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# Atroposelective Desymmetrization of Resorcinol-Bearing Quinazolinones via Cu-Catalyzed C–O Bond Formation

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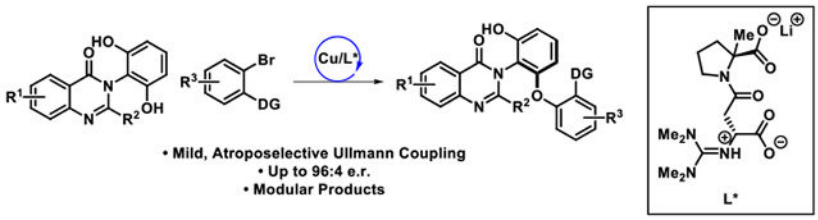
## Abstract

Enantioselective Cu-catalyzed C–O cross coupling reactions yielding atropisomeric resorcinol-bearing quinazolinones have been developed. Utilizing a new guanidinylated dimeric peptidic ligand, a set of products were generated in good yields with excellent stereocontrol. The transformation was readily scalable and a range of product derivatizations were performed.

## Graphical Abstract




The selective functionalization of complex, multifunctional compounds is a frontier for both the fields of catalysis and medicinal chemistry, where there is a premium on (a) synthetic efficiency, (b) management of complex stereochemical issues, and (c) the creation of diversified scaffolds that interact selectively with complex biological targets.[1] In this way, there is also a heuristic intersection between complex bioactive molecules like vancomycin, a potent antibiotic (Figure 1A) and enantiomerically pure scaffolds that exhibit isolable atropisomers (Figure 1B), wherein restricted rotation about a single bond defines functionally consequential stereogenicity.[2] Research in our group began to address both of these challenges, with a particular emphasis on atroposelective halogenation.[3] Metal-catalyzed cross coupling also creates powerful opportunities for scaffold diversification,[4] and we have further examined these in the context of vancomycin and teicoplanin.[5] In preliminary model studies of site-selective cross couplings, we also recently discovered a family of desymmetrization reactions based on peptidyl Cu-complexes (Figure 1C).[6] These

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Supporting Information
The Supporting Information is available free of charge on the ACS Publications website.
Experimental procedures, optimization, characterization and X-Ray data (PDF)
X-ray data for **3b** (CIF)
FAIR Data is available as Supporting Information for Publication and includes the primary NMR FID files for compounds **L1, 1a-1f, 3a-3i, 4-7**

reactions built on previous pioneering studies of other Cu-catalyzed cross couplings.[7–10] Our group reported highly enantioselective transformations for the privileged diarylmethane scaffold, but these studies do not provide a direct analogy to the challenges embedded within vancomycin, nor smaller molecules that bear atropisomeric axes. Moreover, these studies focused on site-selectivity within a bis(electrophilic) substrate. Accordingly, we wished to examine whether resorcinol-based functionality, which presents the site-selectivity challenge within a bis(nucleophilic) fragment, is amenable to enantioselective C–O bond-forming cross coupling with the peptidyl Cu-complexes we had developed.[11] Herein, we describe unprecedented Cu-catalyzed atroposelective desymmetrizations of resorcinols within the biologically relevant quinazolinone scaffold (Figure 1D), grounding the viability of the approach for future examination within even more complicated structures.

At the outset of our investigation, we selected the resorcinol bearing quinazolinone **1a** for the optimization of the atroposelective Cu-catalyzed desymmetrization reaction. We first explored the use of tetrameric guanidinylated peptidic ligand **L***, which was previously found to be successful in the C–O cross coupling of diarylmethanes.[6b] Using **L***, quinazolinone **1a** and arylbromide **2a** were subjected to the reaction conditions shown in Figure 2 to give **3a** in a promising 35% yield and 86:14 e.r. Arylbromide **2a** was carefully selected to be the corresponding coupling partner as the trifluoroacetamide group serves as a directing group. After assessment of the reaction parameters, the optimal conditions were found to be CuI, truncated dimer **L1**, and $Cs_2CO_3$ in DMF at 40 °C for 48 h (59% yield, 95:5 e.r., Table 1, entry 1). To summarize our optimization efforts, a series of variations from the standard reaction conditions were performed to indicate their effects on the efficiency of the transformation (Table 1).[12]

Utilizing other copper catalysts (CuBr and $Cu(MeCN)_4PF_6$) yielded **3a** in comparable selectivity, but lower yields (53% and 51% respectively, Table 1, entries 2 and 3). Employing another sterically encumbered peptidic dimer ligand **L2** gave the cross coupled product in significantly lower yield and selectivity (22% yield and 85:15 e.r., entry 4). Additionally, using another dimeric ligand **L3** gave lower yield and slightly lower e.r. (entry 5). Interestingly, using $K_2CO_3$ or $K_3PO_4$ as the exogenous base did not generate any appreciable product, suggesting that the solubility and strength of the base plays a critical role in promoting the reaction (entries 6 and 7). A 1:1 mixture of DMF/PhMe, which was successful in our previous C–C cross coupling studies, led to **3a** in lower yield but comparable e.r. (entry 8).[6a] Unlike the studies found by Ma and coworkers where $H_2O$ was found to be instrumental in providing high yield and enantioselectivity, the addition of water led to no observable product.[8c] Increasing the temperature to 60 °C led to lower yield due to nonproductive pathways such as protodemetalation of **2a** (entry 10). Lastly, attempts to broaden our scope to include arylchlorides were ineffective as no product was observed (entry 11).

With the optimized conditions affording **3a** in 59% yield and 95:5 e.r., we investigated the substrate scope of this reaction (Figure 3). Unsubstituted arylbromide **2b** provided **3b** in similar yield and excellent enantioselectivity (54% yield, 94:6 e.r.). The structure of **3b** was unambiguously determined by single crystal X-ray crystallography.[13] Electron deficient quinazolinone **1c** was found to be effective in the reaction as it provided higher yields

with comparable enantioselectivity (*3c*, 62% yield, 93:7 e.r.). Additionally, nitro-substituted arylbromide **2d** which could be used as a future synthetic handle was tolerated in good yield and selectivity (**3d**, 51% yield, 91:9 e.r.). In the absence of an *ortho*-directing group, other halogen substituents are preserved in the transformation (**3e**). Notably, aza-quinazolinone (**1f**) was proficient in the reaction giving the respective cross coupled product **3f** in 53% yield and 91:9 e.r. Electron rich arylbromides yielded the desired products in good yield and excellent enantioselectivity (**3g** and **3h**). A limitation in this transformation is the tolerability of the arylbromides, wherein electron withdrawing substituents stunted the reactivity.[14] Changing the $-R^2$ group to a slightly larger group such as ethyl gave the product in comparable yield (**3i**). Unfortunately, other large groups including isopropyl, or benzyl were not tolerated in the reaction. Demonstrating the scalability of this transformation, model quinazolinone **1a** (2mmol) underwent the title cross coupling to yield **3a** in comparable yield and selectivity (54% yield and 94:6 e.r.). Interestingly, other nitrogen directing groups including acetyl or tosyl were incompatible with the transformation. We postulate that the trifluoromethyl acetamide group provides the appropriate pKa range necessary for the reaction.

Finally, product derivatization studies were undertaken to assess the synthetic utility of the enantioenriched quinazolinones using product **3a** (Figure 4). Utilizing the remaining hydroxyl group, a SNAr reaction with ethyl 2-chloropyrimidine-5-carboxylate furnished **4** in excellent yield and retention of stereochemistry. Additionally, exploiting the electron rich nature of the resorcinol, we were able to access dibrominated **5** in 90% yield and 95:5 e.r. Deprotection of the trifluoromethyl acetamide, which served as a directing group in our asymmetric reaction, was achieved in excellent yield (**6**, 92% yield, 92:8 e.r.). The pendant hydroxyl group on **3a** could also be removed via reductive coupling in moderate yield while retaining the enantioselectivity (**7**).

Analogous to the reports by the Ma group using ionic ligands,[15] the Cu-catalyzed cross coupling reaction likely proceeds through the generation of bidentate Cu-based catalyst **A** (Figure 5). Then, deprotonation of **2** by $Cs_2CO_3$ gives the trifluoroacetimidate **2'**, which directs the oxidative addition leading to the formation of **B**. Afterwards, atroposelective coordination would give **C** and deprotonation of one hydroxyl group would give **D**. Then product-forming reductive elimination releases **3** and regenerates the active catalyst **A**. An alternative order of events, demonstrated by Hartwig and coworkers for related reactions with neutral ligands on the Cu-center,[16] might also be considered and has not been experimentally excluded.

In conclusion, we have developed an atroposelective Cu-catalyzed C–O cross coupling reaction utilizing a guanidinylated peptidic ligand to form functionalized quinazolinones. The reaction was found to tolerate a range of functional groups including other halogens and heterocycles in good yield and excellent enantioselectivity. To demonstrate the synthetic utility of the products, we performed a diverse set of derivatizations. These findings set the stage for late stage functionalizations in highly complex molecular environments, which we are now actively investigating.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

## ACKNOWLEDGMENT

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(12). Protodemetalation of the arylbromide was observed, alongside decomposition of the quinazolinone.

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(14). Aryliodides are also tolerated in the reaction; however, electron deficient aryliodide equivalents were also ineffective in the transformation.

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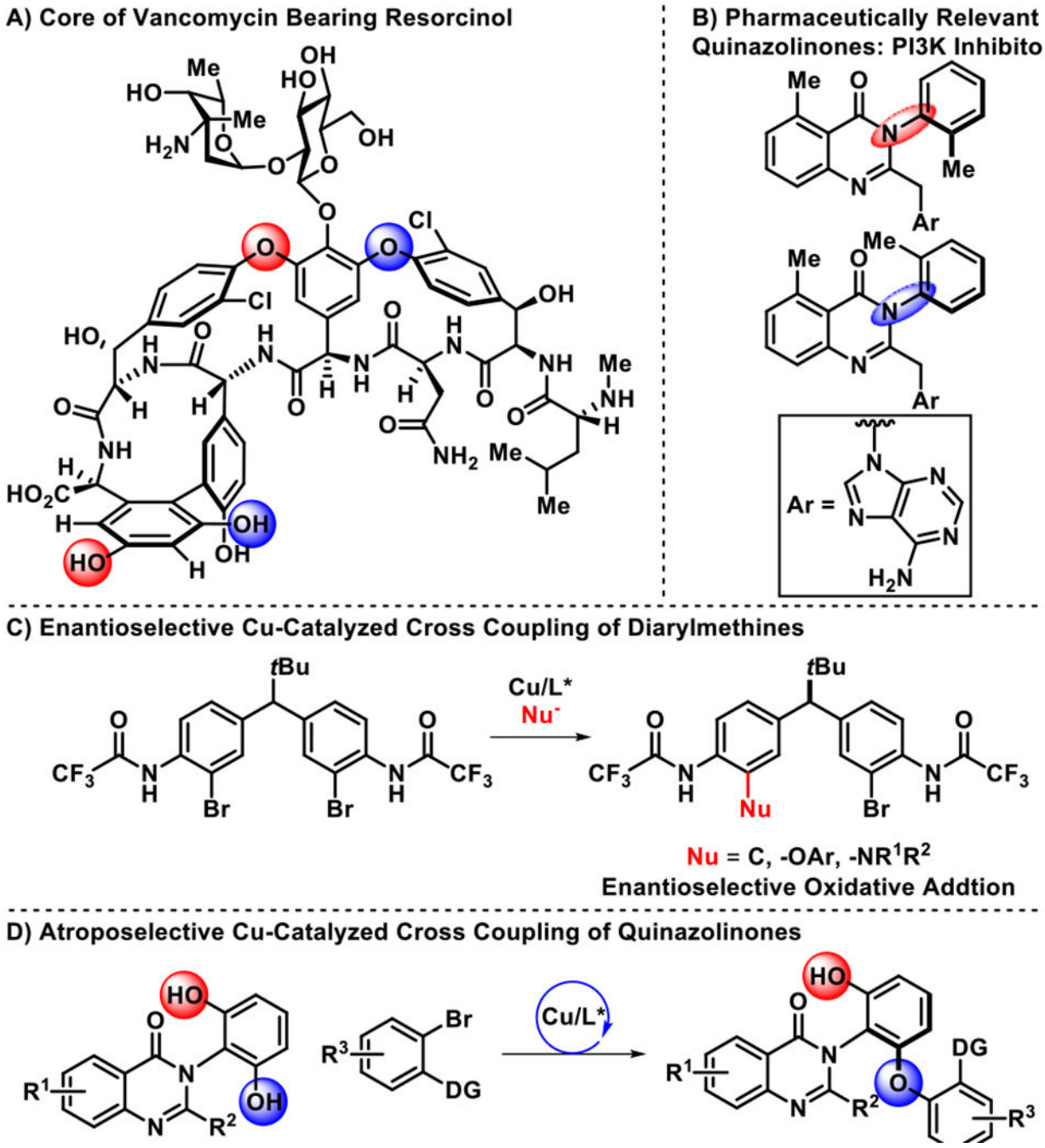



**Figure 1.**
Overview of Bioactive Molecules and Enantioselective Cu-Catalyzed Ullman Coupling

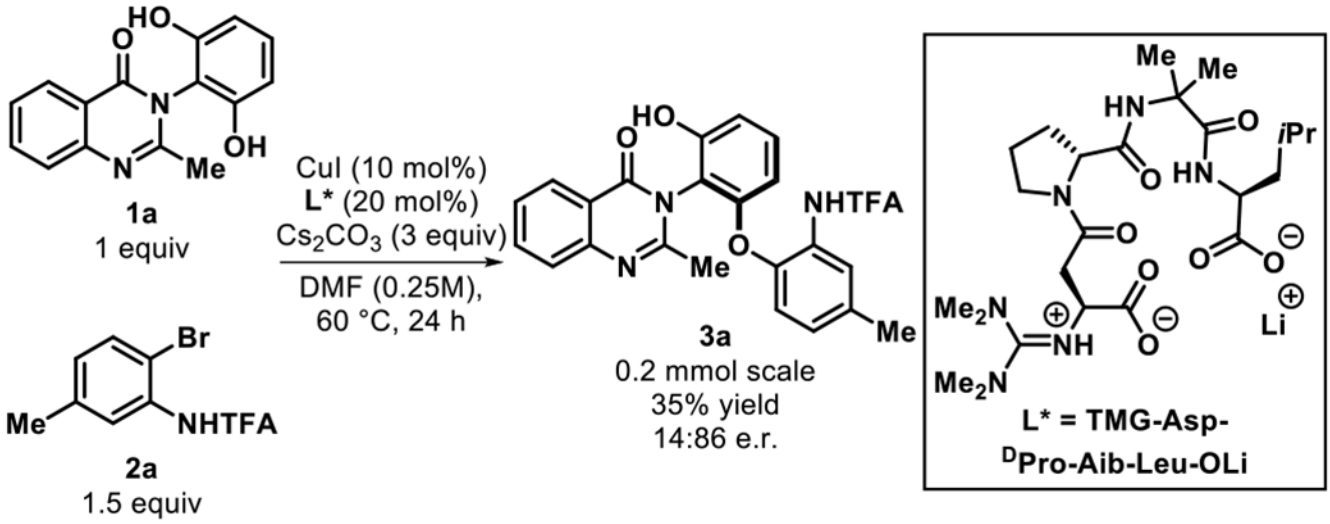



**Figure 2.**
Cu-Catalyzed C–O Cross Coupling of Quinazolinone: Initial Hit

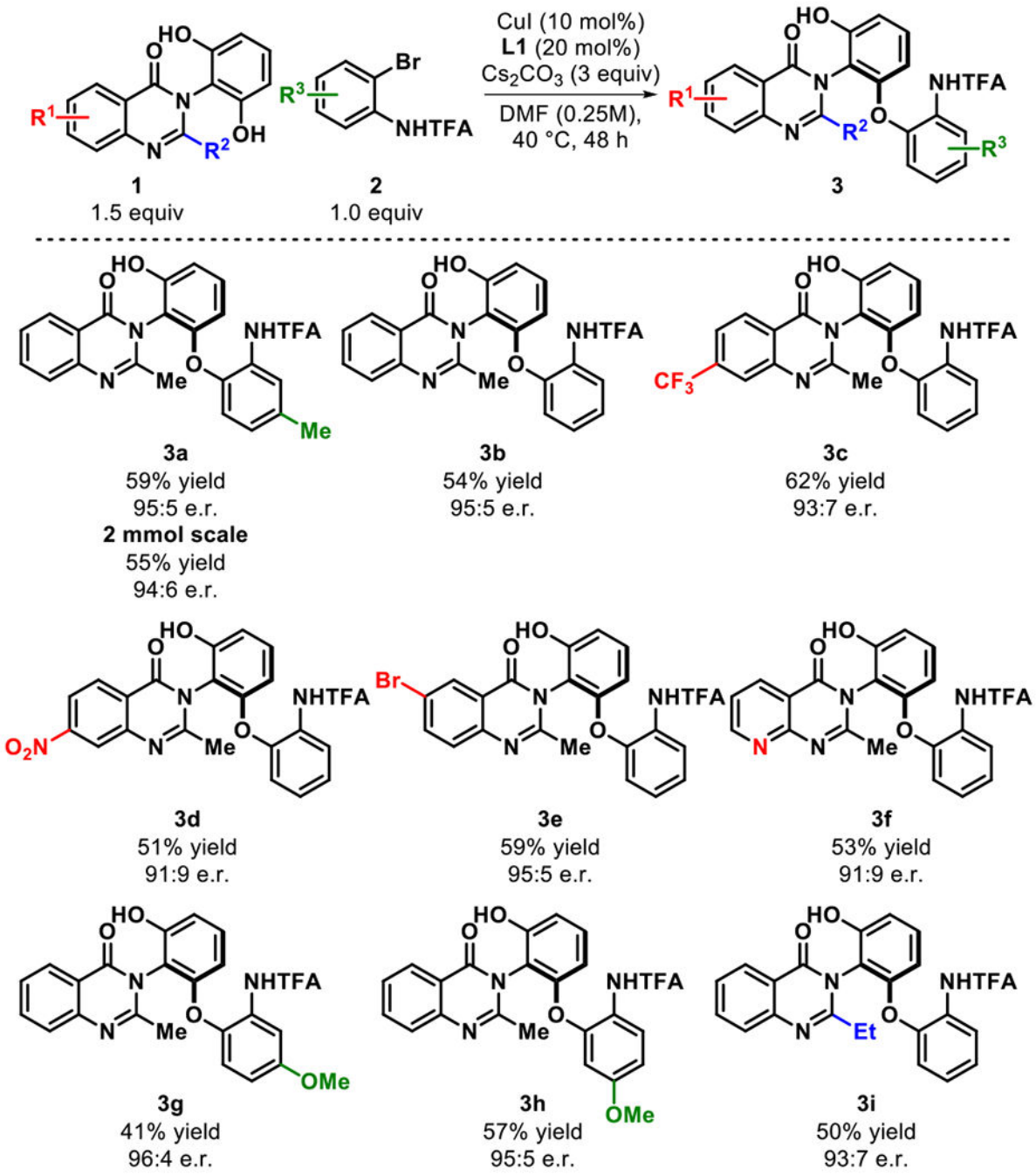



**Figure 3. Cu-Catalyzed C–O Cross Coupling: Substrate Scope**[a]

[a] Reactions run on 0.2 mmol scale. Isolated yields.

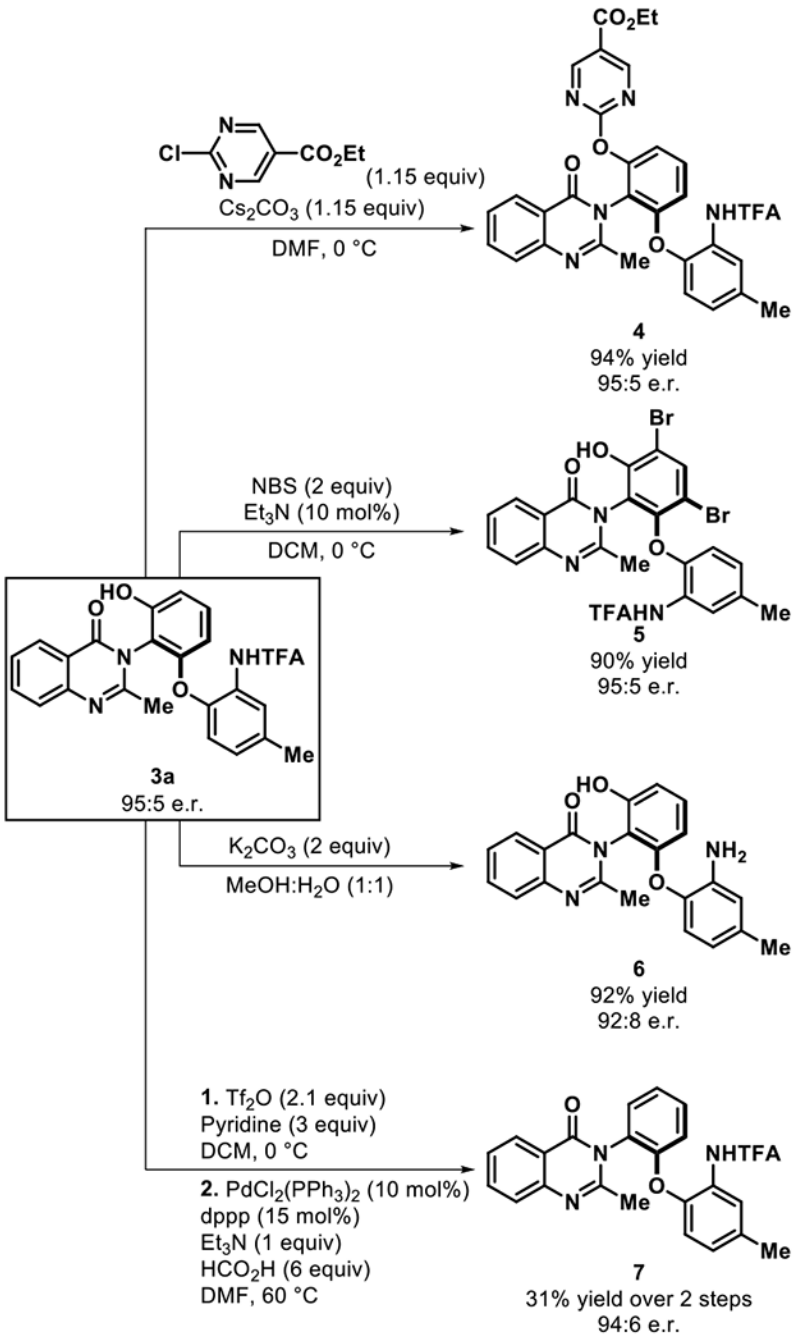



**Figure 4. Derivatization of Quinazolinone 3a**[a]

[a] Reactions run on 0.1 mmol scale. Isolated yields.

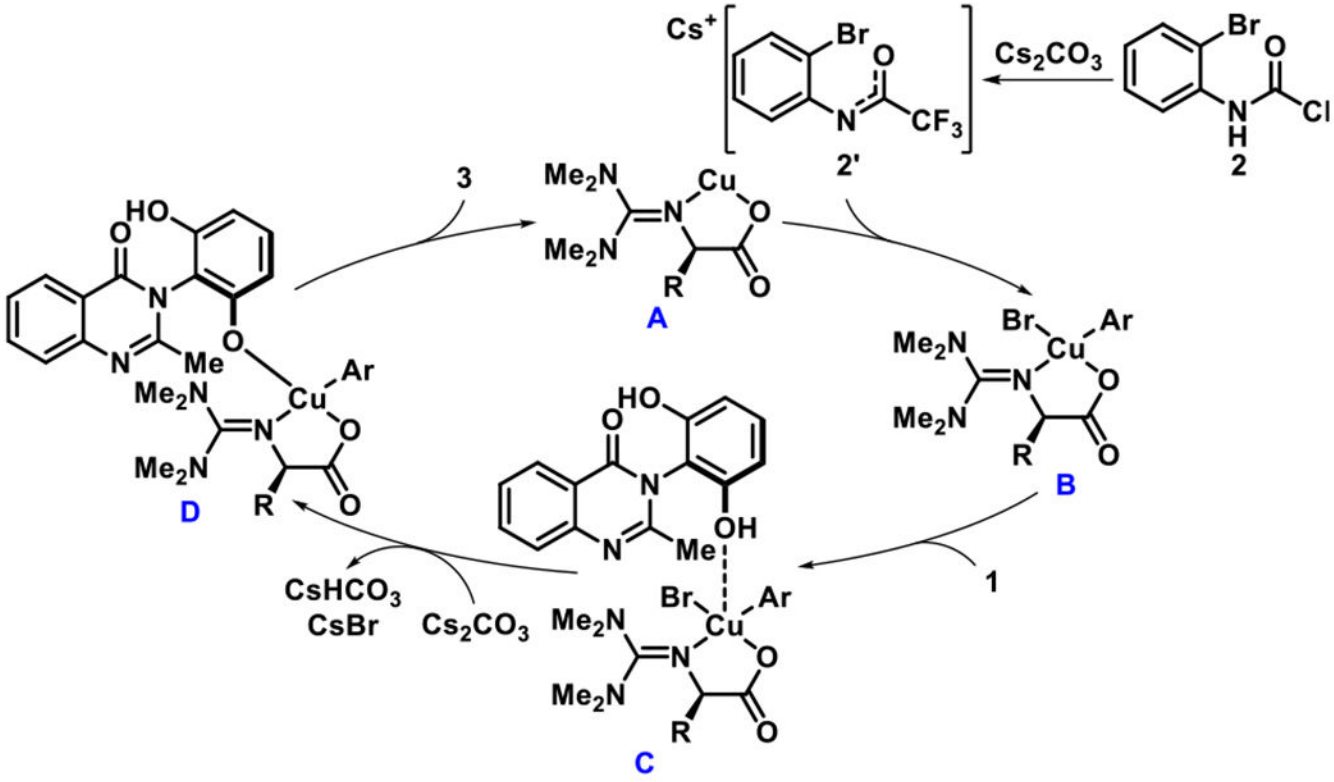
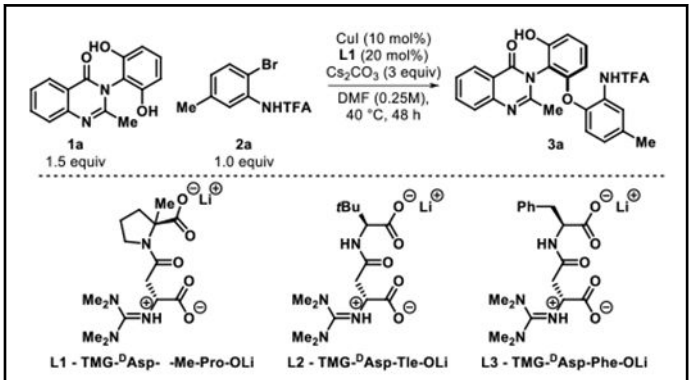



**Figure 5.**
Postulated Mechanism for the Cu-Catalyzed C–O Cross Coupling

**Table 1.**

Atroposelective Cu-Catalyzed C–O Cross Coupling: Variation from the Standard Reaction Conditions[a]




| Entry | Variation from "standard conditions" | Yield 2a (%)[b,c] | e.r. 3a |
|---|---|---|---|
| **1** | **None** | **(59)** | **95:5** |
| 2 | CuBr instead of CuI | 53 | 95:5 |
| 3 | $Cu(MeCN)_4PF_6$ instead of CuI | 51 | 93:7 |
| 4 | **L2** instead of **L1** | 22 | 85:15 |
| 5 | **L3** instead of **L1** | 26 | 92:8 |
| 6 | $K_2CO_3$ instead of $Cs_2CO_3$ | Not observed | - |
| 7 | $K_3PO_4$ instead of $Cs_2CO_3$ | Not observed | - |
| 8 | DMF/PhMe (1:1) instead of DMF | 38 | 95:5 |
| 9[d] | DMF/$H_2O$ instead of DMF | Not observed | - |
| 10 | 60 °C instead of 40 °C | 50 | 93:7 |
| 11 | ArCl instead of ArBr | Not observed | - |

[a] Reactions run on 0.2 mmol scale.

[b] Determined by $^1H$ NMR analysis of the crude reaction mixtures using trimethyl benzene-1,3,5-tricarboxylate as internal standard.

[c] Isolated yields in parenthesis.

[d] 5μL of $H_2O$ was added.