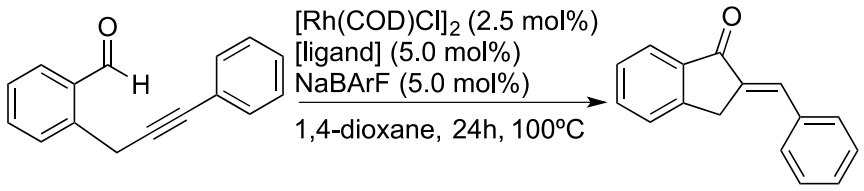
Rhodium-Catalyzed Conjugate Addition of Boronic Acids to α,β-Unsaturated Ketones

Aaron Jacobson
CHEM 399 Undergraduate Research Summary

Background

I worked in the Stanley group in the Spring semester of 2016 investigating the rhodium-catalyzed addition of boronic acids to α,β-unsaturated ketones. The starting α,β-unsaturated ketone can be formed by alkyne hydroacylation using a rhodium precatalyst, bisphosphine ligand and weakly coordinating counteranion (eq 1). Last semester I worked to identify conditions for the alkyne hydroacylation reaction. This semester, work was focused on identifying conditions for rhodium-catalyzed conjugate addition to the hydroacylation product (eq 2). Many examples of palladium- and rhodium-catalyzed conjugate additions using boronic acids have been reported in the literature. However, there are few examples of the rhodium-catalyzed conjugate addition to α,β-unsaturated ketones contain α-substitution. The steric challenges that arise with this substitution pattern have hindered the development of conjugate additions that employ these substrates.



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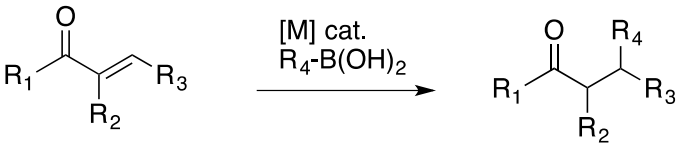

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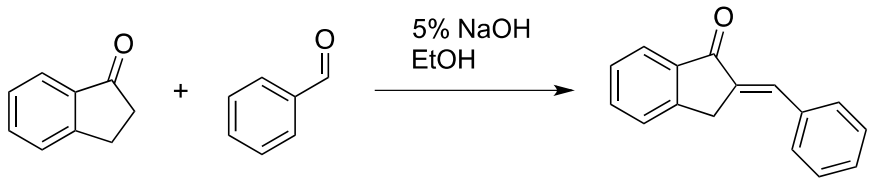
Results/Discussion

In order to generate enough material to evaluate a variety of conditions for the rhodium-catalyzed conjugate addition reaction, I synthesized the hydroacylation product by an alternative method. Aldol condensation of indanone with benzaldehyde generated the hydroacylation product/conjugate addition starting material in 91% yield (eq 3).[1]



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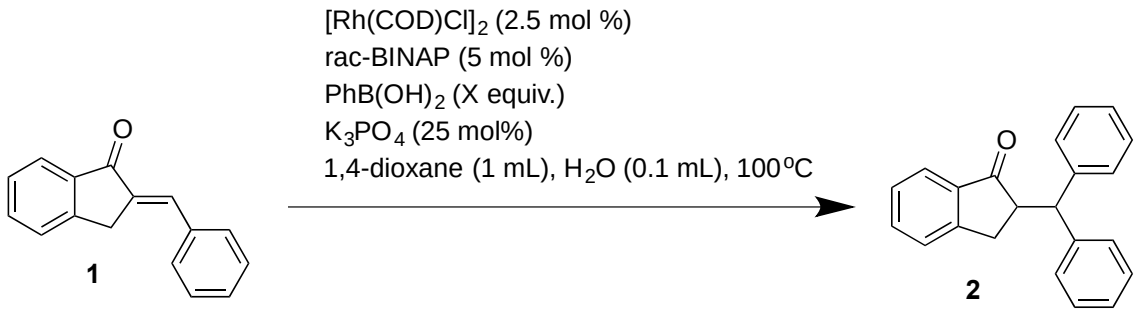

Table 1: Evaluation of equivalents of $PhB(OH)_2$

Entry	Equivalents of $PhB(OH)_2$	Crude yield by ^{1}HNMR[a]
1	2.00	34%
2	3.00	Trial 1: 30% Trial 2: 41%
3	4.00	Trial 1: 40% Trial 2: 35%

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

I first evaluated the conjugate addition of $PhB(OH)_2$ to **1**, starting with conditions based on previous examples of rhodium-catalyzed conjugate addition[2]. I explored the impact of various equivalents of $PhB(OH)_2$ on the yield of **2**. The addition of 3.00 or 4.00 equivalents of $PhB(OH)_2$ led to a slight changes in the yield, but these changes were within error of the original yield when 2.00 equiv of $PhB(OH)_2$ (34%).

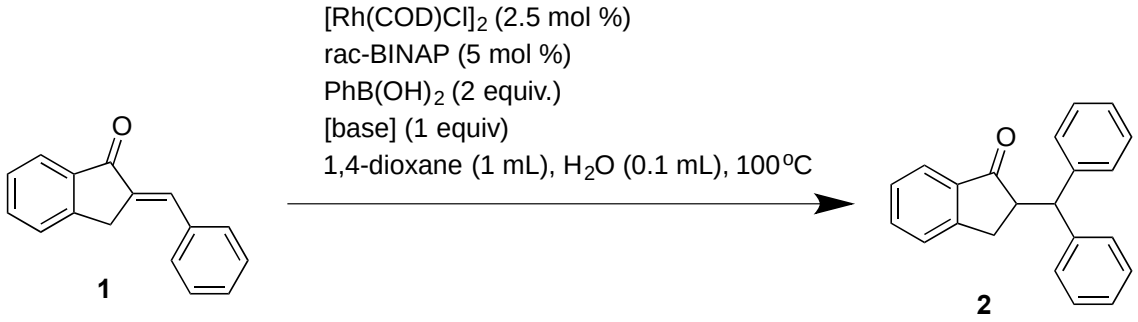

Table 2: Evaluation of bases for conjugate addition

Entry	Base	Corrected yield by ^{1}H NMR[a]
1	K_2CO_3	5%
2	K_3PO_4	34%
3	Cs_2CO_3	20%
4	KOH	33%

5	NaOH	55%

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

I evaluated a variety of different inorganic bases was performed to determine if the identify of the base would improve product yields. Although some bases like NaOH and KOH did facilitate the conjugate addition, we observed another product in the crude reaction mixture. We decided to move forward with K_3PO_4 as the base to evaluate other reaction parameters, since conversion from starting material to product was cleanly observed with this base.

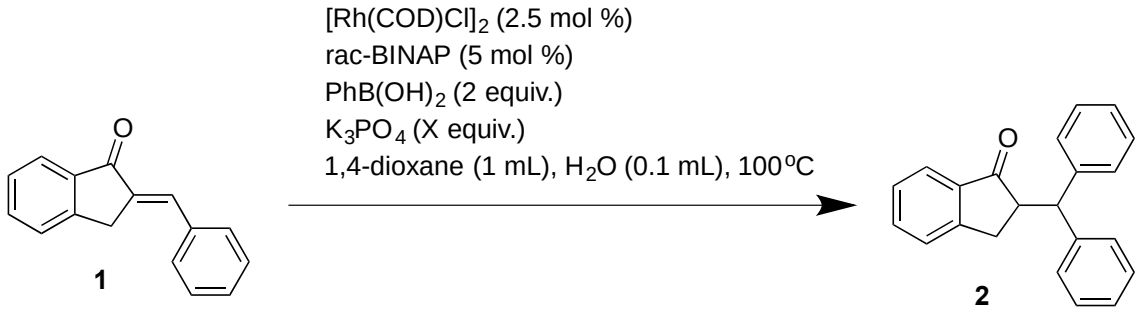

Table 3: Evaluation of equivalents of base for conjugate addition

Entry	Equivalents of K_3PO_4	Corrected yield by ^{1}HNMR[a]
1	1.00	34%
2	0.50	27%
3	0.25	28%
4	0.10	13%
5	0.05	10%

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

In this experiment we explored the amount of base for the rhodium-catalyzed conjugate addition reaction. The presence of too much base might erode enantioselectivity of the product, so we aimed to minimize equivalents of base. It was found that although one full equivalent of base led to the highest yield (entry 1), 0.25 equivalents generated the product in a similar yield (entry 3). Further decreasing the amount base led to a sharp decrease in product yield (entries 4 and 5). We proceeded with 0.25 equivalents of K_3PO_4 for further experiments using this substrate.

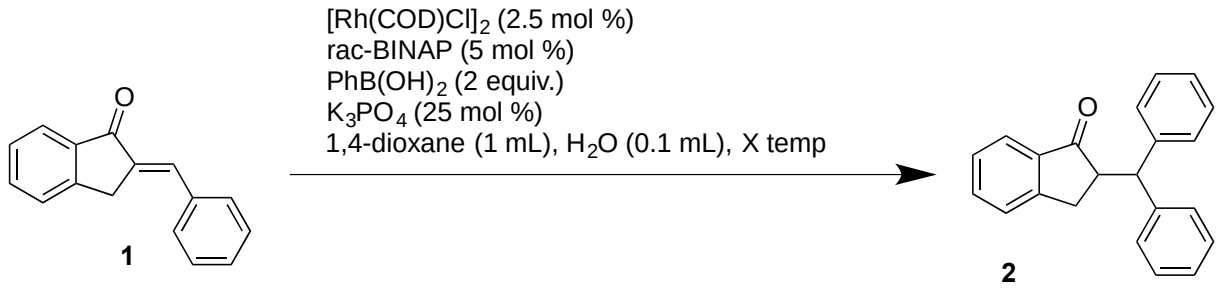

Table 4: Evaluation of reaction temperature for conjugate addition

Entry	Temperature	Corrected Yield by ^{1}HNMR[a]
1	100ºC	34%
2	80ºC	34%
3	60ºC	17%

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

Based on conjugate addition reactions conducted by another graduate student in the Stanley group, temperature conditions were tested to see if lower reaction temperatures might increase the yield by decreasing the rate of background reaction. It was found that 100 ºC and 80 ºC generated the product in comparable yields (entries 1 and 2), but lowering the reaction temperature to 60ºC led to a decrease in reactivity (entry 3).

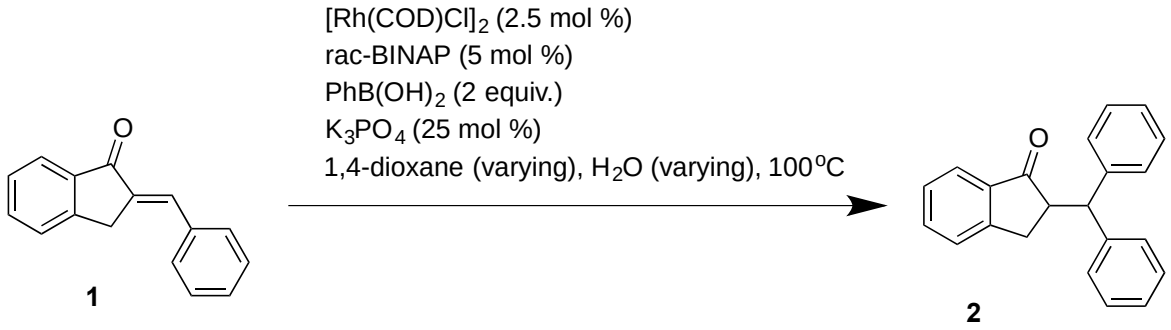

Table 5: Evaluation of concentration for conjugate addition

Entry	Concentration	Corrected Yield by ^{1}HNMR[a]
1	1 mL 1,4-dioxane, 0.1 mL H_2O, 0.18 M	34%
2	0.5 mL 1,4-dioxane, 0.05 mL H_2O, 0.36 M	32%

Based on conjugate addition reactions conducted by another graduate student in the Stanley lab, the reaction concentration was also tested to see if the yield could be improved. The reactions were run on a 0.200 mmol scale of starting material. There was no notable change in

yield from a higher reaction concentration, so less solvent was used for further experiments for efficiency purposes.

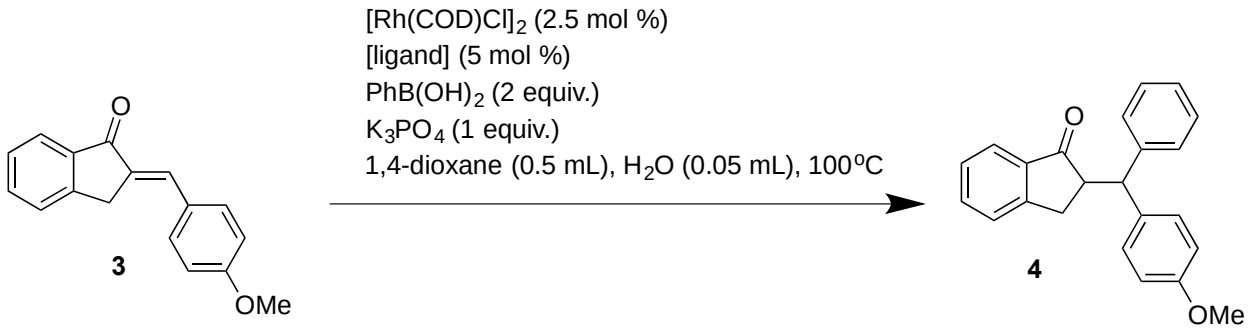

Table 6: Evaluation of bisphosphine ligands for conjugate addition

Entry	Ligand	dr	Corrected ^{1}HNMR Yield[a]
1	(*S*,*S*)-BDPP	1.1:1.0	71%
2	(*R*,*R*)-DIOP	1.0:1.2	16%
3	(1*R*,1*R*′,2*S*,2*S*′)-Duanphos	1.1:1.0	58%
4	(*R*,*R*)-MeDuPhos	1.1:1.0	52%
5	(*S*,*S*)-Bis(diphenylphosphino)butane (Chiraphos)	1.0:1.1	56%
6	rac-BINAP	1.0:1.0	49%

[a]Determined by ^{1}HNMR spectroscopy using dibromomethane as an internal standard. Yields are reported as a mixture of diastereomers.

We synthesized an alternate substrate and conducted the rhodium-catalyzed conjugate addition with $PhB(OH)_2$ to generate a product containing two adjacent chiral centers. We hoped that these processes would be both diastereoselective and enantioselective and evaluated a series of chiral bisphosphine ligands to initially screen for these parameters. We found that a mixture of diastereomers was generated with ratios near 1.0:1.0 in each case, but the yields were much higher than observed with the previous substrate and *rac*-BINAP. (*S*,*S*)-BDPP, (1*R*,1*R*′,2*S*,2*S*′)-Duanphos, and (*S*,*S*)-Bis(diphenylphosphino)butane (Chiraphos) had the highest yields and were used in further experiments.

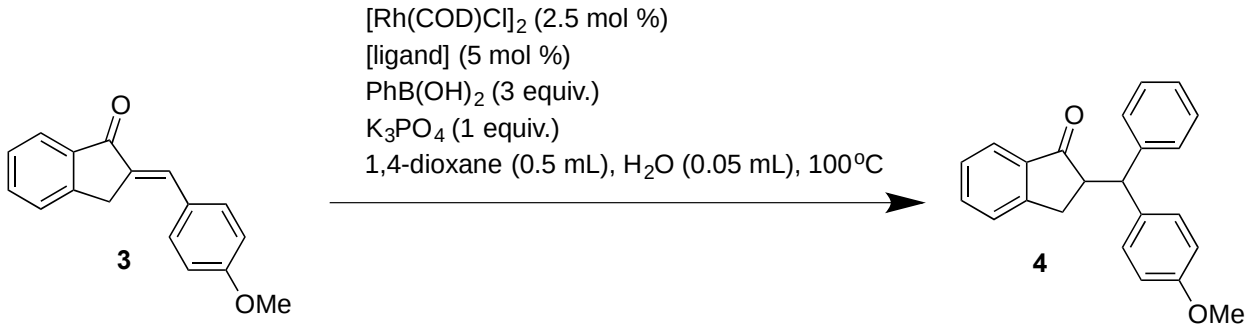

Table 7: Evaluation of chiral ligands with a higher amount of $PhB(OH)_2$ for conjugate addition

Entry	Ligand	Equiv. $PhB(OH)_2$	Corrected ^{1}HNMR Yield[a]
1	(*S*,*S*)-BDPP	2.00	71%
4	(*S*,*S*)-BDPP	3.00	49%
2	(1*R*,1*R*′,2*S*,2*S*′)-Duanphos	2.00	58%
5	(1*R*,1*R*′,2*S*,2*S*′)-Duanphos	3.00	47%
3	(*S*,*S*)-Bis(disphenylphosphino)butane (Chiraphos)	2.00	56%
6	(*S*,*S*)-Bis(disphenylphosphino)butane (Chiraphos)	3.00	52%

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

The best three ligands from above were tested with increased amounts of $PhB(OH)_2$. It was found that Chiraphos had the highest yield when 3.00 equivalents of $PhB(OH)_2$ was used (entries 4-6), but yields were higher with 2.00 equivalents of $PhB(OH)_2$.

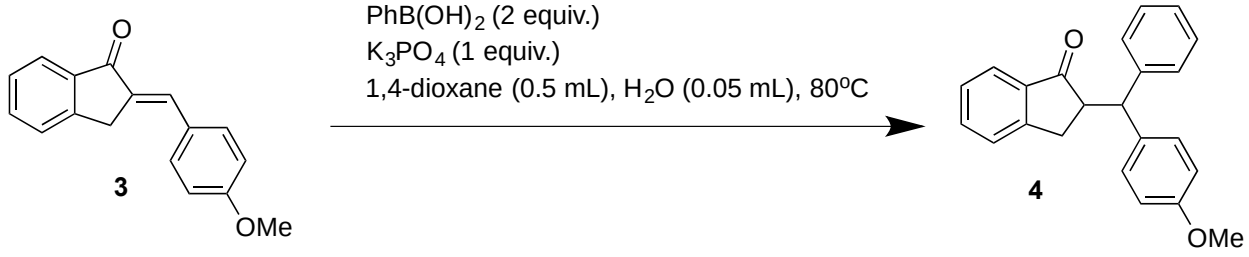

Table 8: Evaluation of chiral ligands with lower reaction temperature for conjugate addition

Entry	Ligand	Temp	Corrected ^{1}HNMR Yield[a]
1	(*S*,*S*)-BDPP	100 ºC	71%
2	(*S*,*S*)-BDPP	80 ºC	51%
3	(1*R*,1*R*′,2*S*,2*S*′)-Duanphos	100 ºC	58%
4	(1*R*,1*R*′,2*S*,2*S*′)-Duanphos	80 ºC	48%
5	(*S*,*S*)-Bis(disphenylphosphino)butane (Chiraphos)	100 ºC	56%
6	(*S*,*S*)-Bis(disphenylphosphino)butane (chiraphos)	80 ºC	56%

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

We also evaluated temperature for the rhodium-catalyzed conjugate addition to this substrate. Lowering the reaction temperature to 80 ºC ring is not detrimental to the yield, but yields were generally lower than reactions run at 100 ºC. To evaluate whether to continue screening conditions with these chiral ligands, we isolated the product from entries 1, 3 and 5 and are attempting to find separation conditions using high-performance liquid chromatography (HPLC) to check for enantioselectivity in each diastereomer. Material from an experiment using *rac*-BINAP was also isolated for comparison in yield and to generate a racemic sample for the identification of separation conditions.

Conclusion

So far this semester, 50-70% yield has been achieved on the rhodium-catalyzed conjugate addition of $PhB(OH)_2$ to the hydroacylation product explored last semester. Future directions will include finding separation conditions on the HPLC to determine enantioselectivity for these reactions. The conjugate addition reaction currently results in about a 1:1 mixture of diastereomers, and determination of the enantioselectivity for these diastereomers will guide future directions for this project. Eventually we aim to pair this reaction with the hydroacylation reaction explored last semester in order to perform both transformations in one pot.

References

1. Kadayat, T. M.; Park, C.; Jun, K.-Y.; Thapa Magar, T. B.; Bist, G.; Yoo, H. Y.; Kwon, Y.; Lee, E.-S., Hydroxylated 2,4-diphenyl indenopyridine derivatives as a selective non-intercalative topoisomerase IIα catalytic inhibitor. European Journal of Medicinal Chemistry 2015, 90, 302-314.

2. Hayashi, T.; Yamasaki, K., Rhodium-Catalyzed Asymmetric 1,4-Addition and Its Related Asymmetric Reactions. *Chemical Reviews*, **2003**, *103*(8), 2829-2844.