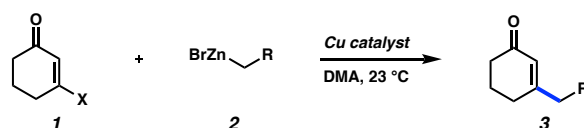


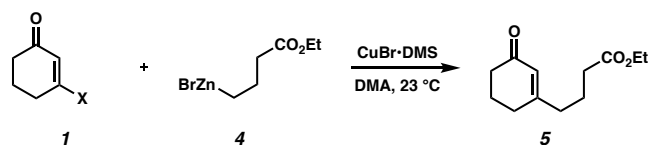
**58488-UN11***Cross-Coupling Approach to  $\beta,\beta$ -Disubstituted Unsaturated Carbonyls*

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The goal of this project is to develop an efficient and general protocol for the preparation of  $\beta,\beta$ -disubstituted unsaturated carbonyls using a cross-coupling approach. The prevalence of these privileged architectures ( $\beta,\beta$ -disubstituted unsaturated carbonyls) in organic synthesis suggest that improved methods to access an array of structures will be of high impact to the chemistry community. Our studies have focused on the use of organozinc nucleophiles due to their enhanced functional group compatibility (i.e., chemoselectivity). Additionally, they are readily prepared from the direct zinc insertion with abundant organobromides. In the work funded by this PRF grant, we began to explore electrophiles that varied the X group (**1**, Scheme 1) in conjunction with a copper catalyst and monoorganozinc reagent (**2**) to produce the desired  $\beta,\beta$ -disubstituted unsaturated carbonyls (**3**).

**Scheme 1.** General Cross-Coupling Reaction

Our work over the first year of this PRF grant has focused on the identification of a reactive electrophile (**1**) that participates in a productive cross-coupling reaction. Inspired by Knochel's work in this area, we focused on vinylogous halide substrates where X = I, Cl, and Br. The base electrophile substrates (**1**) for reaction optimization are readily prepared from 1,3-diketones. Our initial work utilized copper(I) catalysis due to our prior work in this area, as well as Knochel, among others. Preliminary results indicated that good yields of product **5** could be obtained when a stoichiometric quantity of CuBr•DMS was employed in the reaction (Table 1, entry 1). We observed a marked difference in electrophile reactivity, with iodide substrates providing optimal rates and product yields (entries 1–3). Moreover, challenging the reaction with catalytic quantities of CuBr led to diminished product yields and incomplete conversion of substrate **1** (entries 4–5).

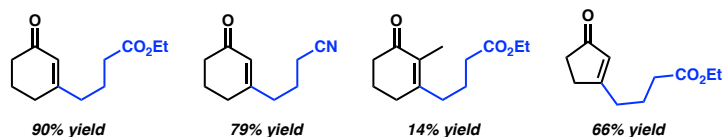
**Table 1.** Preliminary coupling of vinylogous halide **1** with organozinc **4**.

entry	X	CuBr (mol %)	<b>5</b> yield (%) <sup>a</sup>	<b>1</b> conversion (%) <sup>b</sup>
1	I	130	87	100
2	Br	130	37	66
3	Cl	130	4	33
4	I	20	71	88
5	Br	20	19	44
6	Cl	20	1	35

<sup>a</sup> Reactions performed for up to 24 h. <sup>b</sup> Measured by <sup>1</sup>H NMR using an internal standard.

Further optimization of this reaction using a copper(I) catalyst demonstrated an additional challenge for these specific conditions. Reaction additives, such as TMSCl, are common additive for reactions of cuprate reagents with unsaturated carbonyls. We found that employing TMSCl promoted a separate conjugate addition pathway that resulted in the net addition of *two equivalents* of reagent **4**. This diminished the yield of product **5**, and also introduced a challenge for reaction purification via flash chromatography. Alternatively, LiCl has been shown to have a marked impact on reactions of organozinc reagents. We observed a large increase in reactivity of vinylogous iodide **1** (X = I) with 2.0 equiv LiCl and 5 mol% of CuBr•DMS to produce a 90% yield of **5**.

Future work will focus on the understanding of the role of LiCl in this reaction system, as well as the survey of other types of Lewis base additives that may have a positive impact on the reaction. We also plan to explore alternative electrophile substrate structures, as the current scope of this transformation seems to be limited by catalyst efficiency. A sampling of products generated by this procedure is shown in Figure 1. Alternatively, we will be exploring catalyst systems that do not use copper.



**Figure 1.** Reaction Scope of the Cu-Catalyzed Cross-Coupling.

**Project Impacts.** This project has supported four students during the academic year (materials) and one during a summer research session, comprising Chemistry, Sociology, and Biology majors. One student co-worker on this project has graduated and is currently enrolled in a Chemistry Ph.D. program at UC Irvine. Our progress on this project was presented as a poster by one student at the *National Organic Symposium* conference in June 2019, as well as a Regional Conference at Bucknell University in August 2019. The support from this PRF grant has provided opportunities to myself and student co-workers to explore the reactivity of this copper catalyst system to produce interesting reaction products. We have been able to conduct detailed studies that have suggested exciting new directions for this project, and this has led to two publications and a separate grant that has been funded.