *J* = 0.8 Hz, 3H). <sup>13</sup>C NMR (50.3 MHz, CDCl<sub>3</sub>): 197.1, 150.2, 144.9, 143.7, 140.7, 140.2, 128.1, 126.8, 124.4, 123.4, 118.5, 38.6, 29.7, 25.7, 20.5. HRMS (EI, [M]<sup>+</sup>): calcd for C<sub>15</sub>H<sub>16</sub>O, 212.1201; found, 212.1198 (1.8), 197.0948 (100), 129.0699 (10.5), 128.0625 (10.9).

**1-[2-(2-Methyl-propenyl)-4,5,6,7-tetrahydro-3H-inden-1-yl]-ethanone (35).** To a test tube containing **12** (61 mg, 0.22 mmol) were added acetone (2.2 mL), water (5  $\mu$ L, 0.27 mmol), and catalyst **16** (9.5 mg, 0.022 mmol) under argon. The resulting yellow-orange solution was then stirred for 1 h, after which it was filtered through a pad of silica gel with Et<sub>2</sub>O as the eluent. The solvent was then removed in vacuo to give the crude product which was further purified by silica gel chromatography (20% Et<sub>2</sub>O/petroleum ether) to yield 30 mg (63%) of **35**.

*R<sub>f</sub>* (40% Et<sub>2</sub>O/petroleum ether): 0.60. IR (neat): 2926, 2854, 1696, 1668, 1633, 1558, 1540, 1506, 1436, 1374, 1255, 1203, 1167 cm<sup>-1</sup>. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): 6.39 (s, 1H), 3.16 (broad s, 2H), 2.35 (s, 3H), 2.32 (m, 4H), 1.88 (s, 3H), 1.81 (s, 3H), 1.68 (m, 4H). <sup>13</sup>C NMR (75.4 MHz, CDCl<sub>3</sub>): 200.4, 146.9, 142.9, 138.9, 137.7, 136.4, 120.9, 46.7, 31.2, 28.1, 25.5, 24.8, 23.1, 22.8, 20.5. HRMS (EI, [M]<sup>+</sup>): calcd for C<sub>15</sub>H<sub>20</sub>O, 216.1514; found, 216.1518 (2.9), 201.1291 (14.7), 82.9459 (100).

**2-(2-Methyl-propenyl)-cyclohex-1-enecarbaldehyde (59).** To a test tube containing **58** (33 mg, 0.2 mmol), malonic acid (21 mg, 0.2 mmol), acetone (3.6 mL), and water (0.4 mL) was added catalyst **16** (8.6 mg, 0.02 mmol) under argon. The resulting yellow solution was stirred at 60 °C for 1 h, after which it was filtered through a pad of silica with ether as the eluent. The solvent was then removed in vacuo to give the

crude product which was further purified on silica (20% ether/petroleum ether) to yield 29 mg (90%) of **59**, which agreed with the <sup>1</sup>H NMR data for this known compound.

*R<sub>f</sub>* (40% Et<sub>2</sub>O/petroleum ether): 0.65. IR (neat): 2932, 2858, 1671, 1615, 1447, 1383, 1361, 1273, 1225, 1193, 1154, 1127, 1043, 965, 828, 745 cm<sup>-1</sup>. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): 9.69 (s, 1H), 5.74 (s, 1H), 2.23 (m, 2H), 2.16 (m, 2H), 1.83 (s, 3H), 1.63 (m, 4H), 1.59 (s, 3H). <sup>13</sup>C NMR (75.4 MHz, CDCl<sub>3</sub>): 194.1, 157.0, 139.1, 135.0, 123.1, 32.1, 25.9, 22.2, 21.9, 21.8, 19.7. HRMS (EI, [M]<sup>+</sup>): calcd for C<sub>11</sub>H<sub>16</sub>O, 164.1201; found, 164.1194 (1.0), 163.1137(1.1), 150.1022 (10.6), 149.0990 (100), 147.1187 (2.4), 97.0647 (18.0), 91.0537 (16.3), 83.0849 (10.3).

**2-(3-Methyl-but-1-enyl)-cyclohex-1-enecarbaldehyde (69).** To a test tube containing **68** (32 mg, 0.18 mmol), acetone (1.8 mL), and water (5  $\mu$ L, 0.3 mmol) was added catalyst **16** (8 mg, 0.018 mmol) under argon. The resulting yellow solution was stirred at room temperature for 2 h, after which it was filtered through a pad of silica with ether containing 2% Et<sub>3</sub>N as the eluent. The solvent was then removed in vacuo to give the crude product which was purified on silica (10% ether/petroleum ether) to yield 29.5 mg (60%) of **69**.

*R<sub>f</sub>* (40% Et<sub>2</sub>O/petroleum ether): 0.80. IR (neat): 2931, 2858, 1664, 1631, 1582, 1460, 1373, 1274, 1234, 1154, 961 cm<sup>-1</sup>. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): 10.32 (s, 1H), 6.95 (d, *J* = 16.0 Hz, 1H), 5.99 (dd, *J* = 16.0 Hz, *J* = 7.0 Hz, 1H), 2.47 (m, 1H), 2.42 (m, 2H), 2.29 (m, 2H), 1.7–1.6 (m, 4H), 1.08 (d, *J* = 7.0 Hz, 6H). <sup>13</sup>C NMR (75.4 MHz, CDCl<sub>3</sub>): 191.2, 153.2, 144.1, 134.4, 122.6, 32.3, 28.2, 23.1, 22.5, 22.2, 21.8. HRMS (EI, [M]<sup>+</sup>): calcd for C<sub>12</sub>H<sub>18</sub>O, 178.1358; found, 178.1345 (3.8), 163.1124 (2.7), 161.1335 (13.4), 145.1014 (11.2), 135.0801 (100).

**1-[5-Benzyloxymethyl-1-(toluene-4-sulfonyl)-4-vinyl-2,5-dihydro-1H-pyrrol-3-yl]-ethanone (125).** (±)-**125**: To a test tube containing **118** (29 mg, 0.07 mmol), acetone (1 mL), and water (0.1 mL) were added **16** (3 mg, 0.007 mmol) and malonic acid (7.3 mg, 0.07 mmol) under argon. The resulting yellow solution was sealed and stirred at 45 °C for 1 h and filtered through a pad of silica with ether as the eluent. The solvent was then removed in vacuo to yield a yellow oil which was further purified on silica (60% ether/petroleum ether) to yield 23 mg (80%) of (±)-**125**.

(+)-**125**: To a flask containing **124** (1.4 g, 2.66 mmol), acetone (27 mL), and water (0.54 mL) were added **16** (116 mg, 0.266 mmol) and malonic acid (280 mg, 2.66 mmol) under argon. The resulting yellow solution was sealed and stirred at 40 °C for 3 h and filtered through a pad of silica with ether as the eluent. The solvent was then removed in vacuo to yield a yellow oil which was further purified on silica (60% ether/petroleum ether) to yield 870 mg (80%) of (+)-**125**.

*R<sub>f</sub>* (60% ether/petroleum ether): 0.35. IR (neat): 3089, 3031, 2922, 2867, 1732, 1681, 1652, 1622, 1597, 1580, 1495, 1454, 1343, 1262, 1163, 1099, 1049, 1017, 925, 816, 740, 698, 665 cm<sup>-1</sup>. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): 7.74 (d, *J* = 8.1 Hz, 2H), 7.3–7.2 (m, 7H), 7.15 (dd, *J* = 17.8 Hz, *J* = 11.4 Hz, 1H), 5.53 (d, *J* = 11.4 Hz, 1H), 5.47 (d, *J* = 17.8 Hz, 1H), 5.12 (bs, 1H), 4.56 (d, *J* = 12.3 Hz, 1H), 4.45 (s, 2H), 4.48 (d, *J* = 12.3 Hz, 1H), 3.38 (m, 2H), 2.44 (s, 3H), 2.24 (s, 3H). <sup>13</sup>C NMR (75.4 MHz, CDCl<sub>3</sub>): 194.6, 144.8, 143.9, 138.0, 135.2, 132.8, 129.9, 128.6, 128.3, 127.6, 127.4, 127.1, 123.3, 73.5, 71.7, 67.9, 55.9, 30.6, 21.6. HRMS (EI, [M]<sup>+</sup>): calcd for C<sub>25</sub>H<sub>25</sub>NO<sub>4</sub>S, 411.1504; found, 411.1509 (0.9), 290.0851 (45.3, -CH<sub>2</sub>OBN), 248.0738 (59.4), 155.0170 (25.4). [α]<sub>D</sub><sup>25</sup> = 69.64 (*c* = 0.1, MeOH). The ee was evaluated using a chiral HPLC: OD column, flow rate = 1 mL/min, solvent = 90/10 IPA/heptane, retention times = 17.30 (+), 20.66 (-) min.

**1-[5-Benzyloxymethyl-4-[2-(dimethyl-phenyl-silanyl)-ethylidene]-1-(toluene-4-sulfonyl)-pyrrolidin-3-yl]-ethanone (131).** The solution of Li(SiMe<sub>2</sub>Ph) was prepared as follows: To a cooled, dry flask with a Schlenk fitting on top was added Li granules (0.208 g, 30 mmol). The flask was then cooled to 0 °C, and THF (15 mL) and phenyldimethylsilyl chloride (1.66 mL, 10 mmol) were added under argon. Over 30 min the solution turned a dark red color, and the reaction was stirred a further 4 h at 0 °C. The flask was then placed in a -15 °C freezer

(98) Trost, B. M.; Rudd, M. T. *J. Am. Chem. Soc.* **2003**, *125*, 11516.

overnight. The concentration was then measured by the Gillman double titration method: A 0.5 mL aliquot was quenched with 2 mL of water and titrated with standardized 0.1 M HCl using phenolphthalein to give the total base. A second 0.5 mL aliquot was then quenched with 2 mL of 1,2-dibromoethane in a dry test tube. After mixing for 30 s, 2 mL of water was added and titrated with standardized 0.1 M HCl using phenolphthalein to give the amount of alkoxide base. The amount of alkoxide is subtracted from the total base to give the concentration of silyllithium. The concentration was generally  $\sim 0.5$  M.

To a cooled, dry flask containing CuCN (0.142 g, 1.58 mmol) was added THF (5.5 mL) at 0 °C. The 0.52 M solution of Li(SiMe<sub>2</sub>Ph) (8.0 mL, 4.1 mmol) was then added and stirred 25 min at this temperature and then cooled to  $-78$  °C. (+)-**125** (0.62 g, 1.51 mmol) in THF (5.5 mL, washed with 2 mL) was then added slowly. After 1 h, the reaction was warmed to 0 °C and stirred an additional 4 h. Saturated aqueous NH<sub>4</sub>Cl was then added to quench the reaction, which was then filtered through Celite to remove most of the copper residues. The biphasic mixture was then extracted with ether and more NH<sub>4</sub>Cl. The organic layers were then dried over MgSO<sub>4</sub> and filtered, and the solvent was removed in vacuo to yield a yellow oil which was further purified on silica (50% ether/petroleum ether) to yield 0.82 g of a 2.8:1 mixture of diastereomers **131**. The diastereomers can be separated on silica (40% ether/petroleum ether) but were generally carried on as a mixture.

Data for major diastereomer of **131**: *R<sub>f</sub>* (50% ether/petroleum ether): 0.2. IR (neat): 3067, 3029, 2955, 2922, 2856, 1715, 1598, 1495, 1454, 1427, 1403, 1347, 1249, 1161, 1113, 1093, 1027, 835, 734, 700, 666 cm<sup>-1</sup>. <sup>1</sup>H NMR (400 MHz, C<sub>6</sub>D<sub>6</sub>): 7.78 (d, *J* = 8 Hz, 2H), 7.31 (m, 2H), 7.17–7.0 (m, 8H), 6.74 (d, *J* = 8 Hz, 2H), 5.13 (t, *J* = 7.6 Hz, 1H), 4.56 (bs, 1H), 4.21 (dd, *J* = 10 Hz, *J* = 2.8 Hz, 1H), 4.18 (d, *J* = 12 Hz, 1H), 4.13 (d, *J* = 12 Hz, 1H), 3.57 (m, 2H), 3.17 (dd, *J* = 10 Hz, *J* = 8 Hz, 1H), 2.54 (d, *J* = 4.8 Hz, 1H), 1.83 (s, 3H), 1.67 (s, 3H), 1.50 (t, *J* = 7.6 Hz, 2H), 0.058 (s, 3H), 0.051 (s, 3H). <sup>13</sup>C NMR (125 MHz, C<sub>6</sub>D<sub>6</sub>): 202.9, 142.9, 138.3, 138.0, 136.5, 134.4, 133.7, 129.6, 129.5, 128.4, 128.2, 127.8, 127.6, 73.5, 73.0, 60.6, 57.2, 47.8, 30.1, 26.6, 21.0, 19.5,  $-3.2$ . HRMS (EI, [M]<sup>+</sup>): calcd for C<sub>31</sub>H<sub>37</sub>NO<sub>4</sub>SSi, 547.2213; found, 547.2233 (0.1), 504.2039 (0.5), 426.1570 (38.0), 135.0623 (100).

**1-[5-Benzyloxymethyl-4-[2-(dimethyl-phenyl-silanyl)-ethyl]-1-(toluene-4-sulfonyl)-2,5-dihydro-1H-pyrrol-3-yl]-ethanone (132)**. To a cooled, dry flask containing **131** (0.82 g, 1.5 mmol) were added benzene (55 mL) and DBU (45  $\mu$ L, 0.3 mmol). The solution was then heated at reflux for 7 h and extracted with ether and dilute HCl. The organic layers were dried over MgSO<sub>4</sub> and filtered, and the solvent was removed in vacuo to yield a yellow oil which was further purified on silica (30% ether/petroleum ether) to yield **132** (0.72 g, 87% over two steps).

*R<sub>f</sub>* (50% ether/petroleum ether): 0.25. IR (neat): 3058, 3030, 2958, 2923, 2854, 1687, 1658, 1626, 1598, 1495, 1454, 1427, 1347, 1259, 1163, 1112, 1093, 816, 734, 700, 665 cm<sup>-1</sup>. <sup>1</sup>H NMR (400 MHz, C<sub>6</sub>D<sub>6</sub>): 7.69 (d, *J* = 8 Hz, 2H), 7.34 (m, 2H), 7.2–7.0 (m, 8H), 6.68 (d, *J* = 8 Hz, 2H), 4.69 (m, 1H), 4.43 (d, *J* = 14 Hz, 1H), 4.34 (ddd, *J* = 13.6 Hz, *J* = 4.4 Hz, *J* = 2 Hz, 1H), 4.30 (d, *J* = 12 Hz, 1H), 4.18 (d, *J* = 12 Hz, 1H), 3.76 (dd, *J* = 10 Hz, *J* = 4.8 Hz, 1H), 3.66 (dd, *J* = 10 Hz, *J* = 2.4 Hz, 1H), 2.69 (td, *J* = 13.2, *J* = 4.4 Hz, 1H), 2.0 (td, *J* = 13.2, *J* = 4 Hz, 1H), 1.76 (s, 3H), 1.45 (s, 3H), 0.69 (td, *J* = 14.2 Hz, *J* = 4.4 Hz, 1H), 0.45 (td, *J* = 14.2 Hz, *J* = 4.4 Hz, 1H), 0.14 (s, 3H), 0.13 (s, 3H). <sup>13</sup>C NMR (100 MHz, C<sub>6</sub>D<sub>6</sub>): 193.2, 154.2, 143.2, 138.4, 138.3, 135.8, 133.7, 130.2, 129.7, 129.2, 128.5, 128.0, 127.8, 127.6, 73.5, 71.7, 69.4, 56.2, 29.4, 21.3, 20.9, 14.2,  $-3.5$ ,  $-3.6$ . HRMS (EI, [M]<sup>+</sup>): calcd for C<sub>31</sub>H<sub>37</sub>NO<sub>4</sub>SSi, 547.2213; found, 547.2224 (0.2), 426.1501 (16.5), 398.1307 (26.2), 348.1115 (16.2), 306.1022 (21.9), 135.0621 (100). [ $\alpha$ ]<sub>D</sub><sup>25</sup> = 109.35 (*c* = 0.24, MeOH). The ee was evaluated using a chiral HPLC: OD column, flow rate = 1 mL/min, solvent = 90/10 IPA/heptane, retention times = 15.14 (+), 18.66 (–) min.

**1-[4-[2-(Dimethyl-phenyl-silanyl)-ethyl]-5-hydroxymethyl-1-(toluene-4-sulfonyl)-pyrrolidin-3-yl]-ethanone (135)**. To a cooled, dry flask under hydrogen containing **133** (121 mg, 0.265 mmol) were added degassed (freeze–pump–thaw 3 $\times$ ) and hydrogen-purged (15 min H<sub>2</sub> bubble through) DCM (13.2 mL) and B(O-Pr)<sub>3</sub> (61  $\mu$ L, 0.265 mmol). Crabtree's catalyst [Ir(cod)Py(PCy<sub>3</sub>)PF<sub>6</sub>] (43 mg, 0.053 mmol) was then added quickly under hydrogen. The flask was then added to a Parr apparatus, sealed quickly under hydrogen, purged 2 times with 1000 psi hydrogen, and then sealed under 2000 psi hydrogen. The reaction was stirred for 24 h, the pressure was released, and petroleum ether was added to precipitate most of the iridium. The crude product was then filtered through silica using ether as the eluent. The solvent was then removed in vacuo to yield a yellow oil which was further purified on silica (80% ether/petroleum ether) to yield **135** (79 mg, 65%) and recovered **133** (40 mg).

*R<sub>f</sub>* (50% ether/petroleum ether): 0.10. IR (neat): 3516, 3058, 2958, 2922, 2849, 1710, 1596, 1426, 1343, 1248, 1162, 1113, 1091, 1055, 835, 816, 731, 702, 667 cm<sup>-1</sup>. <sup>1</sup>H NMR (400 MHz, C<sub>6</sub>D<sub>6</sub>): 7.70 (d, *J* = 8.4 Hz, 2H), 7.28 (m, 2H), 7.13 (m, 3H), 6.72 (d, *J* = 8.4 Hz, 2H), 3.82 (m, 2H), 3.6 (m, 3H), 3.05 (m, 1H), 2.99 (bs, 1H), 2.10 (m, 1H), 1.87 (s, 3H), 1.49 (s, 3H), 0.64 (m, 1H), 0.41 (m, 1H), 0.17 (m, 2H),  $-0.06$  (s, 3H),  $-0.11$  (s, 3H). <sup>13</sup>C NMR (100 MHz, C<sub>6</sub>D<sub>6</sub>): 204.5, 143.3, 138.6, 133.8, 133.6, 129.8, 129.2, 128.0, 127.9, 66.1, 65.6, 53.2, 48.2, 46.6, 28.6, 22.4, 21.1, 13.2,  $-3.06$ ,  $-3.90$ . LRMS (CI, [M + 1]<sup>+</sup>): calcd for C<sub>24</sub>H<sub>33</sub>NO<sub>4</sub>SSi, 460.1; found, 460.1. HRMS (EI, [M – CH<sub>2</sub>OH]<sup>+</sup>): calcd for C<sub>23</sub>H<sub>30</sub>NO<sub>3</sub>SSi, 428.1716; found, 428.1730 (34.4), 306.1008 (6.4), 135.0627 (100). [ $\alpha$ ]<sub>D</sub><sup>25</sup> =  $-15.83$  (*c* = 0.75, MeOH).

**1-[4-(2-Hydroxy-ethyl)-5-hydroxymethyl-1-(toluene-4-sulfonyl)-pyrrolidin-3-yl]-ethanone (136)**. To a solution of **134** (58 mg, 0.3 mmol) in acetone (15 mL) was added pTSA monohydrate (150 mg, 0.3 mmol). The reaction was stirred for 24 h and filtered through silica (50% DCM/acetone) with ether as the eluent. The solvent was then removed in vacuo. The crude product was purified further (50% DCM/acetone) to yield 89 mg (87%) **136** as a mixture of acetal and open hydroxy ketone isomers.

*R<sub>f</sub>* (50% acetone/DCM): 0.55. IR (neat): 3454, 2951, 2882, 1709, 1597, 1453, 1341, 1162, 1049, 918, 668 cm<sup>-1</sup>. <sup>1</sup>H NMR (300 MHz, CD<sub>2</sub>Cl<sub>2</sub>): 7.72 (d, *J* = 8.4 Hz, 2H), 7.37 (d, *J* = 8.4 Hz, 2H), 3.79–3.47 (m, 4H), 3.25 (m, 2H), 3.00 (dd, *J* = 11.7 Hz, *J* = 9 Hz, 1H), 2.43 (s, 3H), 2.30 (m, 2H), 1.24 (s, 3H). <sup>13</sup>C NMR (75.4 MHz, CD<sub>2</sub>-Cl<sub>2</sub>): 144.6, 133.5, 130.2, 127.9, 94.6, 68.7, 65.6, 59.0, 49.0, 43.2, 36.6, 28.3, 24.9, 21.7. HRMS (EI, [M – CH<sub>2</sub>OH]<sup>+</sup>): calcd for C<sub>15</sub>H<sub>20</sub>NO<sub>4</sub>S, 310.1113; found, 310.1123 (97.3).

**$\delta$ -Kainic Acid. ( $\pm$ )- $\delta$ -Kainic Acid**: To a cooled, dry flask containing ( $\pm$ )-**139** (8 mg, 0.022 mmol) was added THF (0.2 mL). The flask was cooled to  $-78$  °C, and liquid ammonia ( $\sim 1$  mL) was added. Li granules ( $\sim 1$  mg, 0.16 mmol) were then dropped into the flask. A blue color immediately developed. The reaction was stirred 30 min and quenched with isoprene ( $\sim 1$  mL or until the blue color disappeared). The mixture was warmed to room temperature, and all the volatile components were blown off under argon. Water (0.2 mL) was then added, and the pH was adjusted to  $\sim 7$ . The solution was then passed through an ion exchange column (Amberlight CG-50) eluting with water and then 3% ammonium hydroxide. The fractions containing kainic acid were then collected, and water was removed on a lyophilizer to yield kainic acid, which was recrystallized from ethanol/water (3.8 mg, 80%).

**(+)- $\delta$ -Kainic Acid**: To a cooled, dry flask containing (–)-**139** (10 mg, 0.025 mmol) was added THF (0.3 mL). The flask was cooled to  $-78$  °C, and liquid ammonia ( $\sim 1.5$  mL) was added. Li granules ( $\sim 1$  mg, 0.16 mmol) were then dropped into the flask. A blue color immediately developed. The reaction was stirred 30 min and quenched with isoprene ( $\sim 1$  mL or until the blue color disappeared). The mixture was warmed to room temperature, and all the volatile components were blown off under argon. Water (0.2 mL) was then added, and the pH was adjusted to  $\sim 7$ . The solution was then passed through an ion

exchange column (Amberlight CG-50) eluting with water and then 3% ammonium hydroxide. The fractions containing kainic acid were then collected, and water was removed on a lyophilizer to yield kainic acid, which was recrystallized from ethanol/water (4.2 mg, 80%). The  $^1\text{H}$  NMR was consistent with the known spectra, but the exact location of signals is known to vary somewhat with concentration. The pictured spectrum has a mis-referenced  $\text{H}_2\text{O}$  peak (the values below are corrected).

Mp = 240–245 °C (lit. mp 243–244 °C).  $^1\text{H}$  NMR (500 MHz,  $\text{D}_2\text{O}$ ): 5.0 (s, 1H), 4.71 (s, 1H), 4.03 (d,  $J = 3.0$  Hz, 1H), 3.60 (dd,  $J = 12.5$  Hz,  $J = 7.0$  Hz, 1H), 3.41 (t,  $J = 11.0$  Hz, 1H), 2.91 (m, 2H), 2.23 (dd,  $J = 15.5$  Hz,  $J = 6.5$  Hz, 1H), 2.12 (dd,  $J = 15.5$  Hz,  $J = 8.0$  Hz, 1H), 1.76 (s, 3H).  $[\alpha]_{\text{D}}^{25} = +13.7$  ( $c = 0.13$ ,  $\text{H}_2\text{O}$ ). (lit.  $[\alpha]_{\text{D}}^{25} = -14.2$  ( $c = 0.18$ ,  $\text{H}_2\text{O}$ )).

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**Supporting Information Available:** Experimental procedures and spectroscopic characterization (IR,  $^1\text{H}$  and  $^{13}\text{C}$  NMR, HRMS, or combustion analysis) for all other compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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