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**Regioselectivity in the Au-Catalyzed Hydration and Hydroalkoxylation of Alkynes**

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Over the past decade and a half, homogenous gold catalysis has emerged as a diverse and rich field of research resulting in the continuous development of new methods for organic synthesis. The activation of alkynes towards nucleophilic attack by Au(I) and Au(III) complexes is a well-established mode of reactivity and the gold-catalyzed hydration and hydroalkoxylation of alkynes are two of the more well-explored reaction pathways. Although these classes of reactions have seen continuous development since their initial reports, achieving regioselectivity persists as one of the most challenging issues for this chemistry. This article aims to draw attention to the general problem of regioselectivity in these reactions. A select set of examples is presented to highlight the challenges and survey some of the strategies employed to address this problem.

1. Introduction

The addition of oxygen nucleophiles to carbon-carbon triple bonds is a classic research area that has generated many highly useful transformations for organic synthesis. These reactions can be catalyzed by a variety of metal complexes including mercury,1 palladium,2 ruthenium,3 rhodium,4 platinum,5 and other metals with varying levels of success.6 In addition to catalysts based on these metals, the gold-catalyzed hydration and hydroalkoxylation of alkynes is a well-developed general class of reactions that has been brought to the forefront of organic synthesis over the past 15 years.7 A variety of Au(I) and Au(III) catalyst systems have been shown to effect these transformations with such high efficiency that they might now be considered the standard for alkyne hydration and hydroalkoxylation.8

![Figure 1. General Metal-catalyzed addition to C-C triple bonds](image_url)

The high atom economy coupled with the ability for rapid generation of structural complexity and high functional group tolerance has established Au-catalyzed alkyne addition as an invaluable synthetic tool. For example, a recent report from Fürstner and coworkers demonstrated the power of these transformations in their formal synthesis of (-)-polycavernoside A.9 The Au(I)-catalyzed hydroalkoxylation of alkyne 5 afforded the advanced intermediate 6 that could be further elaborated to the desired natural product (Scheme 1).10

![Scheme 1. Gold-catalyzed hydroalkoxylation in the formal synthesis of (-)-polycavernoside A](image_url)

Although this research platform has been greatly advanced in recent times, there is significant room for improvement, particularly in the area of the regioselective hydration and...
hydroalkoxylation of internal alkynes. Our interest in this chemistry stems from our own attempts to develop a tandem hydroalkoxylation / Claisen rearrangement sequence that proved to be extremely challenging (vide infra). This article is not intended to be a comprehensive review of gold-catalyzed alkyne hydration and hydroalkoxylation, but aims to use select recent examples to outline the inherent challenge of this issue and to highlight some of the unique strategies employed to address this problem.

2. Hydration of Alkynes

2.1 General Introduction/Current State-Of-The-Art

Although the gold-catalyzed hydration of alkynes was first reported over 100 years ago,8 further exploration of this significant finding was not undertaken until 1976 when Thomas and coworkers reported the conversion of phenylacetylene to acetoephonone using tetrachloroauric acid.9 Over the past decade and a half, much progress has been made in the gold-catalyzed hydration of alkynes.6,14 This methodology provides rapid access to a variety of ketone products. It is well known that hydration of terminal alkynes 7 proceeds with a high level of regioselectivity to furnish predominately the Markovnikov products 8 (Figure 2); however, hydration of internal alkynes often results in multiple regioisomeric products and the problem is illustrated by the hydration of 9 to form 10 and 11.

![Figure 2. Gold-Catalyzed hydration of alkynes](image-url)

Currently, a recent report by Nolan and coworkers could be considered the benchmark in the hydration of alkynes with respect to reaction conditions (Scheme 2, eq 1). Through the use of N-heterocyclic carbene (NHC) ligands, they were able to develop a highly efficient catalyst system requiring only parts-per-million loadings for addition to internal alkyl and aryl alkynes.15 This mild catalytic system provides a significant advantage as it obviates the need for high temperatures or acid additives. In a subsequent report, they later demonstrated that the process could also be conducted without a silver salt (Scheme 2, eq 2). This was achieved by activating a mononuclear gold hydroxide complex with HBF₄ to generate a dinuclear gold hydroxide species that efficiently catalyzed the hydration of alkynes.16

Scheme 2. Current state-of-the-art conditions for gold-catalyzed alkyne hydration

![Scheme 2](image-url)
Scheme 3. Early example of Au(III)-catalyzed alkyne hydration

While Utimoto’s work is one of the earliest reports in this area, recent examples further illustrate the persistence of regiochemical issues with internal alkyne hydration. Exploring different ligands and counterions, Leyva and Corma observed that both yield and selectivity could be increased to varying extents in the hydration of internal alkyne \( \text{12} \) (Scheme 4).\(^{15}\) A series of cationic gold complexes bearing phosphine ligands were screened. In all examples, a mixture of ketone products \( \text{13} \) and \( \text{14} \) was observed. Employing the catalytic \( \text{Ph}_3\text{PAuNTf}_2 \) complex gave a 50:50 mixture of products in low yield. Switching to more highly donating phosphines such as \( \text{SPhos} \), greatly improved the reaction yield but provided the products in a 60:40 ratio favoring the aryl ketone \( \text{13} \). This small enhancement in selectivity may arise from either the increased steric bulk or enhanced electron donating ability of the phosphine ligand.

\[
\begin{array}{c}
\text{Ph} & \xrightarrow{\text{Catalyst, H}_2\text{O}} & \text{Ph} = \text{Ph} & \xrightarrow{\text{MeOH}} & \text{Ph} \\
\text{12} & & \text{13} & + & \text{14}
\end{array}
\]

Catalyst | % yield | 13:14
--- | --- | ---
\( \text{AuPPh}_3\text{NTf}_2 \) | 30 | 50:50
\( \text{AuSPhosNTf}_2 \) | 100 | 60:40
\( \text{AuSPhosOTf} \) | 100 | 60:40

Scheme 4. Phosphine ligand effects in gold (I) catalyzed alkyne hydration

Interestingly, using a gold NHC catalyst system, Nolan and coworkers reported higher, albeit modest, selectivities for the hydration of internal alkynes \( \text{9} \) (Scheme 5).\(^{15,19}\) Hydration of 1-phenyl-1-butyne gave a mixture of ketones \( \text{10a} \) and \( \text{11a} \) in a 19:81 ratio. It is noteworthy that this selectivity is opposite of that reported by Utimoto and coworkers. Hydration of 2-octyne afforded a mixture of \( \text{10c} \) and \( \text{11c} \), favoring formation of the methyl ketone, while hydration of non-4-yn-1-ol exclusively gave product \( \text{10d} \) in high yield. The exquisite selectivity observed with this substrate is presumably due to a directing effect of the alkyne substituent.

Figure 3. Directing group strategy for alkyne hydration

As briefly described above, one particularly effective method used to induce selectivity is the inclusion of a tethered nucleophile as a substituent on the alkyne (Figure 4). Initial selective intramolecular attack by the pendant nucleophile onto the alkyne \( \text{15} \) would lead to intermediate \( \text{17} \) and the selectivity of this initial attack would be governed by Baldwin’s rules.\(^{20}\) This intermediate could then be attacked by water to liberate the directing group. Upon protodeauration, ketone \( \text{16} \) would be generated regioselectively. This strategy has been effectively used with a variety of nucleophilic directing groups and several examples are described below.
Hammond and coworkers demonstrated that esters 18 could be employed to furnish alkyn e hydration products 19 with complete selectivity (Scheme 6). The authors proposed that an initial attack of the ester group would generate intermediate 20 via a 5-endo-dig cyclization, which is favored over the alternative 4-exo-dig process. Hydrolysis of the resulting oxonium ion and protodeauration would then form the desired \( \gamma \)-keto esters 19.

In a similar fashion, Oh and coworkers showed that aldehydes were suitable directing groups for the regioselective hydration of internal alkynes (Scheme 7). Treatment of ortho-alkynyl arylaldehydes 21 under cationic gold conditions in the presence of water generated hydration products 22 selectively. An initial 6-endo-dig cyclization by the aldehyde was proposed to direct the attack of water. When the aldehyde substituent on the aromatic ring was changed to a ketone, a complete reversal of selectivity was observed, suggesting that the reaction proceeded through an unexpected 5-exo-dig pathway to produce the opposite regiosomer. Interestingly, when a substrate lacking a directing group was treated under the reaction conditions, the authors report that no reaction occurred.

### 3. Hydroalkoxylation of Alkynes

#### 3.1 Introduction

A similar class of reactions, the metal-catalyzed addition of alcohol nucleophiles to alkynes (hydroalkoxylation) has been...
The intramolecular hydroalkoxylation of terminal alkynes generally proceeds through the initial attack of a tethered alcohol nucleophile and a wide variety of gold-catalyzed intramolecular cyclizations have been developed in recent times.[79] These reactions have been shown to proceed with selectivity for attack at the internal position to generate a vinyl gold intermediate that is often used in an additional tandem process. Barluenga and coworkers demonstrated the selective attack in their tandem hydroalkoxylation/Prins-type cyclization (Scheme 9).[30] Initial gold-catalyzed \textit{exo} addition of the hydroxyl group in alkynols 33 selectively furnished enol ether 35 via protodeauration of the organogold intermediate. A subsequent Prins-type cyclization[31] involving the allyl group then afforded the desired products 34 in high yield.

Manzo and coworkers further demonstrated this selectivity pattern in their intramolecular hydroalkoxylation of 2-alkynyl-substituted phenols 38 (Scheme 11).[33] Treatment with AuCl and potassium carbonate induced a 6-\textit{exo}-dig cyclization of the phenol onto the tethered alkyne to exclusively afford the corresponding enol ether products 39.
Internal Alkynes

In contrast to their terminal alkyne counterparts, internal alkynes pose a more significant regiochemical problem for intramolecular hydroalkoxylation because attack at both positions of the alkyne is frequently observed unless the substrates are engineered such that the ring size formed or electronics of the alkyne favor the formation of one regiosomer. When there is little electronic bias, the initial cyclization generally adheres to Baldwin’s rules. Krause and coworkers demonstrated that, in the presence of an external nucleophile, hydroalkoxylation of homopropargyl alcohols 40 proceeds to give the five-membered acetal products 41 selectively (Scheme 12). An initial 5-endo cyclization furnished a dihydrofuran intermediate, which could be further converted to the desired products by the Bronsted acid catalyst and external nucleophile.

Scheme 12. Tandem cycloisomerization/hydroalkoxylation of homopropargylic alcohols

Further highlighting the preference for formation of the favored ring size, Reddy and coworkers showed that 4-bromo-3-yn-1-ols 42 were smoothly converted to the corresponding γ-butyrolactone products 43 upon treatment with AuCl₃ (Scheme 13). Selective attack at the bromine bearing terminal position of the alkyne exclusively afforded the five-membered lactones.

Scheme 13. Hydroalkoxylation of 4-bromo-3-yn-1-ols

Tuning the electronic nature of the alkyne substituents can greatly influence the regioselectivity of the intramolecular attack of a pendant nucleophile onto an internal alkyne. Vazquez and colleagues demonstrated the gold-catalyzed synthesis of five-, six-, and seven-membered cyclic acetics 45 via an oxo Michael-type reaction sequence (Scheme 14). Treatment of the corresponding hydroxyalkynoates 44 with AuCl₃ initiated the selective alkyne hydroalkoxylation and conversion to the corresponding acetal product in the presence of the external alcohol nucleophile. 7-hydroxyhexynoates proceeded through a 6-endo cyclization whereas 6-hydroxyhexynoates followed a 5-endo pathway. The electronic nature of the ester substituent favored the conjugate addition to the ester β-carbon, dictating the selectivity of the cyclization.

Scheme 14. Hydroalkoxylation of conjugated ynoates

With less biased systems, controlling the regioselectivity is much more problematic. The double hydroalkoxylation of internal alkynes, which is an example of this, is a useful transformation to rapidly generate complex structures from alkynes. A variety of metal-catalyzed strategies to convert alkynes into spiroketal products have been developed. In terms of regioselectivity, the gold-catalyzed addition of the two nucleophiles has been reported to produce mixtures of spiroketal products, as observed by several groups (Scheme 15).
In their spiroketalization studies, De Brabander and coworkers showed that the identity of the catalyst and having the alcohols protected plays a significant role in the product distribution. The [6.6]-spiroketal motif 47 is more commonly found in natural products and is often the desired product of this reaction; however, treatment of the diol 46a favors formation of the [7.5]-spiroketal 48 (Scheme 16). Monoprotected diols were explored and it was found that when $R^1=$TBS and $R^2=$H (46b), the [7.5]-spiroketal 48 is still the major product. In contrast, when the protecting group is placed on the other alcohol, $R^2=$THP (46c-e), the [6,6]-spiroketal 47 was then favored over spiroketal 48.

Aponick and coworkers recently reported a strategy for controlling the regiochemistry of spiroketalization of alkyne triols employing an acetonide protecting group.40 Previously, the group reported that the gold-catalyzed cyclization of triol 59 gave a mixture of the three regiosomeric spiroketal products 60-62 in a combined 80% yield (Scheme 17).41 By masking one of the alcohol nucleophiles as an acetonide (63), the regioselectivity of the reaction could be completely controlled and spiroketal 60 was formed exclusively in comparable yield. As illustrated, this approach offers an alternative strategy for spiroketalization when regiochemistry problems arise.

Scheme 15. Spiroketalization of alkyndiols

Scheme 16. Substituent effect on alkyndiol spiroketalization

Scheme 17. Regiochemical control of alkyne hydroalkoxylation using an acetonide; JohnPhos= [P(t-Bu)$_2$(o-biphenyl)]
Scheme 18. Spiroketalization studies on the γ-rubromycin core

Recently, Hashmi and co-workers reported the use of gold(I) catalysts bearing phosphite ligands with sterically imposing substituents for the intramolecular hydroalkoxylation of alkyndiols. Spiroketalization of diol 54 afforded a mixture of spirokets 55 and 56 with the formation of 55 being favored in a 67:33 ratio (Scheme 19). This preference is consistent with the previous findings of Li and coworkers, but the level of selectivity is somewhat improved.

![Scheme 19. Sterically imposing ligand effects in alkyndiol spiroketalization](image)

Although the problem of controlling the regiochemistry of intramolecular alkyne hydroalkoxylation has yet to be completely resolved, a significant amount of progress has been made in the development of strategies to address this issue. Further progress in this area could lead to more widespread use of this transformation in a variety of settings.

3.3 Intermolecular Hydroalkoxylation

Terminal Alkynes

The gold-catalyzed intermolecular hydroalkoxylation of alkynes is extremely challenging from a regioselectivity standpoint; however, as expected, terminal alkynes have been shown to exhibit very high selectivities. In their seminal report, Utimoto and coworkers demonstrated that terminal alkynes 7 reacted in the presence of NaAuCl4 in refluxing methanol to afford the corresponding dimethyl acetals 64, (Scheme 20). Only a single regioisomer resulting from addition at the internal carbon was observed.

![Scheme 20. Gold (III)-catalyzed hydroalkoxylation](image)

In a subsequent report, Teles and coworkers further demonstrated the high selectivity of the hydroalkoxylation of terminal alkynes. Treatment of terminal alkynes 7 with a gold (I) catalyst in the presence of an acid co-catalyst and an alcohol nucleophile provided the corresponding dimethyl acetals 65 with exclusive selectivity for addition at the more substituted position (Scheme 21). Acetal formation was observed in nearly all cases. Interestingly, reaction of phenylacetylene with bulkier alcohol nucleophiles such as isopropanol resulted in a mixture of the acetal product 65 and enol ether product 66.

![Scheme 21. Gold (I)-catalyzed hydroalkoxylation](image)

Corma and co-workers demonstrated that diol nucleophiles also selectively added to the internal carbon of terminal alkynes. Treatment of the alkynes 7 under cationic gold (I) conditions in the presence of a diol produced the desired cyclic ketals 67 (Scheme 22). Nucleophilic attack of unsubstituted diols occurred exclusively at the more substituted position of the alkyne and the corresponding 5-, 6-, 7-, and 8-membered ketals 67a-d could be generated. When diols bearing an additional substituent were employed with phenylacetylene, the desired ketals 67g-h were isolated as the major product but a small amount of the cyclic acetal (68g-h) was also observed.

![Scheme 22. Gold-catalyzed addition of diols to alkynes](image)

<table>
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<tr>
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<td>H</td>
<td>H</td>
<td>O</td>
<td>O</td>
<td>O</td>
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<tr>
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<td>O</td>
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<td>H</td>
<td>O</td>
<td>O</td>
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</tr>
<tr>
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<td>H</td>
<td>H</td>
<td>O</td>
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^dr not indicated
Carboxylic acids can also be used as nucleophiles and this was recently demonstrated by the Kim lab.46 Treatment of terminal alkynes 7 with a gold (I) salt and silver activator catalyzed the selective addition of carboxylic acids 69 to give the corresponding enol esters 70 (Scheme 23). For alkyl substituted terminal alkynes only the Markovnikov addition products 70a/b were observed. Reactions employing phenylacetylene gave a mixture of products with a significant amount of the anti-Markovnikov product 71 seen.

\[
\text{R}^1 = \text{H} + \text{R}^2 = \text{OH} \quad \rightarrow \quad \text{Ph} + \text{AuClAgPF_6} \quad \text{toluene at } 60^\circ \text{C} \quad \rightarrow \quad \text{O} + \text{R}^1 + \text{R}^2 \quad \rightarrow \quad \text{COR}_2
\]

**Scheme 23.** Gold-catalyzed hydroacylation of terminal alkynes

While the examples mentioned above involved studies on different types of nucleophiles, the catalyst may also affect product distribution and aspects such as the ratio of acetol to enol could also be influenced.47 To this end, a series of gold catalysts were screened for the addition of n-BuOH to phenyl acetylene 72 (Scheme 24). In these examples, the predicted product of addition to the internal carbon was observed; however, the results demonstrate that the electronic nature of the phosphine ligand greatly affects the product distribution. Although both electronic and steric factors may affect the selectivity, when catalysts containing phosphine ligands with all aryl substituents were employed, the enol ether product 73 was heavily favored (entries 1,2). Conversely, complexes containing an electron donating alkyl phosphines favored the formation of the ketal product 74 (entries 3-5).

\[
\text{Ph} + \text{AuCl-n-BuOH} \quad \xrightarrow{\text{DCM rt}} \quad \text{PhOBu + BuO} + \text{BuO}
\]

**Scheme 24.** Effect of the nature of phosphine ligands on regioselectivity of mono-hydroalkoxylation; DavePhos=2-Dicyclohexylphosphino-2’-(N,N-dimethylamino)biphenyl

Although addition to terminal alkynes has been shown to be highly regioselective for nucleophilic attack at the internal alkynyl position, a gold-catalyzed variant favoring addition to the terminal carbon has yet to be reported. Further development in this area would provide a valuable addition to this class of reactions.

**Internal Alkynes**

In contrast to the selectivity observed for terminal alkynes, internal alkynes can generally be attacked by the nucleophile at both positions. The substituents on the alkynyl as well as the identity of the nucleophile play a large role in the regioselectivity. In the earliest example of regioselective addition to an internal alkynyl, Teles and coworkers reported the selective addition of methanol to alkynyl 75 (Scheme 25).44 Limited details are described, but the authors state that the nucleophile added exclusively to the methyl substituted position to give dimethyl ketal 76 as the major product with only a small amount of enol ether 77 detected. The authors suggest that this selectivity is derived from the steric nature of the substituents with attack being favored at the least sterically hindered position.

\[
\text{H}_2\text{C} = \text{CH}_3 \quad \xrightarrow{\text{PhP} + \text{AuMeMsOH}} \quad \text{MeO} \quad \text{MeO} \quad \text{Pr} + \text{H}_2\text{C} \quad \text{Pr}
\]

**Scheme 25.** Steric effect on regioselective hydroalkoxylation

Corma and coworkers also demonstrated that bisaddition to internal alkynes to form a cyclic ketal was possible, but led to a mixture of products (Scheme 26).45,47 Addition of diols to alkynes 9 afforded the corresponding cyclic ketal products 78 and 79. When R₁ = alkyl, R₂ = aryl, addition was selective for the alkyl substituted carbon of the alkynyl in all reported examples. The identity of the diol substituent had a moderate effect on the regioselectivity of the reaction. Employing ethylene glycol afforded the corresponding cyclic ketals 78a and 78c with a slight enhancement in regioselectivity when compared to substituted glycols.
During their studies on the addition of carboxylic acids to internal alkynes, Kim and coworkers reported excellent regioselectivities with aryl alkynes. Addition of carboxylic acids 80 to internal alkynes 9 resulted in vinyl acetate products 81 in high yields as single regioisomers (Scheme 27). Addition to the β-carbon of an anion occurred selectively to afford 81a. Interestingly, addition to 1-phenylpropyne also afforded the vinyl acetate 81b as a single product.

Scheme 27. Gold-catalyzed hydroacylation of internal alkynes

Sahoo and coworkers reported the gold (III) catalyzed intermolecular addition of substituted phenol nucleophiles 82 to unsymmetrical internal alkynes 9 to generate vinyl ethers 83 and 84 (Scheme 28). The authors varied the electronics of both the alkyny substituents as well as the substituents on the phenol nucleophile and the effect on regioselectivity can be observed. When an electron rich unsymmetrical alkynyl was employed using 4-nitrophenol as the nucleophile a slight preference for attack at the phenyl substituted position to give enol ether 84a was observed. Phenyl alkyl acetylenes reacted with similar regioselectivity to give enol ethers 84b and 84c as the major products. When a meta-substituted phenol was employed with an unsymmetrical electron rich alkynyl, the selectivity was reversed to give enol ether 83d in tenfold excess. Addition of para-phenylphenol to an electron deficient alkynyl showed modest selectivity for formation of enol ether 84e, albeit in low yield.

Scheme 28. Au(III)-catalyzed intermolecular hydroalkoxylation of alkynes

Catalyst modification also imparts changes to the level of regioselectivity in this reaction. In a recent report, Nolan and coworkers demonstrated the use of cooperative gold catalysis for the hydrophenoxylation of alkynes (Scheme 29). Reaction of unsymmetrical internal alkynes 9 with a dinuclear gold hydroxide species and phenol nucleophiles 82 afforded the corresponding vinyl ethers 83 and 84. The assorted substituents on both the alkynyl as well as the phenol nucleophile were screened to assess the regioselectivity of the transformation. Alkynes bearing a p-methoxyaryl substituent demonstrated moderate regioselectivities with attack at the electron rich aromatic substituted position to give vinyl ethers 83f and 83h as...
the major products. Treatment of 1-phenylpropyne gave the opposite regioselectivity observed by Sahoo and coworkers to generate enol ethers 83i and 83b, when phenol and 4-nitrophenol were employed as nucleophiles. The dependence of regioselectivity on the nucleophile employed (85:15 versus 74:26) indicates that the electronic nature of both the alkyne and the nucleophile plays a role in determining the regioselectivity of the transformation. The authors also demonstrated that the regioselectivity could be controlled by the inclusion of directing group substituents to give single regioisomeric products 83j and 83k, albeit in reduced yields.

![Scheme 29. Au(I)-catalyzed intermolecular hydroalkoxylation](image)

Enol ethers are valuable synthetic intermediates and they are easily produced in these reactions. Aponick and coworkers reported a tandem hydroalkoxylation/Claisen rearrangement in which the first step of the transformation was the Au(I) catalyzed hydroalkoxylation of internal alkynes. Treatment of alkynes 9 under cationic Au(I) conditions in the presence of an allylic alcohol generated the desired ketone products 86 (Scheme 30). A variety of unsymmetrical internal alkynes with varying alkyne substituents were screened. Interestingly, an electron rich alkyl aryl alkynone afforded the aryl ketone as the major product but, when electron deficient alkynes were employed, the selectivity was reversed to give the α-aryl ketone (e.g. 86a vs. 86b). When an ether or acetate substituent was incorporated on electron rich alkynes, the selectivity was improved to give ketones 86d and 86e as the major products in a 90:10 and 89:11 ratio respectively. When ester or phthalimide substituents were included, the regioselectivity was vastly improved and the corresponding ketones 86f and 86g were produced as single regioisomers. This dramatic improvement in regioselectivity could be attributed to an inductive effect and or neighboring group participation. When the authors subjected 1-phenyl-1-propyne to their conditions, the opposite regioselectivity from Sahoo and coworkers was observed with attack at the alkyl substituted position to generate ketone 86h favored in an 80:20 ratio. Nolan and coworkers later reported a solvent and silver free variant of this tandem hydroalkoxylation/Claisen rearrangement. The authors observed similar levels of regioselectivity for addition to unsymmetrical alkynes.

![Scheme 30. Tandem hydroalkoxylation Claisen rearrangement](image)

4. Conclusions

Over the past decade and a half, gold-catalyzed hydration and hydroalkoxylation reactions of alkynes have been extensively explored and vast improvements in these research platforms have been made. Overall, these transformations have been demonstrated to be reliable synthetic tools for the rapid and atom economical generation of valuable synthetic building...
blocks or complex natural products. Various highly efficient catalyst systems have been developed to effect these transformations, but in general these classes of reactions are still plagued by selectivity issues. The regioselectivity has been shown to vary depending on the catalyst system, nature of the substituents on the alkyne, and identity of the incoming nucleophile. Much progress has been made in developing measures to control the regioselectivity of these reactions and inventive solutions have been devised for many substrate classes. Scheme 31 attempts to classify these reactions by substrate class and reaction type in a general sense as follows: Terminal alkynes have been widely shown to give almost exclusively the Markovnikov products. While reacting with hydride nucleophiles often affords moderate levels of selectivity.

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**Notes and references**


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**Scheme 31. Overview of selectivity**

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