The University of Texas at Austin

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Cu-Catalyzed Three-Component 1,5-Carboamination of Vinylcyclopropanes: Exploring The Nucleophile Scope

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Introduction and Background

Nitrogen-containing compounds are ubiquitous in the field of pharmaceuticals, as they often play a crucial role in drug design and synthesis[1,2]. As a result, the development of new and efficient methods for incorporating nitrogen into organic molecules is of great interest to synthetic chemists. In pursuit of this goal, members of the Hull Group have been investigating novel methodologies, such as olefin carboamination reaction (Figure **1a**)[3,4]. This reaction involves the addition of a nitrogen-containing species to a carbon-carbon double bond within a single step. Earlier, the Hull group reported several examples of radical olefin carboamination using α-halocarbonyl compounds as reducible radical sources[5,6] as well as boronic acid derivatives as oxidizable radical sources[7].

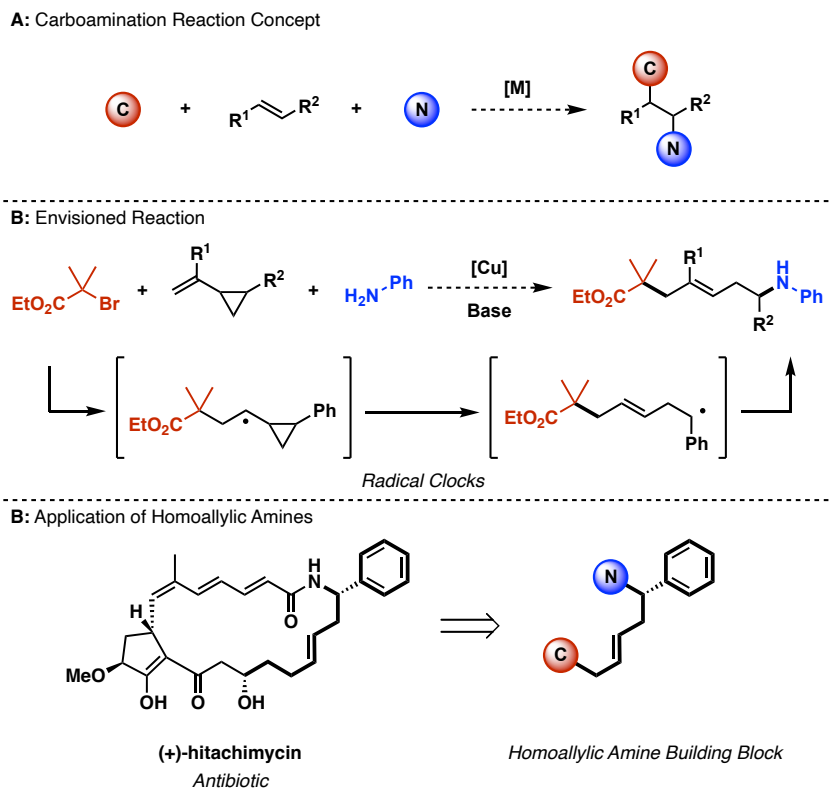
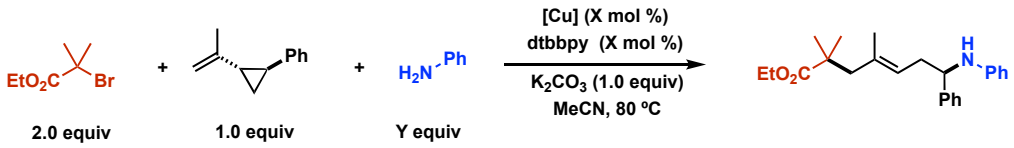


Figure 1. Carboamination Reaction

To improve the synthetic applicability and expand the scope of possible disconnections we sought promising candidates for this transformation and referred to vinylcyclopropanes (Figure **1b**). Vinylcyclopropanes are commonly used as a mechanistic tool for radical reactions[8]. For example, if a radical undergoes the addition across the olefin fragment of vinylcyclopropane, the resulting

radical adduct undergoes a rapid ring opening to relocate the radical density and form a double bond[1]. However, we believe this reaction is also of a great interest from a synthetic perspective because it opens the avenue for an efficient assembly of complex homoallylic amines (Figure **1c**)[9,10].

My role in this project was to explore the nucleophilic scope of the reaction, with the aim of developing a useful synthetic tool for the construction of nitrogen-containing molecules. Prior to my involvement in the project, members of the Hull Group had already optimized the primary reaction by testing a variety of equivalencies, catalysts, ligands, and solvents. The goal of this optimization process was to identify the ideal conditions for achieving high yields of the desired products while minimizing unwanted side reactions. The group systematically tested different combinations of reactants, catalysts, and solvents, and evaluated the reaction outcomes using a variety of analytical techniques. They also explored the effects of different reaction conditions, such as temperature and time, on the reaction outcomes. The results of this optimization process are presented in Table **1**.



Entry	Y (equiv)	[Cu]	Base	Concentration	Yield, %	*E/Z*
1	1	CuCl (8 mol %)	K_2CO_3	0.5 M	38	4.7
2	1	CuCl (4 mol %)	K_2CO_3	0.5 M	39	4.4
3	1	$[Cu(MeCN)_4]BF_4$ (4 mol %)	K_2CO_3	0.5 M	42	4.3
4	3	CuCl (4 mol %)	K_2CO_3	0.5 M	60	5.5:1
5	3	CuCl (4 mol %)	K_2CO_3	1.0 M	76	5.5:1
6	3	–	K_2CO_3	1.0 M	*NR*	–
7	3	CuCl (4 mol %)	–	1.0 M	12	5.6:1

Table 1. The previously formulated 1,5-Carboamination Reaction Optimization.

Results and Discussion

Now that an optimized model reaction was formulated, we began to explore the substrate scope of the reaction. We started with applying various anilines as nucleophilic partners (Table **2**). Gratifyingly, we found that both electron-rich and electron-poor anilines provide homoallylic amine products with good yields and moderate *E/Z* selectivity[11]. We also observed that the reaction tolerates halides and sterically hindered anilines, which expands the range of possible nucleophiles that can be used in the reaction and open the pathway for further functionalization.

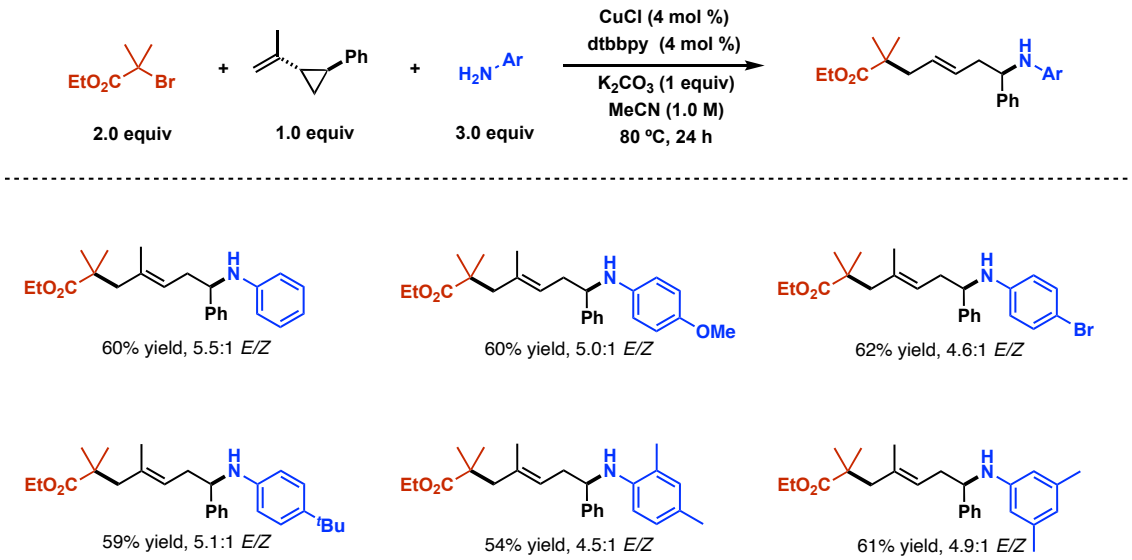


Table 2. Current Aniline Scope.

However, we found that aliphatic amines were exhibiting poor reactivity and chemoselectivity under current conditions, giving a significant amount of Ullmann coupling products with the respectively used alkyl halide. We sought to bypass this limitation by adjusting the reaction conditions. We hypothesized that the reaction may be redirected towards the atom transfer radical addition (ATRA) product intermediacy *via* using a different solvent, such as chlorobenzene (Figure **2**)[12]. Indeed, replacing the solvent with chlorobenzene, we found that both primary and

secondary aliphatic amines deliver the carboamination product with moderate to good yields. We also observed the reaction is accompanied by formation of considerable amount of Ullmann coupling products, that were found to be inseparable from the target molecules. We are currently working on the strategies to overcome this limitation[13].

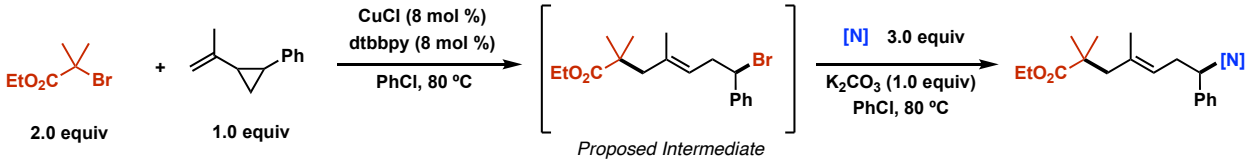
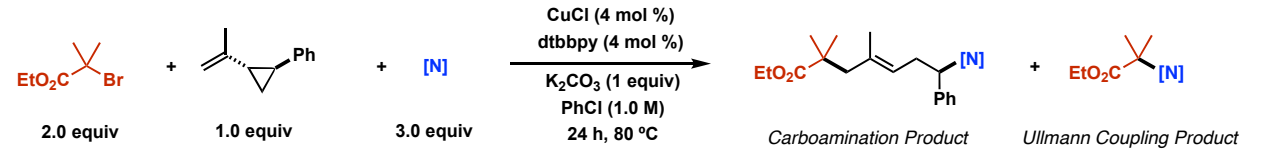
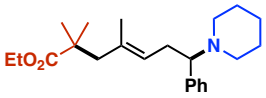
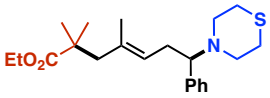


Figure 2. ATRA Intermediate Hypothesis

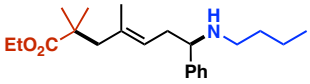




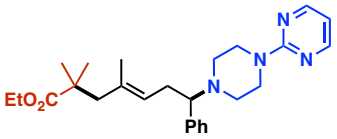
66% yield, 4.7:1 *E/Z*



60% yield, 4.2:1 *E/Z*



57% yield, 4.5:1 *E/Z*



59% yield, 4.5:1 *E/Z*

Table 3. Current Aliphatic Amine Scope.

Summary

In our study, we have successfully demonstrated that homoallylamine derivatives can be formed through Cu-catalyzed carboamination of vinylcyclopropanes using nucleophilic amines as suitable

partners. Moving forward, we aim to expand the substrate scope by exploring activated and unactivated vinylcyclopropanes, vinylcyclobutanes, and cyclopropanes with a diene fragment. Additionally, we are interested in investigating the use of various alkyl halide radical precursors.

Acknowledgements

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[11] Product structures and *E/Z* values were confirmed *via* GC, GCMS and NMR analysis.

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[13] Considered among the possible solutions are performing time screening to determine when the Ullmann products starts to accumulate; decreasing the loadings of nucleophile; conducting the reaction in a one-pot two-step mode.