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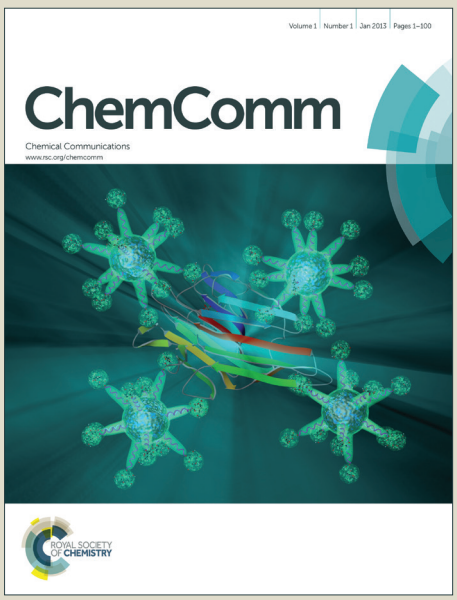

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FEATURE ARTICLE

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]

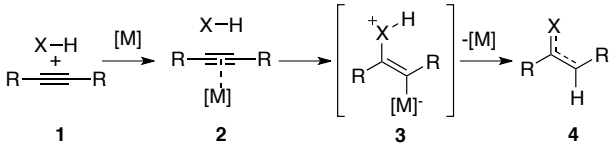
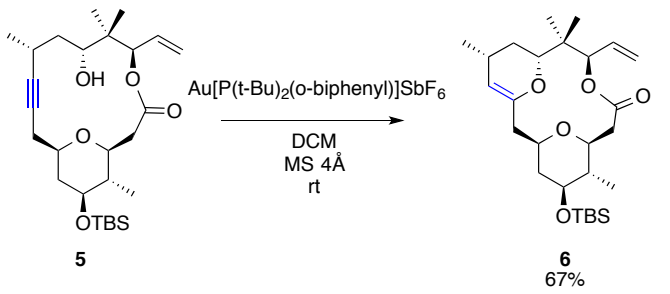


Figure 1. General Metal-catalyzed addition to C-C triple bonds

The utility of this class of reactions has been demonstrated by a multitude of examples in natural product total syntheses.[9] 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.[10] 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).[11]



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

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,[12] further exploration of this significant finding was not undertaken until 1976 when Thomas and coworkers reported the conversion of phenylacetylene to acetophenone using tetrachloroauric acid.[13] 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**.

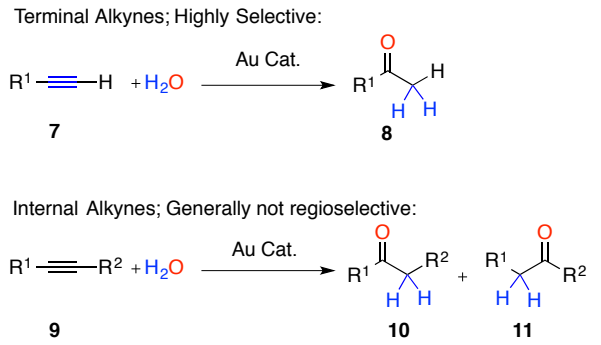
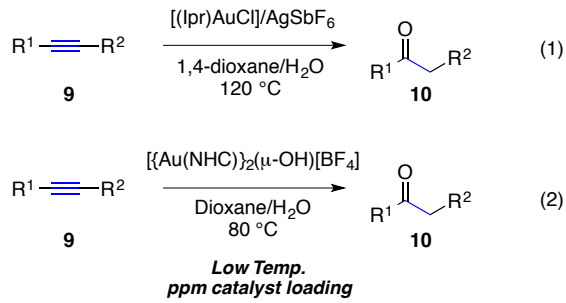


Figure 2. Gold-Catalyzed hydration of alkynes

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 part-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 HBF_4 to generate a dinuclear gold hydroxide species that efficiently catalyzed the hydration of alkynes.[16]

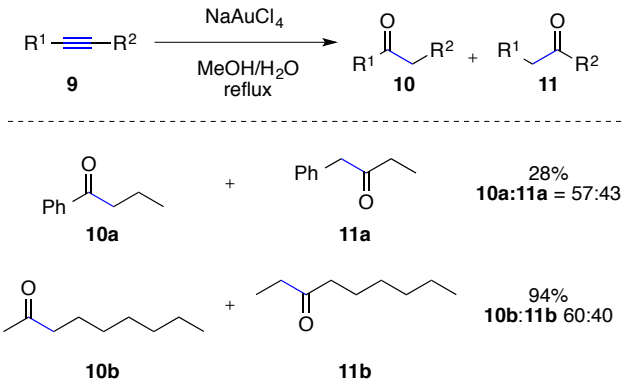


Scheme 2. Current state-of-the-art conditions for gold-catalyzed alkyne hydration

While great strides have been made in terms of improving the catalytic efficiency of the title transformation, there is room for further development in this class of reactions. Specifically, internal alkyne hydration leaves much to be desired with respect to regioselectivity.

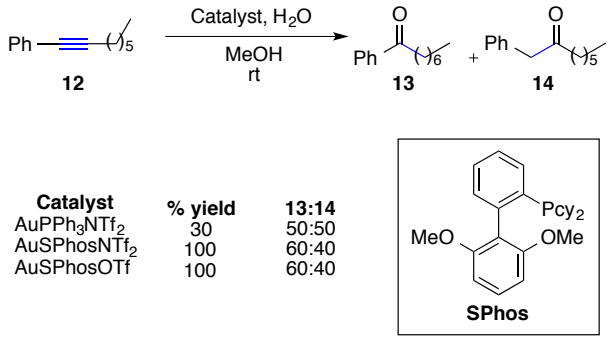
2.2 Hydration of Internal Alkynes

As mentioned above, the hydration of terminal alkynes has been well established and proceeds with high levels of selectivity; however, in contrast, the hydration of internal alkynes often leads to the formation of regioisomeric products. Several factors appear to influence which position of the alkyne is attacked including both the steric and electronic nature of the substituents. As a general observation, the selectivity for the intramolecular hydration of internal alkynes is low and is highly substrate dependent. This observation was made early on and, in their initial report, Utimoto and coworkers reported the hydration of internal alkynes **9** to generate a mixture of the desired ketone products **10** and **11** (Scheme 3).[17] 1-Phenyl-1-butyne was treated with $NaAuCl_4$ in water and methanol to afford a mixture of ketones **10a** and **11a** in low yield with a slight preference for attack at the phenyl substituted alkyne carbon. It should be noted that this level of selectivity requires only a very small difference in energy between the two product-forming pathways. Interestingly, hydration of 2-nonyne gave a mixture of **10b** and **11b** in high yield with a similar level of selectivity, modestly favoring the formation of the methyl ketone.



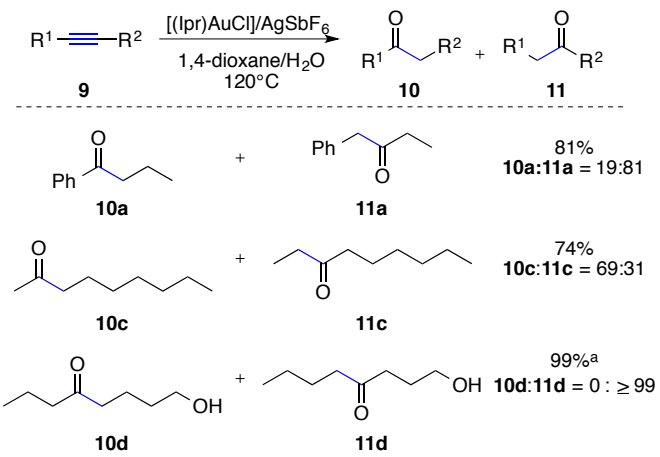
Scheme 3. Early example of Au(III)-catalyzed alkyne hydration

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 **12** (Scheme 4).[18] A series of cationic gold complexes bearing phosphine ligands were screened. In all examples, a mixture of ketone products **13** and **14** was observed. Employing the catalytic $Ph_3PAuNTf_2$ complex gave a 50:50 mixture of products in low yield. Switching to more highly donating phosphines such as SPhos, greatly improved the reaction yield but provided the products in a 60:40 ratio favoring the aryl ketone **13.** This small enhancement in selectivity may arise from either the increased steric bulk or enhanced electron donating ability of the phosphine ligand.



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 **9** (Scheme 5).[15,19] Hydration of 1-phenyl-1-butyne gave a mixture of ketones **10a** and **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 **10c** and **11c**, favoring formation of the methyl ketone, while hydration of non-4-yn-1-ol exclusively gave product **10d** in high yield. The exquisite selectivity observed with this substrate is presumably due to a directing effect of the alkyne substituent.



[a] Conditions: [(IPr)AuOH], $HSbF_6$, 24h

Scheme 5. Employment of a NHC gold catalyst system to furnish regioselective alkyne hydration

2.3.1 Substrate directing group strategies

Although a general solution to the regioselective hydration of internal alkynes remains an unsolved problem, several strategies employing either substrate or catalyst design have been implemented to address this challenge. One particular strategy that has proven to be successful is the manipulation of the alkyne substituents to direct attack of the incoming nucleophile. By including a directing group as a substituent on the alkyne, selective hydration can be achieved generating a single regioisomer (Figure 3).

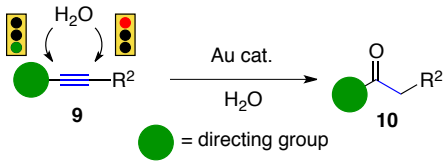


Figure 3. Directing group strategy for alkyne hydration

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 **15** would lead to intermediate **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 **16** would be generated regioselectively. This strategy has been effectively used with a variety of nucleophilic directing groups and several examples are described below.

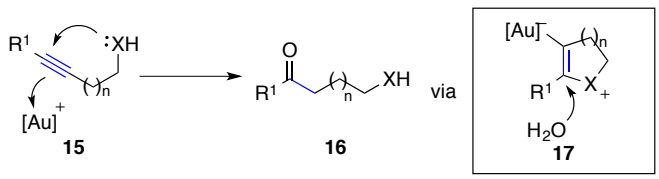
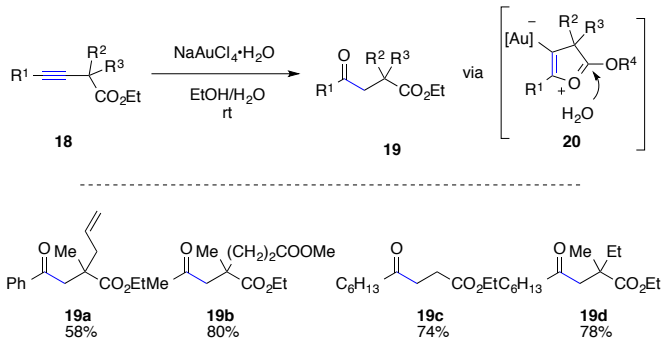


Figure 4. Regioselective alkyne hydration directed by pendant nucleophile

Hammond and coworkers demonstrated that esters **18** could be employed to furnish alkyne hydration products **19** with complete selectivity (Scheme 6).[21] 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 γ-keto esters **19**.

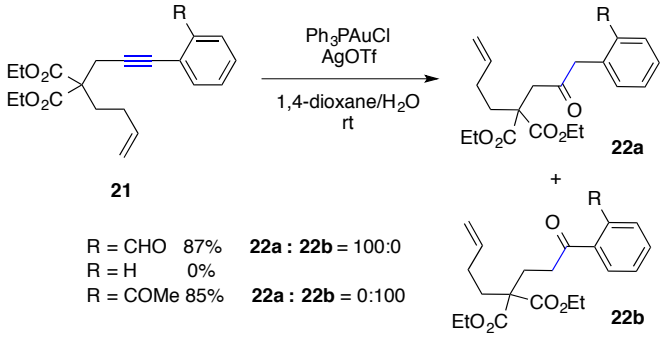


Scheme 6. Use of a neighboring ester to direct alkyne hydration

In a similar fashion, Oh and coworkers showed that aldehydes were suitable directing groups for the regioselective hydration of internal alkynes (Scheme 7).[22] 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 regioisomer. Interestingly, when a substrate lacking a directing group was treated under the reaction conditions, the authors report that no reaction occurred.

2.3.2 Catalyst design strategies

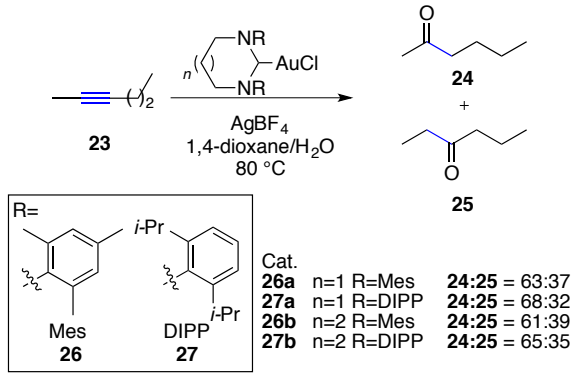
While including directing groups in the substrate can provide highly regioselective examples, by definition the selectivity observed using this approach will always be directly related to the functional groups incorporated into each substrate. A more general approach may be achieved if a catalyst could be designed to provide regioselectivity based either on steric or electronic considerations. Many examples of different catalyst systems have been reported, but to the best of our knowledge, this has not yet been achieved. Differences in selectivity based



Scheme 7. Use of an aldehyde directing group for alkyne hydration

on catalyst, albeit small, have been observed suggesting that this may be possible with further development.

During their studies on bulkier NHC ligands, Cavell and coworkers screened a variety of sterically imposing six and seven membered ring ligands.[23] The steric demand imparted by these ligands was shown to be beneficial in the hydration of substrates such as 4-octyne, which was previously shown to be ineffective under similar conditions employing 5-membered ring NHC ligands bearing mesityl substituents.[15] Hydration of 2-hexyne was accomplished in high yields but only moderate levels of selectivity were observed (Scheme 8). Interestingly, the bulkier DIPP ligand **27** gave slightly higher selectivity than the less bulky Mes ligand **26**, suggesting that this could eventually be an effective strategy for addressing regioselectivity issues. The development of selective new ligands could lead to vast improvements in this field.



Scheme 8. Effect of bulky NHC ligands on alkyne hydration

3. Hydroalkoxylation of Alkynes

3.1 Introduction

A similar class of reactions, the metal-catalyzed addition of alcohol nucleophiles to alkynes (hydroalkoxylation) has been

extensively explored with a variety of metal catalysts,[24] and a gold-catalyzed version of this reaction was first reported by Utimoto in 1991.[17] Over the past two decades, this gold-catalyzed variant has been well explored.[25] Recently, several experimental studies have been performed to gain insight into the mechanism of this transformation[26] as well as to determine the effect of a silver salt[27] and its counterion[28] when employed in gold-catalyzed additions to alkynes. In general, addition to terminal alkynes occurs at the internal carbon to give the corresponding ketal **29** or enol ether **30** products (Figure 5). In contrast, internal alkynes can potentially furnish the two possible enol ether products. Depending on which position of the alkyne is attacked by the nucleophile, **31a** and **31b**, in addition to the corresponding ketals **32a** and **32b**, could all be formed. There are several considerations for determining the selectivity of these reactions including sterics, electronics, and the identity of the nucleophile, but the effects of these factors can often be difficult to predict.

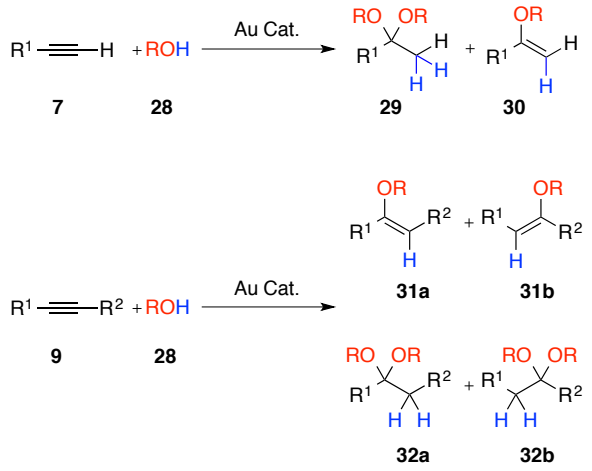
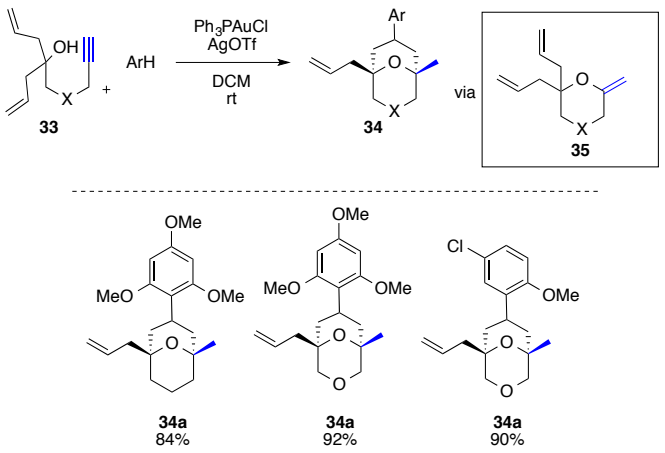


Figure 5. Gold-catalyzed hydroalkoxylation of alkynes

3.2 Intramolecular Hydroalkoxylation

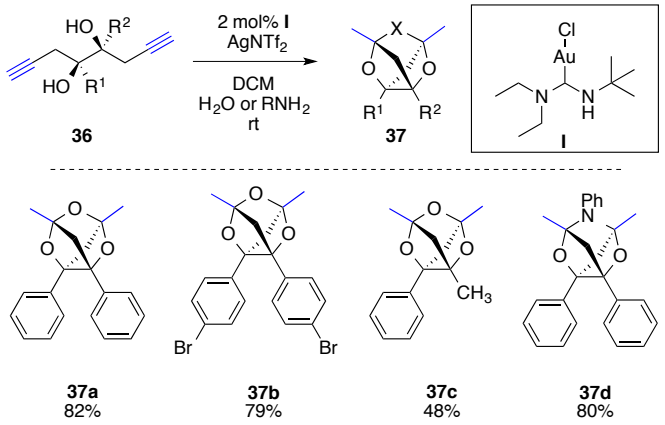
Terminal Alkynes

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.[29] 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 *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.



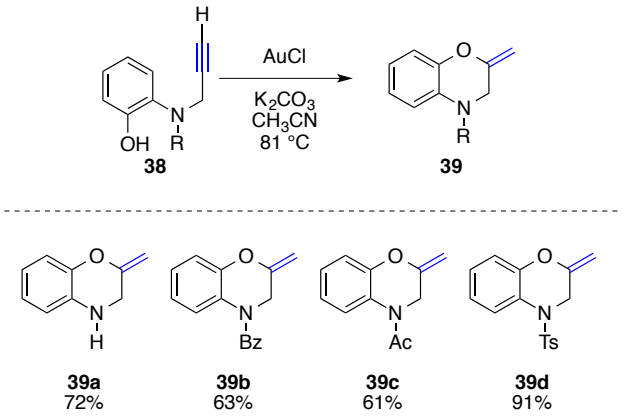
Scheme 9. Tandem Au (I)-catalyzed hydroalkoxylation Prins-type cyclization

In similar fashion, Hashmi and co-workers also demonstrated nucleophilic attack exclusively at the internal position.[32] Treatment of diyne-diols **36** with the acyclic carbene complex **I** initiated a hydroalkoxylation sequence to form bis-enol ethers via 5-*exo*-dig cyclization. These intermediates were trapped with an external nucleophile such as water to afford the bis-ketal products **37** (Scheme 8).



Scheme 10. Double intramolecular hydroalkoxylation of terminal alkynes

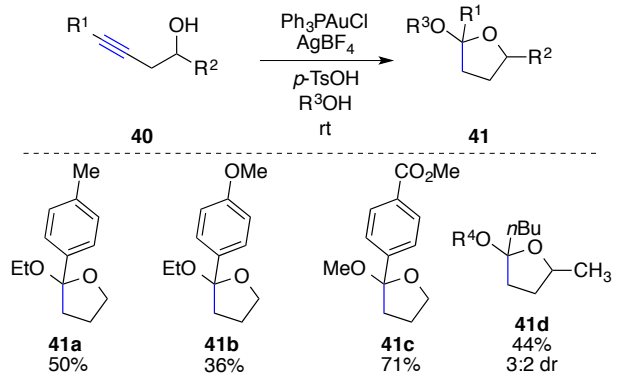
Manzo and coworkers further demonstrated this selectivity pattern in their intramolecular hydroalkoxylation of 2-alkynyl-substituted phenols **38** (Scheme 11).[33] Treatment with AuCl and potassium carbonate induced a 6-*exo*-dig cyclization of the phenol onto the tethered alkyne to exclusively afford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



Scheme 11. Intramolecular hydroalkoxylation of 2-(prop-2-yn-1-ylamino)phenols

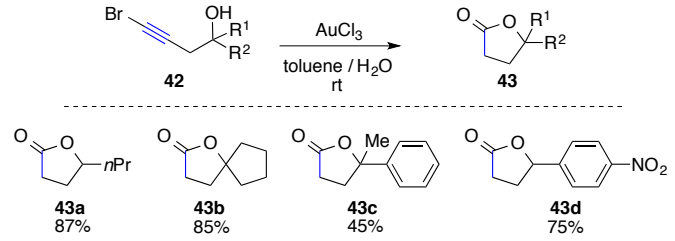
Internal Alkynes

In contrast to their terminal alkyne counterparts, internal alkynes pose a more significant regiochemical problem for intramolecular hydroalkoxylations 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 regiosisomer. 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 acetals **41** selectively (Scheme 12).[34] An initial 5-*endo* cyclization furnished a dihydrofuran intermediate, which could be further converted to the desired products by the Brønsted acid catalyst and external nucleophile.



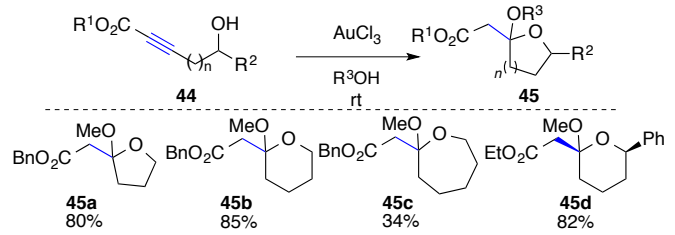
Scheme 12. Tandem cycloisomerization/hydroalkoxylation of homopropargylic alcohols

Further highlighting the preference for formation of the favored ring size, Reddy and coworkers showed that 4-bromo-3-yn-ols **42** were smoothly converted to the corresponding γ-butyrolactone products **43** upon treatment with $AuCl_3$ (Scheme 13).[35] Selective attack at the bromine bearing terminal position of the alkyne exclusively afforded the five-membered lactones.



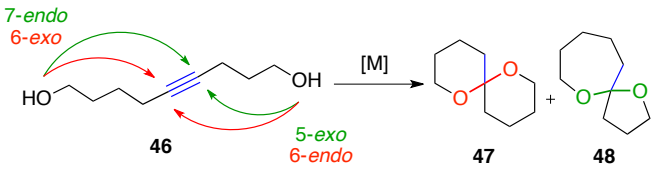
Scheme 13 . Hydroalkoxylation of 4-bromo-3-yn-1-ols

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 acetals **45** via an oxo Michael-type reaction sequence (Scheme 14).[36] Treatment of the corresponding hydroxyalkyneoates **44** with $AuCl_3$ initiated the selective alkyne hydroalkoxylation and conversion to the corresponding acetal product in the presence of the external alcohol nucleophile. 7-hydroxyheptynoates proceeded through a 6-*exo* cyclization whereas 6-hydroxyhexynoates followed a 5-*exo* 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 spiroketals have been developed.[37] 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).[38]



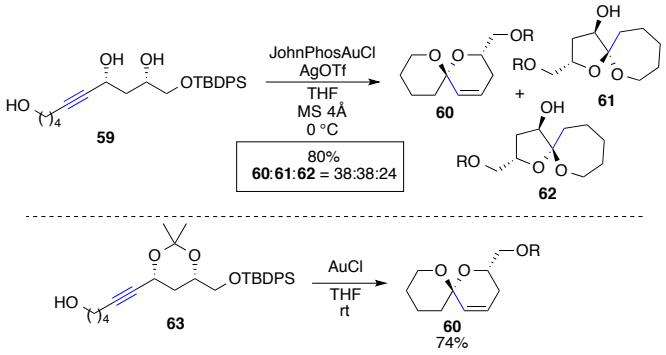
Scheme 15. Spiroketalization of alkynediols

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.[39] 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**.

			Catalyst		47:48
46a	$R^1 = R^2 = H$		$MeAuPPh_3$, $AgPF_6$	92%	21:79
46b	R^1 = TBS	$R^2 = H$	$MeAuPPh_3$, $AgPF_6$	73%	13:87
46c	$R^1 = H$	R^2 = THP	$MeAuPPh_3$, TfOH	40%	57:43
46d	$R^1 = H$	R^2 = THP	PPh_3AuCl, AgOTf	36%	67:33
46e	$R^1 = H$	R^2 = THP	$AuCl_3$	41%	69:31

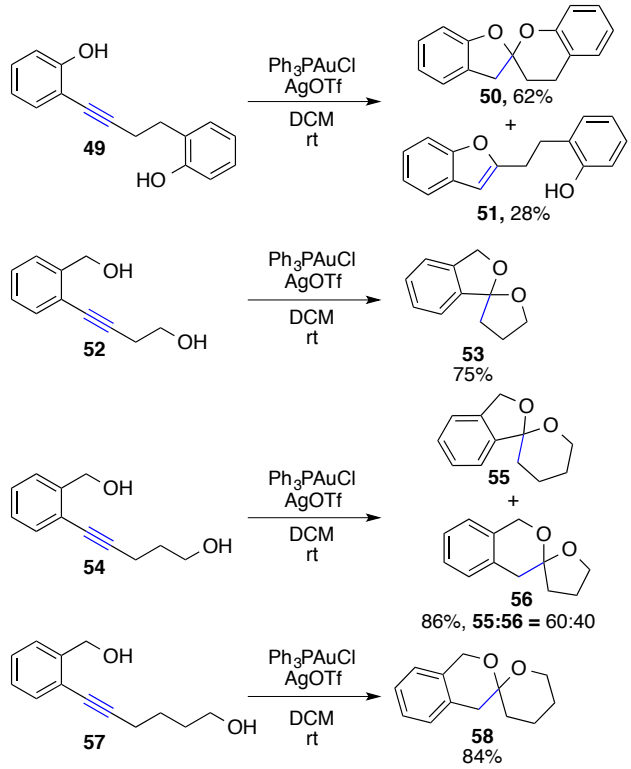
Scheme 16. Substituent effect on alkynediol spiroketalization

Aponick and coworkers recently reported a strategy for controlling the regiochemistry of spiroketalization of alkyne triols emoloying an acetonide protecting group.[40] Previously, the group reported that the gold-catalyzed cyclization of triol **59** gave a mixture of the three regioisomeric 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.



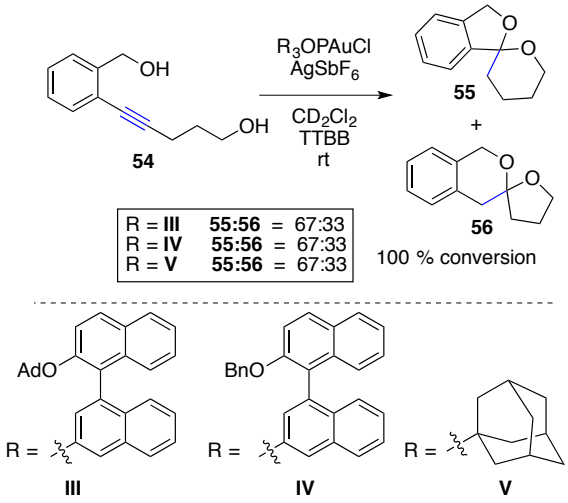
Scheme 17. Regiochemical control of alkyne hydroalkoxylation using an acetonide; JohnPhos= [P(*t*-Bu)$_2$(o-biphenyl)]

In other systems, such as arene containing spiroketals, additional problems may arise. During their studies on the synthesis of the spiroketal core of the rubromycin class of natural products, Li and coworkers screened a variety of substrates in a gold-catalyzed double intramolecular hydroalkoxylation of substituted alkynes (Scheme 18).[42] When bisphenol **49** was treated under cationic gold conditions only spiroketal **50** was observed along with the aromatized product, benzofuran **51**. The authors also screened a series of benzyl alcohol nucleophiles. Diols **52** and **57** cyclized smoothly to give the corresponding spiroketal products **53** and **58** as single regioisomers. Conversely, diol **54** cyclized with poor selectivity and afforded a mixture of regioisomeric spiroketals **55** and **56** in a 60:40 ratio.



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 alkynediols.[43] Spiroketalization of diol **54** afforded a mixture of spiroketals **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.



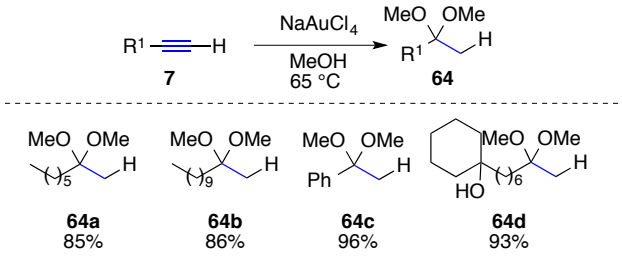
Scheme 19. Sterically imposing ligand effects in alkynediol spiroketalization

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

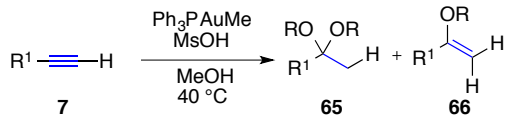
Terminal Alkynes

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 $NaAuCl_4$ in refluxing methanol to afford the corresponding dimethyl acetals **64,** (Scheme 20).[17] Only a single regioisomer resulting from addition at the internal carbon was observed.



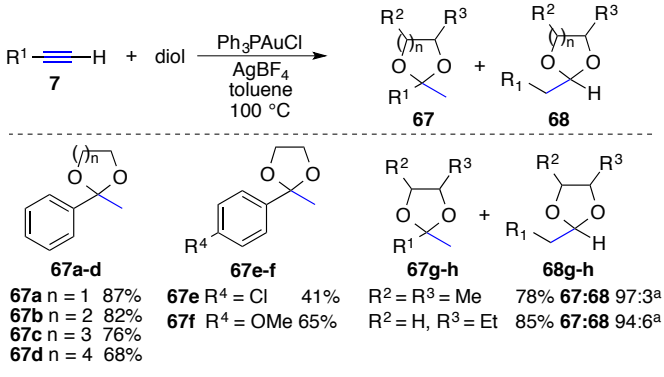
Scheme 20. Gold (III)-catalyzed hydroalkoxylation

In a subsequent report, Teles and coworkers further demonstrated the high selectivity of the hydroalkoxylation of terminal alkynes.[44] 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

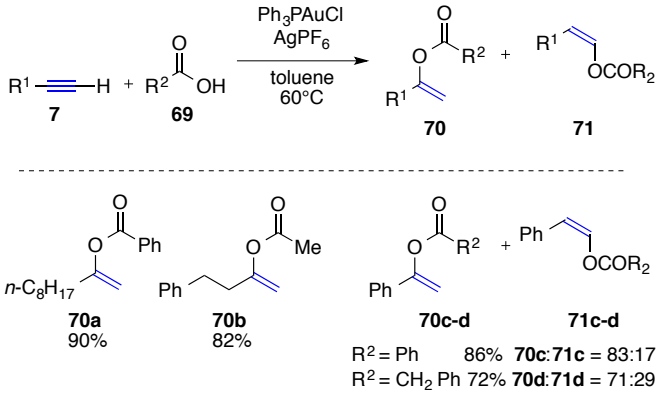
Corma and co-workers demonstrated that diol nucleophiles also selectively added to the internal carbon of terminal alkynes.[45] Treatment of the alkynes **7** under cationic gold (I) conditions in the presence of a diol produced the desired cyclic ketals **67** (Scheme 22). Nucleophilic attack of unsubstituted 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 phenylactylene, the desired ketals **67g-h** were isolated as the major product but a small amount of the cyclic acetal (**68g-h**) was also observed.



[a] dr not indicated

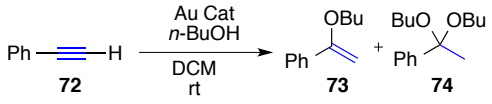
Scheme 22. Gold-catalyzed addition of diols to alkynes

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.



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 acetal 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).



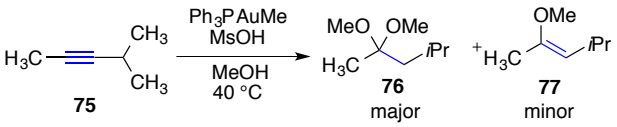
Entry	Catalyst	% conversion	73:74
1	$AuPPh_3NTf_2$	98	88:5
2	$AuP[(2,4,6\text{-tris-}CF_3)C_6H_2]_3NTf_2$	96	92:2
3	$AuDavePhosNTf_2$	>99	10:88
4	$AuSPhosNTf_2$	98	34:63
5	$AuP(t\text{-Bu})_3NTf_2$	97	28:69

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 alkyne 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.

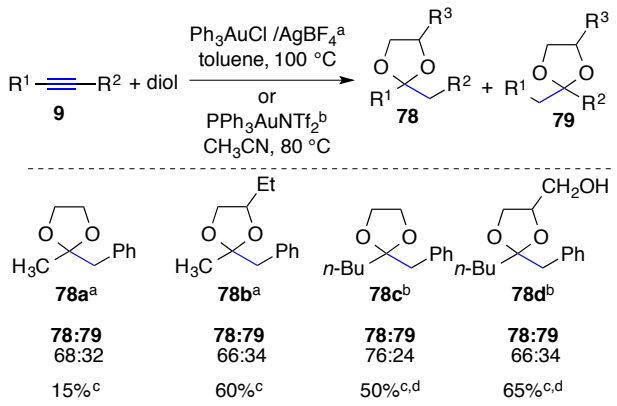
Internal Alkynes

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 alkyne 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 alkyne, Teles and coworkers reported the selective addition of methanol to alkyne **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.



Scheme 25. Steric effect on regioselective hydroalkoxylation

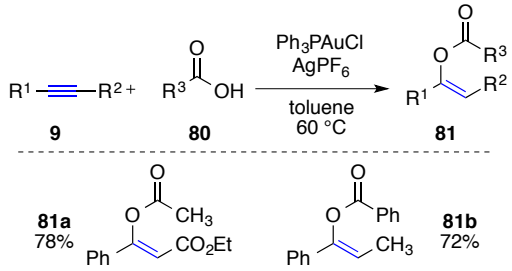
Corma and coworkers also demonstrated that bisaddition to internal alkynes to form a cyclic ketal was possible, but led to a mixture of products (Scheme 26).[45,47] Addition of diols to alkynes **9** afforded the corresponding cyclic ketal products **78** and **79**. When R_1 = alkyl, R_2 = aryl, addition was selective for the alkyl substituted carbon of the alkyne 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.



[a] Conditions A; [b] Conditions B; [c] % conversion of alkyne (GC); [d] % conversion includes formation of hydrolysis products

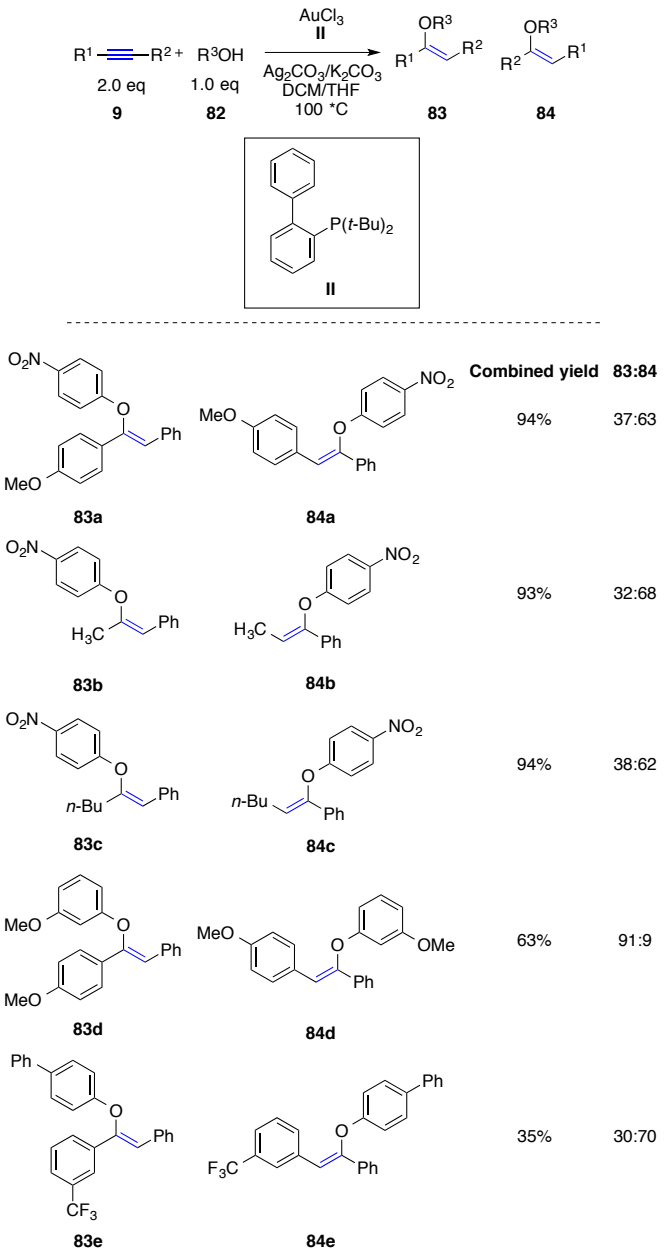
Scheme 26. Regioselective alkyne hydroalkoxylation with diols

During their studies on the addition of carboxylic acids to internal alkynes, Kim and coworkers reported excellent regioselectivities with aryl alkynes.[46] 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 ynoate 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

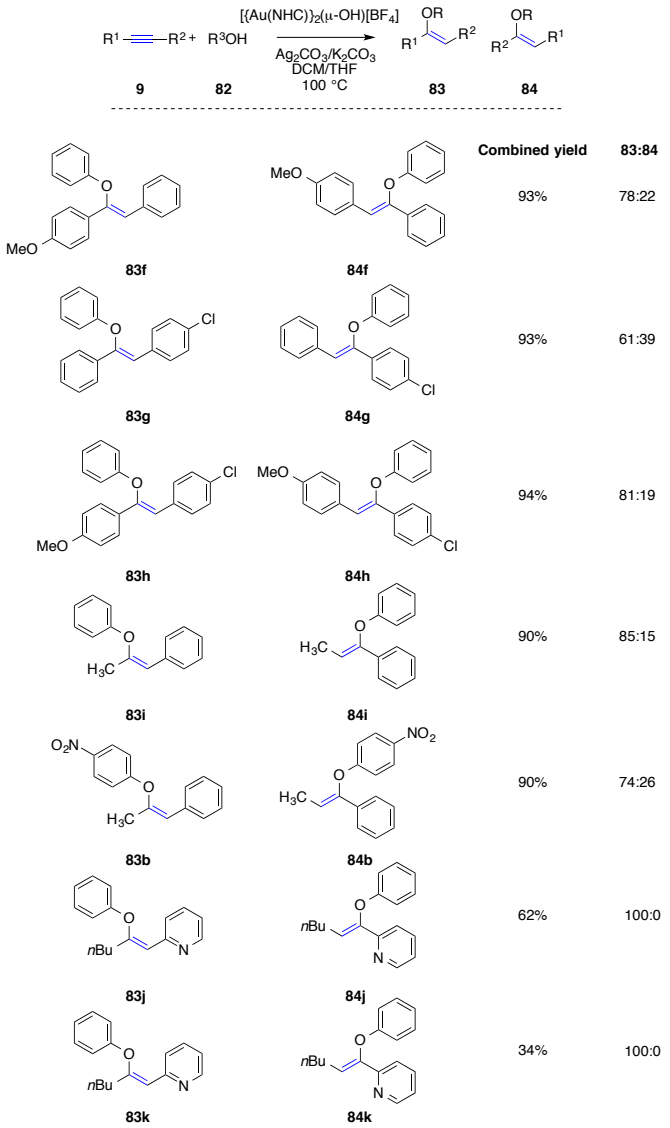
Sahoo and coworkers reported the gold (III) catalyzed intermolecular addition of substituted phenol nucleophiles **82** to unsymmetrical internal alkynes **9** to generate vinyl ethers **83** and **84** (Scheme 28).[48] The authors varied the electronics of both the alkyne substituents as well as the substituents on the phenol nucleophile and the effect on regioselectivity can be observed. When an electron rich unsymmetrical alkyne 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 alkyne, the selectivity was reversed to give enol ether **83d** in tenfold excess. Addition of *para*-phenylphenol to an electron deficient alkyne showed modest selectivity for formation of enol ether **84e**, albeit in low yield.



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

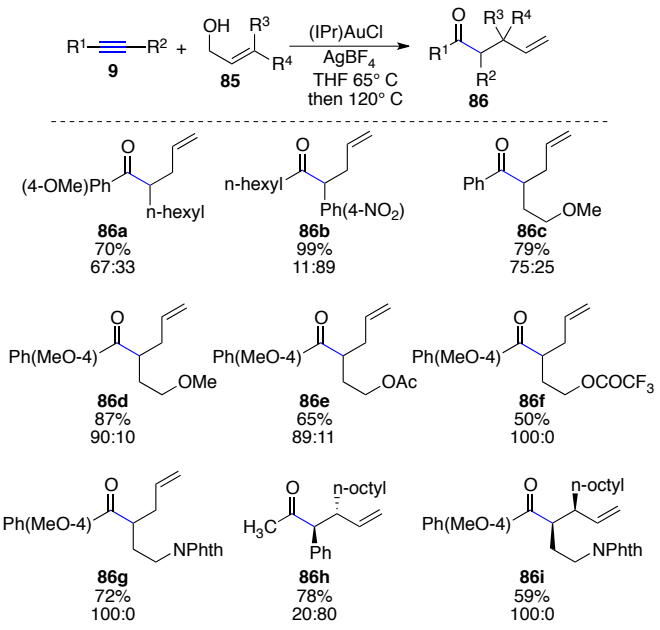
Catalyst modification also imparts changes to the level of regioselectivity in this reaction. In a recent report, Nolan and coworkers demonstrated the use of cooperative gold catalysis for the hydrophenoxylation of alkynes (Scheme 29).[49] Reaction of unsymmetrical internal alkynes **9** with a dinuclear gold hydroxide species and phenol nucleophiles **82** afforded the corresponding vinyl ethers **83** and **84**. The assorted substituents on both the alkyne 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

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.[50] 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 alkyne 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[48] (Scheme 28) 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.[51] The authors observed similar levels of regioselectivity for addition to unsymmetrical alkynes.



Scheme 30. Tandem hydroalkoxylation Claisen rearrangement

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 regioselectivity issues still plague the hydration of alkyl-alkyl substituted alkynes in the absence of directing groups (e.g. Schemes 3-5), the hydroalkoxylation of alkyl-alkyl substituted alkynes can offer moderate levels of selectivity. Although not always entirely, regioselectivity in intramolecular reactions can be dictated by the size of the ring being formed (e.g. schemes 12, 16) or the electronic nature of the substituents (e.g. schemes 13, 14). Intermolecular variants employing alkyl-alkyl substituted alkynes have not been widely reported, but limited examples suggest that differentiation based on the steric nature of the substituents could be possible (e.g. scheme 25). When the substituents are relatively dissimilar, such as the case of alkyl-aryl substituted alkynes, product distribution for alkyne hydration can be difficult to control (e.g. schemes 3, 4), but moderate levels of selectivity can be observed under carefully developed conditions and well designed substrates (e.g. scheme 5). Hydroalkoxylation reactions offer similar challenges with regards to regioselective addition (e.g. schemes 28-30). The product distribution for these reactions seems to be very substrate dependent. Intermolecular hydroalkoxylation of aryl-aryl substituted alkynes offers modest control of regioselectivity (e.g. schemes 28-30). The electronic nature of the substituents plays a key role in product distribution with attack at the more electron deficient alkyne position usually favored. Directing group strategies have been developed for to control hydration of both alkyl and aryl substituted alkynes, but there is still room for development of directing groups for hydroalkoxylation reactions. While it may be difficult to engineer a catalyst system that can offer high levels of selectivity when the alkyne substituents are very similar, there is still ample room for improvement and ideally a general catalytic system to control regioselectivity for alkynes with differing substituents could be realized. Advances in this area are likely to be made in the future as innovative new ligand systems are developed.

Alkyne Substituents	Hydration	Intramolecular Hydroalkoxylation	Intermolecular Hydroalkoxylation
Terminal Alkynes	+	+	+
Alkyl—≡—Alkyl	-	+/-	n/a
Alkyl—≡—Aryl	+/-	+/-	+/-
Aryl—≡—Aryl	n/a	n/a	+/-
Alkyl—≡—Directing	+	+	n/a
Aryl—≡—Directing	+	n/a	+

+ = high levels of selectivity, +/- = moderate levels achieved but highly substrate dependent, - = little to no selectivity, n/a = not enough reported examples to generalize.

Scheme 31. Overview of selectivity

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Notes and references

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