Selective C-C Bond Formation Mediated by Modularly Assembled Catalysts
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Narrative Progress Report 2018-2019

Research Progress

For our initial proof of concept, we were aiming to prepare the thiol substituted triazolium salts 2a-2d (Figure 1a), explore their disulfide coupling with cysteine derivatives 3 to prepare the chiral bifunctional catalysts [2-3] (Figure 1b), and investigate selective C,C-bond formation reactions such as the enantioselective Benzoin condensation (Figure 1c).

While the synthesis of 1a and the subsequent deprotection to 2a proceeded without problems (Scheme 1a), the preparation of the aryl substituted triazolium salts 1b-1d proved to be more challenging, and the traditional method starting from the corresponding aryl hydrazine only afforded 1b in acceptable yield (Scheme 1b). We therefore decided to investigate alternative routes to 1,4-diaryl substituted 1,2,4-triazolium salts. Scheme 1c shows our approach in which the primary amine RNH₂ is first converted to the 4-R-4H-1,2,4-triazole, followed by a copper catalyzed N-arylation using diaryliodonium salts. Since there have been no previous reports on the 1-arylation of 4-R-4H-1,2,4-triazoles, we decided to optimize the reaction conditions (Table 1) and investigate the scope of the copper catalyzed quaternization using diphenyliodonium tetrafluoroborate (Table 2a),
dimesitylodonium triflate (Table 2b), and other diarylidonium species as reagents (manuscript has been submitted for publication).

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<th>Table 2. Copper catalyzed arylation (submitted for publication).</th>
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<td><img src="image1" alt="Chemical structures" /></td>
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<td><img src="image2" alt="Chemical structures" /></td>
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Deprotection of 1a-1d as depicted in Figure 1a afforded compounds 2a-2d cleanly. As expected, disulfide formation occurs under oxidative conditions. However, as depicted in Scheme 2, the resulting disulfide (e.g. [2a·2a] or [2a·3]) is susceptible to an intramolecular nucleophilic attack by the deprotonated carbene, thus leading to a tricyclic aromatic thiazolium salt (e.g. 4a). We are currently investigating this cyclization reaction with respect to functional group tolerance and expect to submit a publication with our initial results within the next 2-4 weeks.

### Impact

The ACS PRF DNI award has allowed the PI to explore a relatively risky project. While the initial outcomes suggest that the major part of the proposed research will not work as originally planned, we were able to develop a new research direction based on the observed side reactions. Up to date, one publication has been submitted for publication and a second manuscript is in preparation which we intend to submit within the next 2-4 weeks.

Two graduate students and two undergraduate students were either directly (salary) or indirectly (chemicals and supplies) supported by this award. They have gained significant experience in standard experimental synthetic and catalytic procedures. Additionally, both graduate students have gained valuable experience for their future career in academia by being involved in the writing process of the submitted publication as well as by presenting their work at various conferences (2018 SWRM, 2019 Pentasectional Meeting).