Rhodium-catalyzed hydroacylation of alkynes

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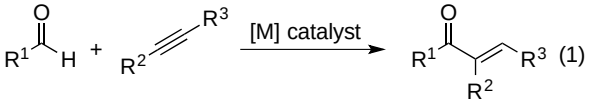
CHEM 399 Undergrad Research Summary

Background

This semester, I worked in the Stanley group investigating the rhodium-catalyzed hydroacylation of alkynes and tandem reactions involving olefin hydroacylation and conjugate addition. Olefin hydroacylation is the addition of an aldehyde across a carbon-carbon multiple bond and is a synthetically useful, atom-economic process for the synthesis of ketones (eq 1).[1] Conjugate addition is the addition of a nucleophile such as a boronic acid to an α,β-unsaturated ketone. We are interested in the development of catalysts for tandem reactions that couple alkyne hydroacylation with conjugate addition reactions to allow for rapid access to complex structures (eq 2). The aims of this project include 1) to synthesize the parent alkyne starting material 2) to identify a catalyst system for the hydroacylation of these alkyne substrates 3) to identify a catalyst system for the conjugate addition of arylboronic acids to the hydroacylation products and 4) to develop a tandem reaction that couples alkyne hydroacylation with the conjugate addition reactions.



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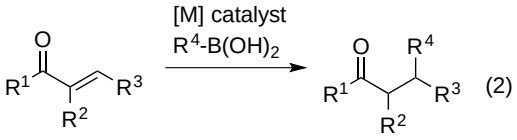

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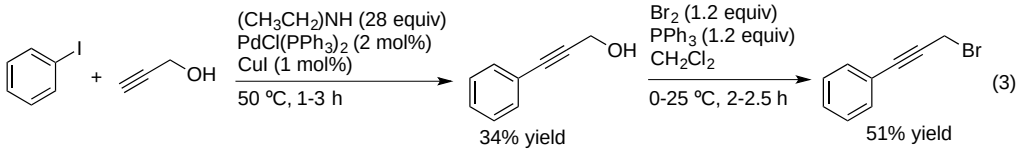
Results/Discussion

First I worked on the synthesis of the alkyne starting material. I followed literature procedures for the five steps required to synthesize this known compound.[2,3]



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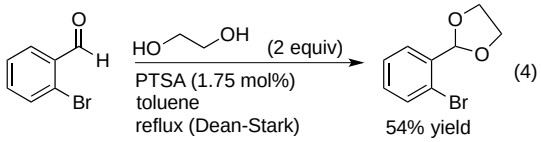

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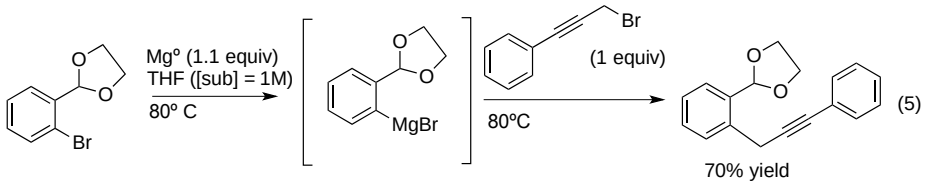

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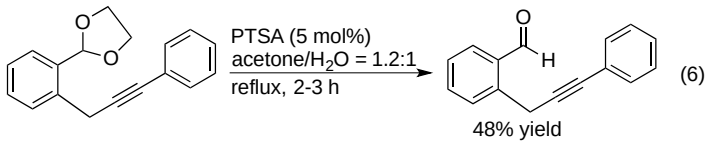

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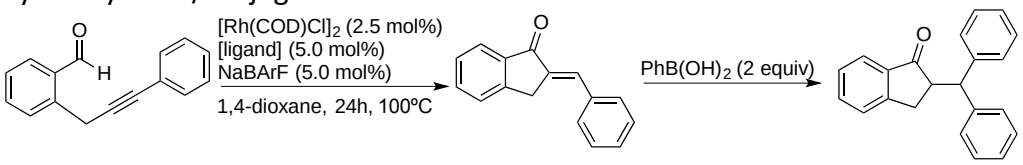
Once I obtained the hydroacylation starting material, I evaluated conditions for the alkyne hydroacylation reaction. In order to identify an efficient catalyst for this reaction, I screened several conditions by varying the identity of bisphosphine ligands, catalyst precursors, and counteranions of a range of coordinating strength. I also conducted initial tests for one-pot alkyne hydroacylation/conjugate addition reactions using phenylboronic acid. These results are summarized in Tables 1-3.

Table 1: Initial results for rhodium-catalyzed alkyne hydroacylation and tandem hydroacylation/conjugate addition

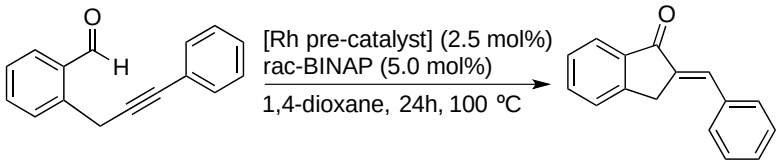


Entry	Ligand	NMR Yield of hydroacylation[a]	NMR Yield of conjugate addition[a]
1	rac-BINAP	46%	N/A
2	DPEphos	60%	N/A
3	JosiPhos	13%	N/A
4	DPEphos	42%	0% (73% SM recovered)
5	DPPF	9%	0% (6% SM recovered)
6[b,c]	DPEPhos	N/A	0% (61% SM recovered)

[a]Determined by ^{1}HNMR spectroscopy using dibromomethane as an internal standard.
[b] Conjugate addition step only. [c]0.1 mL of H_2O was added for conjugate addition step.

I evaluated reaction conditions using a catalyst generated from $[Rh(COD)Cl]_2$, NaBArF and a range of bisphosphine ligands. The highest yields of the hydroacylation product were obtained when DPEPhos or rac-BINAP were used as ligands (entries 1 and 2), so these ligands were used to investigate additional reaction parameters.

Table 2: Evaluation of rhodium precursors for alkyne hydroacylation

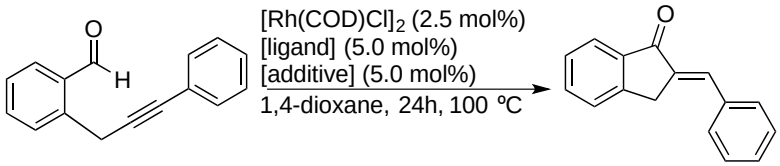


Entry	Rh precatalyst	NMR Yield[a]
1	$[Rh(COD)Cl]_2$	8%
2	$[Rh(COD)OH]_2$	8%

[a]Determined by ^{1}HNMR spectroscopy using dibromomethane as an internal standard.

This experiment was to determine if an alternative rhodium precatalyst would work better than the one we had been using previously, however both $[Rh(COD)Cl]_2$ and $[Rh(COD)OH]_2$ resulted in low yields of the hydroacylation product with rac-BINAP as a ligand in the absence of NaBArF.

Table 3: Evaluation of counteranions for alkyne hydroacylation



Entry	Ligand	Additive	NMR Yield[a]
1	rac-BINAP	-	8%
2	rac-BINAP	AgOTf	10%
3	rac-BINAP	$AgPF_6$	10%
4	rac-BINAP	$AgBF_4$	42%
5	rac-BINAP	$AgSbF_6$	15%
6	rac-BINAP	NaBArF	46%
7	DPEPhos	-	50%
8	DPEPhos	$AgBF_4$	50%
9	DPEPhos	$AgSbF_6$	58%
10	DPEphos	NaBArF	60%

[a]Determined by ^{1}HNMR spectroscopy using dibromomethane as an internal standard.

The experiment with silver salts was to determine whether a weakly coordinating anion was required for the alkyne hydroacylation reaction. Using rac-BINAP as a ligand, there was a significant difference in reactivity with a weakly coordinating anion (entries 1–6). Comparison of entries 7–10 demonstrate that the strength of the coordinating anion does not have a significant affect on the hydroacylation reaction using DPEPhos.

Conclusion

This semester, I learned how to do many standard organic chemistry techniques in the process of my research. I learned how to use both qualitative and quantitative analysis methods including NMR spectroscopy, internal standards, thin-layer chromatography, column chromatography as well as other standard organic laboratory techniques. The opportunity to do research this semester has grown my skills as a scientist and expanded my skillset beyond the regular classroom. My work in the Stanley group will continue next semester and I'll be testing additional bisphosphine ligands, as well as experimenting with solvent, temperature and other reaction conditions for the alkyne hydroacylation reaction. I will also continue to work on conjugate addition reactions with the hydroacylation products by testing the addition of a base and optimizing the choice of bisphosphine ligand, solvent and other reaction conditions. Once

catalyst systems have been identified for both alkyne hydroacylation and conjugate addition steps, I will begin to evaluate conditions for tandem processes that couple these two reactions.

References

1. Willis, M. C., Transition Metal Catalyzed Alkene and Alkyne Hydroacylation. *Chemical Reviews* 2010, *110* (2), 725-748.
2. Dell'Acqua, M.; Pirovano, V.; Confalonieri, G.; Arcadi, A.; Rossi, E.; Abbiati, G., Synthesis of 3-benzylisoquinolines by domino imination/cycloisomerisation of 2-propargylbenzaldehydes. *Organic & Biomolecular Chemistry* **2014,** *12* (40), 8019-8030.
3. Hayashi, T.; Yamasaki, K., Rhodium-Catalyzed Asymmetric 1,4-Addition and Its Related Asymmetric Reactions. *Chemical Reviews* 2003, *103* (8), 2829-2844.