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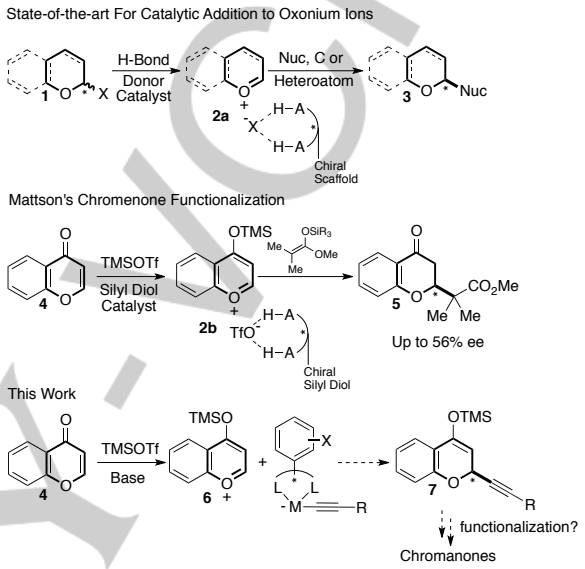
A Facile Enantioselective Alkynylation of Chromones

Lindsey G. DeRatt, Mukesh Pappoppula, and Aaron Aponick*[a]

Abstract: The first catalytic enantioselective alkynylation of chromones is reported. In this process, chromones are silylated to form silyloxybenzopyrylium ions that lead to silyl enol ethers after Cu-catalyzed alkyne addition using StackPhos as ligand. The outcome of the reaction is impacted by distal ligand substituents with differing electronic character and it was found that successful reactions could be achieved with different ligand congeners by using different solvents. This sequence enables access to different products by protonation or further functionalization, thus increasing complexity in a divergent manner. The transformation is high yielding over a broad scope to provide a variety of useful chromanones in high enantioselectivity.

Enantioselective catalysis is one of the principal strategies for the introduction of chirality to molecules used in disciplines throughout the molecular sciences,[1] driving the development of new catalysts and ligands.[2] Although certain privileged structures display applicability across a range of transformations,[3] the discovery of new types of catalysts and ligands is crucial. Small molecule H-bond donor catalysts have now found success in many different types of transformations and one challenging area that has successfully been addressed is the enantioselective addition to oxonium ions whereby H-bond donor catalysts participate in anion binding (Scheme 1).[4] In these reactions, an oxonium ion is often formed by catalyst promoted ionization forming a chiral ion pair **2a**.[5] Many elegant examples demonstrate the applicability of this strategy, resulting in the enantioselective preparation of a variety of different bond motifs.[6] Alternatively, the oxonium can be formed by other means and Mattson showed that **2b** could be formed by silylation of **4**.[7] This work demonstrated the first enantiocontrolled addition to 4-silyloxybenzopyrylium triflates and employed silyldiol catalysts reaching 56% ee. Metal-catalyzed enantioselective addition to oxonium ions is much less common, despite the fact that more basic nucleophiles could be compatible.[8] Watson has reported on the addition to cyclic oxocarbeniums formed by ionization of substrates **1**.[9] Using BOX ligands, they report significant differences between related substrates and the identification of alternative ligand congeners was unsuccessful, necessitating specific substrate types.[9c]

We have recently been exploring the application of stabilizing, non-covalent interactions within imidazole-based biaryls[10] and wondered if our Stack-ligand platform might provide a useful scaffold for addition to oxonium ions. Since oxocarbenium electrophiles have no lone pairs available to engage the catalyst via Lewis acid/base interactions, we were intrigued by the possibility that our arene-rich ligand framework might be able to induce a selective reaction and that non-covalent interactions could possibly play a role (Scheme 1). Successful implementation of this strategy would provide a useful alternative to the anion binding strategy and we set our sights on chromone alkynylation.[11]



Scheme 1. Enantioselective Chromone Alkynylation.

Chromanones constitute an important core that is shared by many biologically active natural products.[12] Diverse bioactivity includes antitumor,[12c] antimicrobial,[12d] and antibacterial activities,[12e] among others. This core has also been incorporated into synthetic analogues such as Krische's chromanone-based bryostatin analogues.[12f] Notably the 2-position is generally substituted and, as such, enantioselective methods have been developed to access this motif.[13] Despite this importance, catalytic enantioselective methods are limited, perhaps because there are issues that may be problematic. Notably, under basic conditions, the reversible elimination of phenoxide can result in racemization.[13a] The addition of aliphatic groups has been reported using basic organometallics,[14] but these groups do not broadly map onto bioactive compounds.[7] In this regard, the direct addition of alkynes is desirable because they are readily available and diverse synthons. This new method would also be advantageous because the silyl enol ether **7**, could potentially be protonated or further elaborated to increase the molecular complexity. Herein, we report our results in this area.

With the goal of developing an enantioselective chromone alkynylation, we set out to explore the proposed transformation using our Stack-ligands. These ligands were designed to have a stabilizing intramolecular catalyst-catalyst interaction between the naphthyl and C_6F_5-groups,[10a,f] and the groups on the backbone were originally incorporated to establish a chiral pocket with quadrants of differing steric demand.[10b] The

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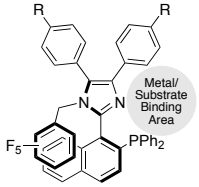
Supporting information for this article is given via a link at the end of the document.

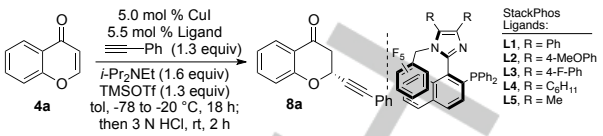
backbone aryl groups can be modified to include electron withdrawing/donating substituents[10f] and we sought to determine if these modifications could impact the reaction, possibly by intermolecular π-π[15] or π-cation[16] interactions. Although the phosphine's aryl groups are also positioned in proximity, and P-aryl-substrate interactions are known,[17] the backbone aryls are unique to this imidazole *P,N*-ligand class and offer tunability without directly impacting the nature of the metal-ligand bond as does phosphine modification.



- R groups distal to binding site with minimal steric impact
- Electronic changes insulated from basic/chelating nitrogen

The study commenced with optimization experiments (see Supporting Information) and the reaction parameters shown in Table 1 were established. Under these conditions, the reaction proceeded without exogenous ligand to provide the chromanone **8a** in 73% yield (entry 1) and it was encouraging to find that the yield was improved by addition of *rac*-StackPhos (entry 2). The reaction was then tested with a variety of chiral ligands to probe how distal changes would impact the selectivity. Using (*S*)-StackPhos **L1**, with unsubstituted phenyl groups on the backbone, the product was isolated 89% yield and the selectivity was excellent (94% ee, entry 3). Interestingly, increasing the electron density on the backbone aryls by incorporation of methoxy groups in **L2** yielded a reduction in both reactivity and selectivity (79% yield, 85% ee, entry 4). Inclusion of 4-fluorophenyl groups in ligand **L3** restored the ee to 94% and **8a** was isolated in 85% yield (entry 5). Surprisingly, these reactivity/selectivity results are opposite to what might be predicted considering catalyst-benzopyrylium interactions.[18] Although the substituents on the backbone aromatic are not able to directly donate to the basic imidazole nitrogen through resonance, these changes may also be due to inductive effects;[19] however, both methoxy and fluoro are inductive withdrawing groups and would likely show a similar trend. Our original hypothesis neglected solvent,[15,16] and the fact that toluene emerged as the solvent of choice in our initial optimization was somewhat surprising. Using benzene instead of toluene with the methoxy ligand **L2**, the selectivity increased to 90% ee, while non-aromatic solvents gave dramatically decreased yield and selectivity (entries 6-8). Furthermore, using benzene as solvent with **L1**, the selectivity was reduced (entry 9 vs 3). These results suggest that the aromatic solvent molecules play an important role, perhaps by mediating interactions with the cationic intermediate. This is further supported by the necessity for aromatic groups on the backbone. With either cyclohexyl- or methyl ligands **L4**/**L5**, the selectivity decreased substantially (entries 10, 11). Although the exact nature of the interactions required for high selectivity are unclear at the moment, the evidence points to the mitigating factors being largely electronic and are suggestive of solvent mediated arene-arene/ arene-cation interactions.

Table 1. Optimization Studies.

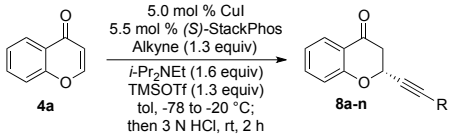


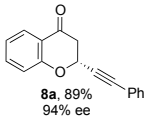
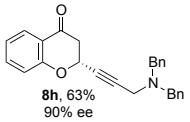
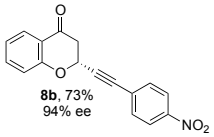
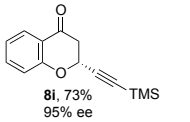
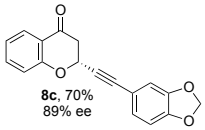
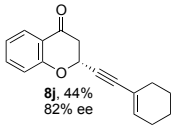
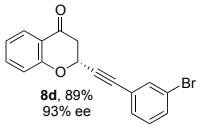
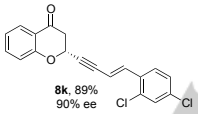
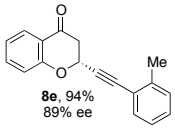
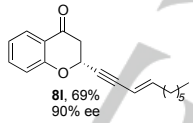
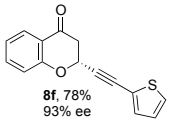
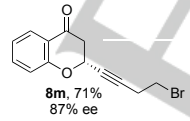
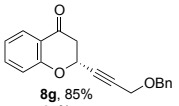
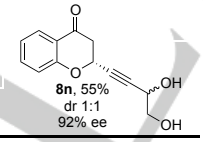
entry	ligand	deviation	yield (%)	ee (%)
1	--	no ligand	73	--
2	*rac*-StackPhos, *rac*-**L1**	*rac*-ligand	91	--
3	*(S)*-StackPhos, **L1**	none	89	94
4	*(S)-p*-OMe-StackPhos, **L2**	none	79	85
5	*(S)-p*-F-Ph-StackPhos, **L3**	none	85	94
6[a]	*(S)-p*-OMe-Ph-StackPhos, **L2**	PhH as solvent	71	90
7	*(S)-p*-OMe-Ph-StackPhos, **L2**	THF as solvent	65	56
8	*(S)-p*-OMe-Ph-StackPhos, **L2**	CH_2Cl_2 as solvent	74	55
9[a]	*(S)*-StackPhos, **L1**	PhH as solvent	89	88
10	*(S)*-Cy-StackPhos, **L4**	none	76	79
11	*(S)*-Me-StackPhos, **L5**	none	92	45

[a] Reaction temperature = -78 °C to 0 °C, 18 h.

Irrespective of the mechanistic underpinnings, the reaction worked quite well. The conditions in Table 1, entry 3 were deemed optimal and the scope of the reaction was explored. As seen in Table 2, it was found that the transformation tolerates a variety of alkynes. In addition to phenylacetylene, both electron withdrawing and donating groups on aromatic alkynes produced **8b** and **8c** in high ee (94% and 89% ee, Table 2, entries 2-3). The reaction also tolerated substitution in the *ortho* and *meta* positions (entries 4-5) as well as heteroaromatics (entry 6). Protected propargyl alcohol and amine worked well under the reaction conditions forming the products **8g** and **8h** in 95% and 90% ee (entries 7-8). The reaction proceeded smoothly using TMS acetylene, giving the alkynylated product **8i** in 73% yield and 95% ee (entry 9), which is important for terminal alkyne synthesis. It was also demonstrated that enynes and aliphatic alkynes were functional under the reaction conditions (entries 10-13). Finally, the presence of additional stereocenters did not affect the reaction and **8n** was formed in 92% ee *vide infra.*

Table 2. Alkyne Scope Studies.

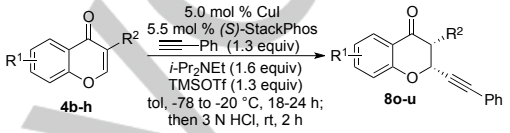


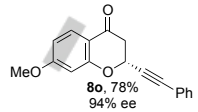
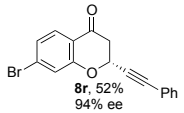
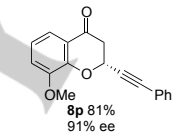
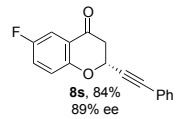
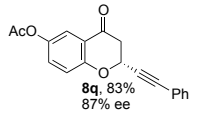
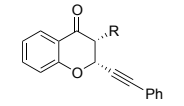
entry	product	entry	product
1	 **8a**, 89% 94% ee	8[a]	 **8h**, 63% 90% ee
2	 **8b**, 73% 94% ee	9[a]	 **8i**, 73% 95% ee
3	 **8c**, 70% 89% ee	10	 **8j**, 44% 82% ee
4	 **8d**, 89% 93% ee	11	 **8k**, 89% 90% ee
5	 **8e**, 94% 89% ee	12[b]	 **8l**, 69% 90% ee
6	 **8f**, 78% 93% ee	13	 **8m**, 71% 87% ee
7	 **8g**, 85% 95% ee	14[c,d]	 **8n**, 55% dr 1:1 92% ee

[a] Reaction temperature = -78 °C to -10 °C; [b] The enyne starting material and the product **8l** were both used and isolated in a (5:1) E:Z ratio; [c] The alkyne bis-acetate was used as starting material and immediately deprotected to form the diol **8n**. Yield is reported over 2 steps; [d] Enantioselectivity determined after Au-catalyzed cyclization to form the furan (Scheme 3).

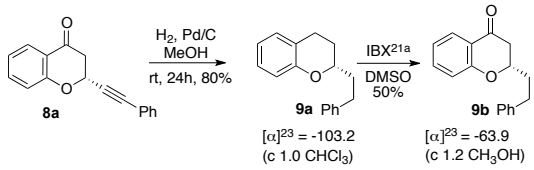
The scope of the chromones was also explored (Table 3). The reaction proceeded smoothly with incorporation of an electron donating methoxy group in the 7-position, which is seen in numerous natural products, to give the product **8o** in 78% yield and 94% ee (Table 3, entry 1). Alkynylation of 7-bromochromone also worked well under the reaction conditions (entry 4), which could allow for further functionalization of the chromone skeleton through cross-coupling reactions. Oxygenation at the 8-position afforded the product **8p** in 91% ee (entry 2). Interestingly, both 6-fluoro and 6-acetoxyl substituents were tolerated under the reaction conditions (entries 5,3). We were also encouraged to find that the reaction functions on substrates bearing a substituent at the 3-postion, allowing for the incorporation of an additional stereocenter on the nucleus. As observed in entries 6 and 7, the 3-substituted products **8t** and **8u** were isolated in good yield and diastereoselectivity favoring the 2,3-*cis* products in high optical purity. Compounds with this relative stereochemistry are likely the kinetic products derived from silyl enol ether protonation.

Table 3. Studies on Chromone Scope.



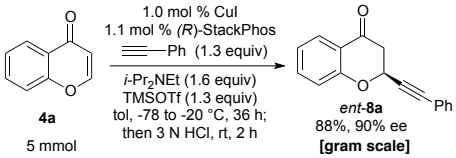
entry	product	entry	product
1	 **8o**, 78% 94% ee	4	 **8r**, 52% 94% ee
2	 **8p** 81% 91% ee	5	 **8s**, 84% 89% ee
3	 **8q**, 83% 87% ee	6	 R = Ph, **8t**, 78% dr 10:1; 95% ee
		7	R = Me, **8u** 81% dr 10:1; 95% ee

With a broad substrate scope established, it was necessary to determine the absolute configuration of the products. To this end, **8a**, formed using the *(S)*-**L1**, was transformed into the natural product flindersiachromanone **9b**,[20] which has been selectively prepared as both enantiomers by chemical synthesis.[13b,21] Comparison of the sign of the optical rotation of both intermediate **9a** and the natural product **9b** revealed the stereochemistry to be *(S)*, as shown in Scheme 2, and the alkyne products **8** were assigned as shown by analogy.



Scheme 2. Determination of Absolute Configuration

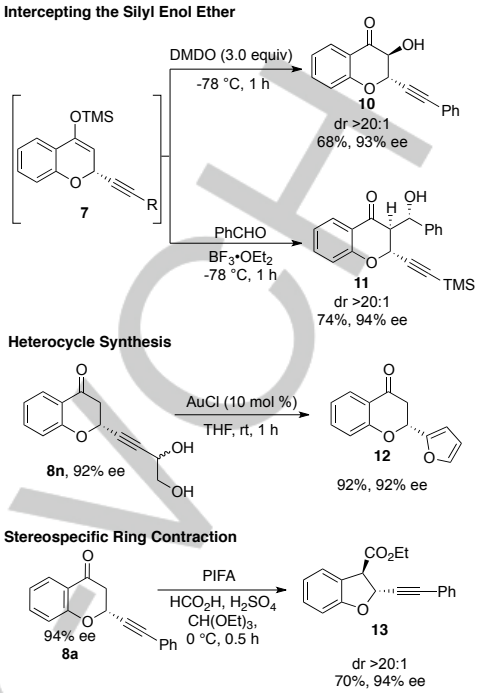
To be synthetically useful, the reaction would need to function on scale, preferably with a reduced catalyst loading, and this was briefly explored. It was found that the loading could be reduced to 1 mol % at 0.2 M in toluene with minimal impact to yield and ee. As seen in equation 1, with (*R*)-StackPhos as ligand, *ent*-**8a** was obtained in 90% ee on gram scale. Judging from this result, the reaction scale could likely be further increased without detrimental effects.



(1)

It was envisioned that this methodology could provide access to a variety of useful compounds in high enantioselectivity. To explore this, we looked at intercepting the ostensibly formed silyl enol ether **7**. In this context, instead of treating the reaction mixture with HCl after alkyne addition, it was cooled to -78 °C and 3 equivalents of dimethyldioxirane were added directly to the reaction vessel to effect Rubottom oxidation.[22] Under these conditions, the corresponding α-hydroxyketone **10** was isolated as a single diastereomer in 68% overall yield (Scheme 3). Additionally, it was found that the silyl enol ether could engage in reactions with other electrophiles such as aldehydes to give the aldol product **11**, also as a single diastereomer. It should be noted that both of these transformations proceeded with the same level of enantioselectivity that was observed for chromanones (93-94% ee) and that the 2,3-*trans* diastereomers were the major products. This stereoselectivity is complementary to the *cis* diastereomers obtained by protonation **8t**/**u** (Table 3). We also envisioned that the alkyne could be further transformed into useful moieties. One such example is included in Scheme 3 using the chromanone **8n** as a starting material. Under Au-catalysis conditions,[23] the propargyl diol moiety was transformed in a straightforward manner to produce the furan **12** in 92% ee. Finally, we were also able to convert the chromanone **8a** to the dihydrobenzofuran **13** in 70% yield,[24] also maintaining the same ee.

In summary, we have developed the first catalytic enantioselective alkynylation of silyloxybenzopyrylium ions. The reaction is effective over a broad substrate scope and the products can be efficiently transformed in a variety of ways. The success of the reaction with respect to both chemical yield and selectivity is influenced by ligand substituents and, although the parent StackPhos ligand was used here, the conditions can be modulated to provide good results with different ligand congeners by solvent choice. Our current interpretation of these data is that the effects are mostly electronic in nature and may impact the reaction via non-covalent interactions; however, further studies to elucidate the nature of the catalyst-substrate interactions are necessary and are underway. Moreover, we are currently developing new reactions taking advantage of this concept and this work will be reported in due course.



Scheme 3. Synthetic utility of the products.

Acknowledgements

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Keywords: Chromanone • Enantioselective Catalysis • Non-Covalent Interactions • Cu-catalysis • StackPhos • Alkynylation

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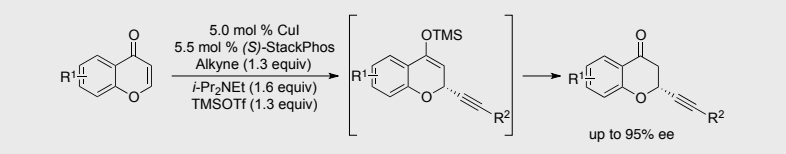

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A Facile Enantioselective Alkynylation of Chromones

The first catalytic enantioselective alkylation of chromones is reported. The reaction, which is both high yielding and highly enantioselectivity over a broad range of substrates, utilizes StackPhos as ligand and proceeds through an intermediate oxonium ion generated in situ. The direct product is a silyl enol ether which can either be protonated or treated with additional electrophilic reagents to build further complexity.