PRF# 58507-DNI1

Selective C-C Bond Formation Mediated by Modularly Assembled Catalysts

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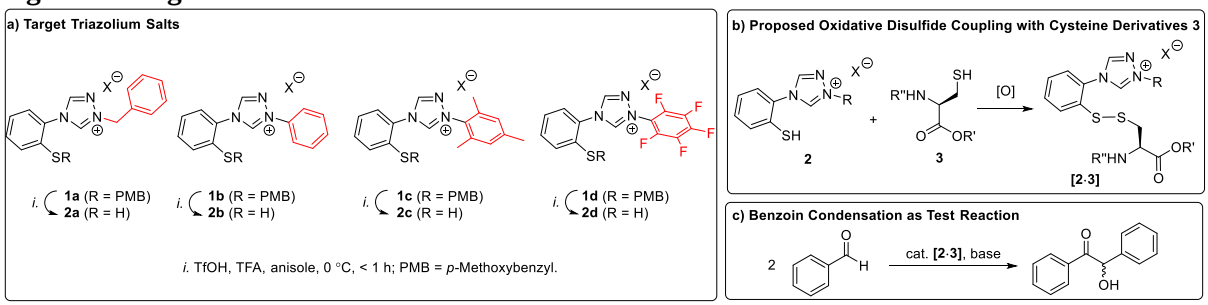
Narrative Progress Report 2018-2019

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).

Figure 1. Target research overview.



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 RNH_2 is first converted to the 4-R-4*H*-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-4*H*-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),

Scheme 1. Synthesis of target triazolium salts.

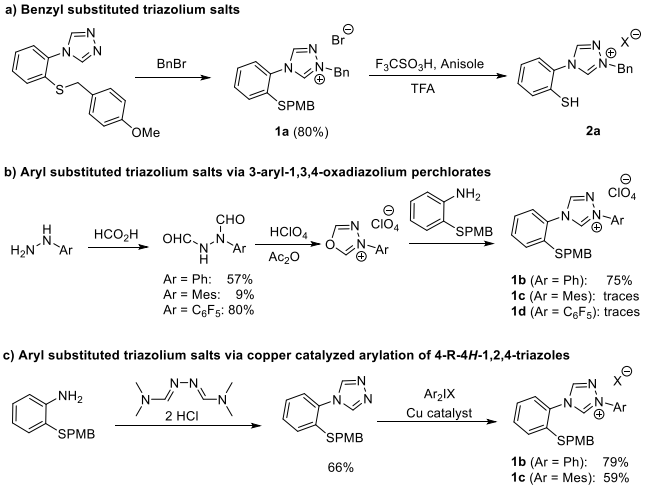
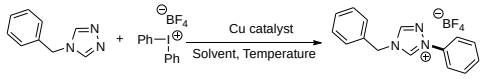


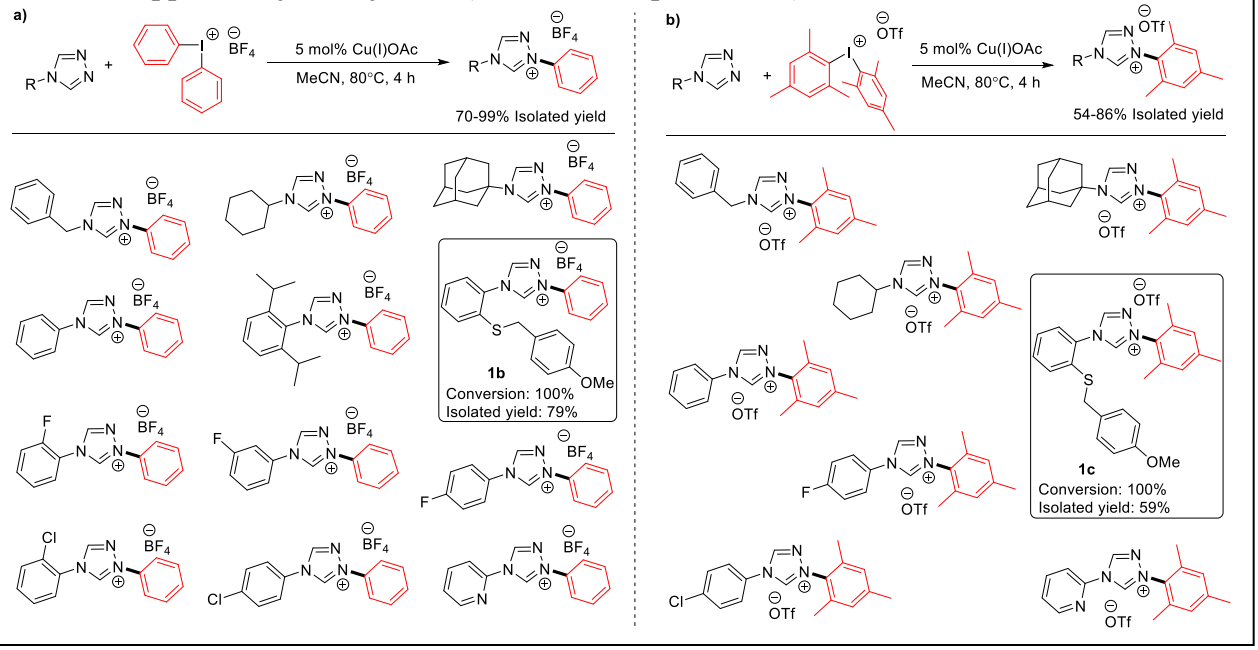
Table 1. Optimization of Cu-catalyzed arylation.



entry	Cu catalyst	catalyst loading	$Ph_2I(BF_4)$ (equiv.)	solvent	temperature	time	conversion
1	$Cu(OAc)_2·H_2O$	5 mol%	1.5	DMF	100 C	4 h	>95%
2	$Cu(OAc)_2$	5 mol%	1.5	DMF	100 C	4 h	>95%
3	Cu(OAc)	5 mol%	1.5	DMF	100 C	4 h	>95%
4[d]	$Cu(OAc)_2$	5 mol%	1.5	H_2O	100 C	4 h	>80%
5[d]	Cu(OAc)	5 mol%	1.5	H_2O	100 C	4 h	>80%
6	$Cu(OAc)_2·H_2O$	5 mol%	1.5	MeCN	100 C	4 h	>95%
7	$Cu(OAc)_2$	5 mol%	1.5	MeCN	100 C	4 h	>95%
8	Cu(OAc)	5 mol%	1.5	MeCN	100 C	4 h	>95%
9	Cu(OTf)·0.5 toluene	5 mol%	1.5	MeCN	100 C	4 h	>95%
10	Cu(TC)	5 mol%	1.5	MeCN	100 C	4 h	>95%
11	$Cu(OTf)_2$	5 mol%	1.5	MeCN	100 C	4 h	>95%
12	$Cu(acac)_2$	5 mol%	1.5	MeCN	100 C	4 h	>95%
13	CuI	5 mol%	1.5	MeCN	100 C	4 h	<30%
14	$Cu(OAc)_2·H_2O$	5 mol%	1.5	MeCN	80 C	4 h	88%
15	$Cu(OAc)_2$	5 mol%	1.5	MeCN	80 C	4 h	87%
16	Cu(OAc)	5 mol%	1.5	MeCN	80 C	4 h	100%
17	none	-	1.5	MeCN	80 C	4 h	17%
18	$Cu(OAc)_2·H_2O$	5 mol%	1.5	MeCN	80 C	1 h	80%
19	$Cu(OAc)_2$	5 mol%	1.5	MeCN	80 C	1 h	79%
20	Cu(OAc)	5 mol%	1.5	MeCN	80 C	1 h	97%

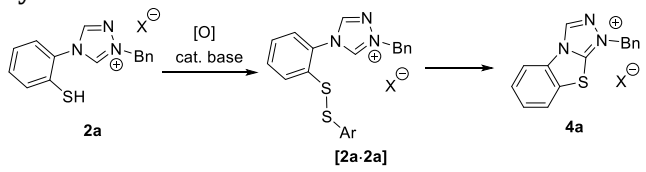
dimesityliodonium triflate (Table 2b), and other diaryliodonium species as reagents (manuscript has been submitted for publication).

Table 2. Copper catalyzed arylation (submitted for publication).



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.

Scheme 2. Oxidative disulfide coupling followed by cyclization.



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).