Summary Report for PRF # 56161-UNI1

New Methods for the Synthesis of Spirocycles via Lewis Acid Catalyzed Dearomative Arene Alkyne Coupling

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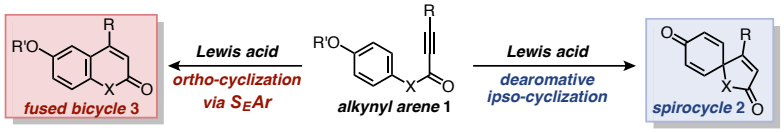
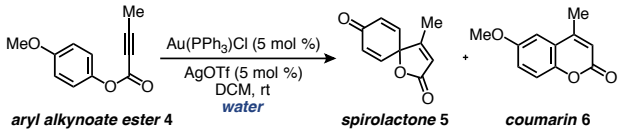
The aim of the research program supported by this grant was to develop new catalytic methods for the intramolecular coupling of arenes with tethered alkynes and alkenes (**1**). I was particularly interested in methods that would proceed via *ipso*-attack of the arene ring onto the catalyst-activated alkyne/alkene (**1**→**2**). This process would proceed via a dearomative spirocyclization, to furnishing valuable spirocyclic compounds (**2**). As such, we have investigated both the scope of this method, to assess its synthetic utility, as well as the mechanism in an attempt to expand beyond the initial substrate scope.



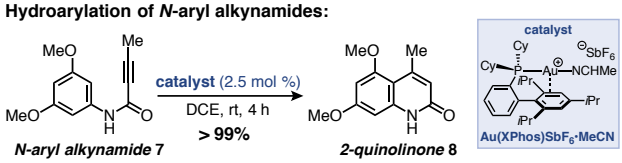
We have shown that alkynyl arenes containing either an ester (**4**) (aryl alkynoate esters) undergo successful spirocyclization in the presence of cationic gold-centered catalysts to furnish spirolactones (**5**). In route to the development of the analogous spirolactamization reaction of *N*-aryl alkynamides (**7**) we found the commercially available complex Au(XPhos)SbF_6•MeCN to be a highly effective catalyst for the hydroarylative *ortho*-cyclization pathway, leading to functionalized 2-quinolinones (**8**). While hydroarylation proved to be the major cyclization pathway for the *N*-aryl alkynamide substrates careful consideration of our proposed mechanism suggested that we might be able to shift the selectivity towards the desired *ipso*-cyclization pathway through a simply substrate modification.

Spirolactonization of aryl alkynoate esters:

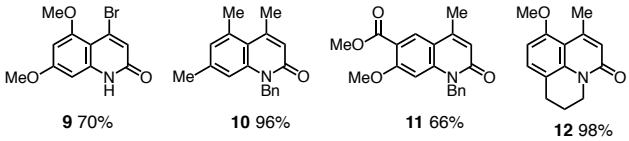


entry	water	time	% yield **5**	% yield **6**
1	---	6 hr	15	61
2	1 equiv	30 min	98	(trace)
3	anhydrous	6 hr	6	85

Hydroarylation of *N*-aryl alkynamides:

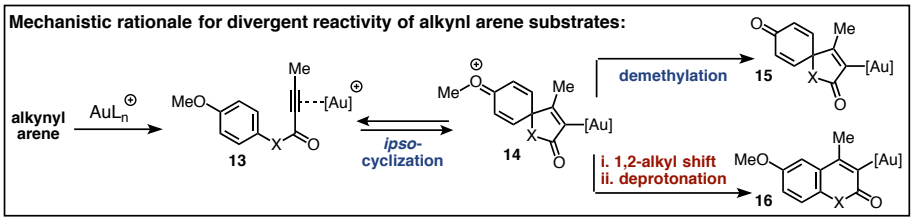


Selected examples of 2-quinolinone products

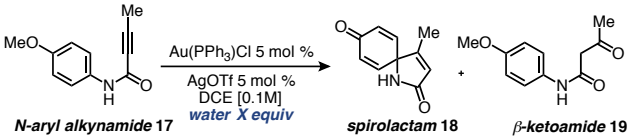


In our study of aryl alkynoate esters we proposed that the alkynyl arene substrates undergo initial *ipso*-cyclization to form intermediate **14**. If the R-group of the *p*-alkoxy group can be removed easily the intermediate completes the catalytic cycle to yield the spirocycle and regenerate the catalyst. However, if the C_R–O bond is stable **14** rearranges via a 1,2-alkyl shift to give **16**, which ultimately yields the fused bicyclic product. In the case of the ester substrates, the addition of one equivalent of water to the reaction mixture resulted in perfect selectivity for the spirocycle, while the coumarin was formed selectively under anhydrous conditions. Unfortunately, the addition of water to the reactions of *N*-aryl alkynamide **17** resulted in hydration of the alkyne and the formation of β-ketoamide **19**.

Mechanistic rationale for divergent reactivity of alkynl arene substrates:

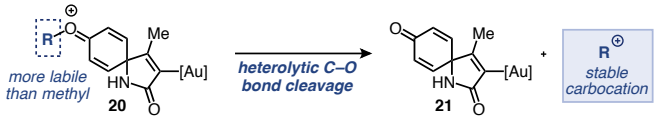


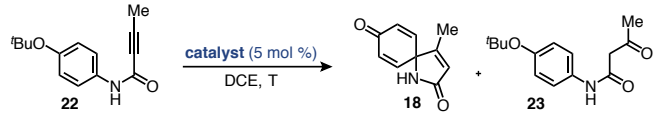
Attempted spirolactamization of *N*-aryl alkynamides:



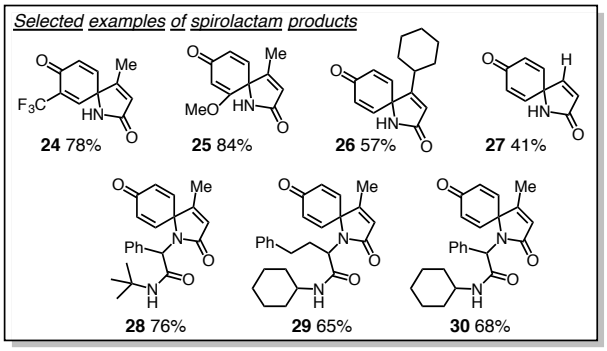
entry	water	T (°C)	% yield **18**	**19**	**(17)**
1	1 equivalent	23	4	81	(6)
2	1 equivalent	50	3	78	(5)
3	---	50	>1	35	(58)
4	---	80	>1	28	(60)

In order to promote the cleavage of the C_R–O bond we considered changing the identity of R on the *p*-alkoxy group to one that could yield a stable carbocation. Such a group might undergo spontaneous C_R–O heterolysis, without the need for an additive (**20**→**21**). Our first choice was the use of a *t*-butyl group, which would cleave to give a *t*-butyl cation. This approach proved very successful. The *p*-*t*-butoxy bearing amide substrates (**22**) now underwent selective *ipso*-cyclization. We have since shown that a wide range of spirolactams can be accessed using this method (**24**-**30**).

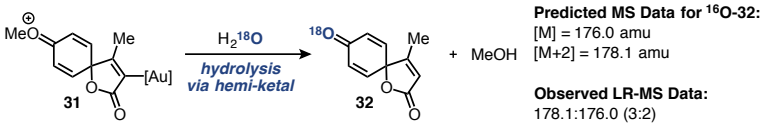




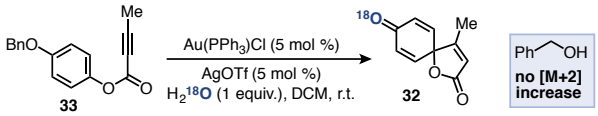
entry	catalyst	activator	T (°C)	yield: 18	23	(22)
1	$Au(PPh_3)Cl$	AgOTf	23	16	35	(30)
2	$Au(PPh_3)Cl$	AgOTf	50	71	16	(9)
3	$Au(PPh_3)Cl$	AgOTf	80	87	4	(0)
4	$Au(XPhos)SbF_6$•MeCN	---	80	70	9	(0)
5	$Au(PPh_3)Cl$	---	80	0	0	(>99)
6	---	AgOTf	80	0	0	(0)
7	TfOH	---	80	0	0	(0)



During the development of these methods we also began to investigate the mechanism of the spirocyclization reaction, with a particular emphasis on understanding both the role of water in the spriolactonization reaction, and the R-group effect in the spirolactamization reaction. These are our latest results, which are currently being prepared for publication. We have found that in the case of the esters, the methyl-group is lost via a hemi-ketal intermediate, and not by an S_N2-type attack of water onto the methyl-group of the oxocarbenium intermediate **31**. After subjecting our lead substrate **4** to our standard conditions run with O-18 labelled water we isolated the spirolactone in comparable yield to the previous conditions. The exact mass of the O-16 compound **5** is 176.0 amu, while the O-18 product **32** is calculated to be 178.1 amu. Analysis of the product by mass spectrometry revealed a significant increase in the 178.1 m/z peak. After correcting for the amount of O-16 water contained in our O-18 water, there was still an unexpectedly high 176.0 m/z peak, which we attribute to the presence of water in our reaction solvent.

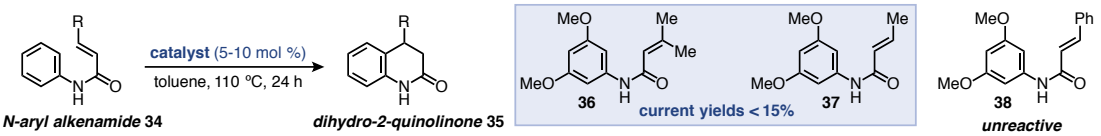


To further confirm the hemi-ketal pathway, we subjected substrate **33** bearing a *p*-benzyloxy group to our reaction under both O-16 and O-18 water conditions. Overall, the substrate proved slower than **4**, but did deliver the same spirolactone product. However, analysis of the crude reaction mixture by GC-MS showed not only an increase in the [M+2] in the O-18 experiment as we saw before, but no such increase for the benzyl alcohol that was generated in the reaction. Thus, we are confident that demethylation of intermediate **31** occurs via the formation of a hemi-ketal. In order to probe the mechanism for the loss of the R-group in our amide substrates we ran our lead spirolactamization reaction with substrate **22** in deuterated chloroform and analyzed the crude mixture by ^{1}H NMR. We were able to identify the presence of both *t*-butanol and dissolved isobutylene in the reaction mixture, suggesting the formation of the *t*-butyl cation.



Most recently, we have investigated the potential cyclizations, either *ipso*- or *ortho*-, of *N*-aryl alkenamides (**34**). Unfortunately, none of our previously established conditions for alkynes translated to this new substrate class. We have begun modifying our conditions and have since observed selective *ortho*-cyclization to the dihydro-2-quinolinone products (**35**), albeit under somewhat forcing conditions. We are currently employing between 5-10 mol % of several newly identified catalysts in refluxing toluene. While our best yield at this time is only 15%, it would appear that the cyclization of these substrates is possible.

Initial results for the hydroarylation of *N*-aryl alkenamides:



During the course of these studies I have mentored nine undergraduate students in my lab, all of whom were supported by this ACS-PRF UNI award. Five of these students have gone on to pursue their doctorates in chemistry, with two more currently in the process of applying. Moreover, seven of these students have appeared as co-authors on our publications in the *Journal of Organic Chemistry*; the other two are co-authors on a pending manuscript. The award of the ACS-PRF grant allowed me to pay students for their labwork during the academic year, and to employ them as full-time research assistants during the summer months. It was due to this support that I was able to accomplish so much with an undergraduate team. They were able to devote significant time to labwork since they did not need to work outside of the lab to support themselves financially. The summer salary I claimed as part of the award also allowed me to devote significant time to my research, when I otherwise would have been teaching during the summer session. In the fall of 2018 I applied for tenure and promotion at DePaul University. This ACS-PRF award and the work supported by the grant constitutes the majority of my research activities, and has been received highly favorably by my internal reviewers. I am grateful to the ACS-PRF for this award, and plan to apply to the ACS-PRF UR mechanism in the next cycle as I look to continue investigating these reactions, and explore new directions in my research program.