Investigation of Transition Metal-Catalyzed Oxidative Amidation of Aldehydes and Aldehyde-Alkyne-Amine Coupling Reactions

by

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Dedication

J'aimerais dédier cette thèse à mes parents, eux qui en plus de m'apporter leur support indéfectible, m'ont poussé à me dépasser et à devenir qui je suis aujourd'hui.

Abstract

This thesis describes the investigation of various amino acids derivatives as reagents for copper-catalyzed, silver-catalyzed and iron-catalyzed reactions and the investigation of an enantioselective cobalt-catalyzed aldehyde-alkyne-amine (A^3) coupling reaction.

The first part focuses on the large-scale optimization of the oxidative amidation of aldehydes in the presence of amine hydrochloride salts as well as our effort to enhance the reaction scope by the use of amino acids derivatives and short peptides.

This is then followed by the development of an enantioselective cobalt-catalyzed A^3-coupling using binaphthol ligands as a source of chirality.

Finally, the last part involves silver-catalyzed alkyne addition to iminoesters as well as silver-catalyzed A^3-coupling.

Résumé

La présente thèse a pour but de présenter l'utilisation de divers dérivés d'acides aminés comme substrats pour plusieurs réactions catalysées par des sels de cuivre, d'argent et de fer, de même que du développement d'une réaction de couplage énantiosélective entre aldéhyde, alcyne et amine (A^3) catalysée par des sels de cobalt.

La première partie met l'emphase sur l'optimisation à grande échelle d'un procédé d'amidation oxydative d'aldéhydes en présence de sels d'amine ainsi que nos efforts pour adapter cette méthode à des substrats tels que courts peptides et dérivés d'acides aminés.

Cela est suivi par le développement d'une réaction de couplage énantiosélective entre aldehyde, alcyne et amine (A^3) catalysée par des sels de cobalt misant sur l'utilisation de binaphtols comme ligands chiraux.

La dernière partie porte sur l'addition d'alcyne à des iminoesters catalysés par des sels d'argent ainsi que sur des réactions de couplage A^3, elles aussi catalysées par des sels d'argent.

Acknowledgements

First and foremost, I would like to thank Prof. Chao-Jun Li for accepting me amongst his research group and showing me what research is all about. Thank you for your assistance, advices and the freedom you gave me in undergoing research.

I would like to thank everybody in the Li group (Leon Sun, Camille Correia, Qi Shuai, Wen-Wen Chen, Xiangyu Guo, Luo Yang, Liang Zhao, Nick Uhlig, Woo-Jin Yoo) for their support and everyday advices. Dr. Chen was also really helpful with the enantioselective cobalt-catalyzed A^3-coupling project. I am also grateful to many staff members, particularly Chantal Marotte for her kind words and discussion.

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Abbreviations

% e.e.	enantiomeric excess
2-MeTHF	2-methyltetrahydrofuran
A^3	Aldehyde-Alkyne-Amine
AA^3	Asymmetric Aldehyde-Alkyne-Amine
acac	Acetylacetonate
Ac	Acetyl
Ar	aromatic
atm	atmosphere
BINAP	2,2`-bis(diphenylphosphino)-1,1`-binaphthyl
BINOL	1,1`-bi(2-naphthol)
br	broad
d	doublet
DCM	dichloromethane
Equiv.	equivalent
Gly	glycine
HPLC	high performance liquid chromatography
iPr	isopropyl
m	multiplet
MeCN	acetonitrile
NMR	nuclear magnetic resonance
OTf	trifluoromethanesulfonate

PyBOX	2,6-bis(4-phenyl-2-oxazolinyl)pyridine
QUINAP	1-(2-diphenylphosphino-1-naphthyl)isoquinoline
s	singlet
SDS	sodium dodecyl sulfate
THF	tetrahydrofuran
T-Hydro©	aqueous solution of tert-butyl hydroperoxide
TMS	trimethylsilyl
t_R	Retention time

Chapter 1: Oxidative Amidation of Aldehyde in the Presence of Amine Hydrochloride Salts

1.1 Synopsis

The first part of this chapter will describe key concepts relevant to the research undergone, followed by a presentation and discussion on the oxidative amidation of aldehydes with amine hydrochloride salts that we investigated.

1.2 Green Chemistry

Green chemistry is a powerful notion or philosophy in modern research; it strives to make chemistry sustainable yet at the same time more efficient.

The risk associated with any activity can be described as a function of hazard and exposure:[1]

Risk = f[hazard, exposure]

Equation 1: Risk equation

One of the most basic concepts behind green chemistry (as laid down by Paul T. Anastas and others) is a different approach in order to minimize the risk of dealing with chemical processes. It focuses on reducing the hazard inherent to a process, as opposed to reducing the exposure of workers or the environment in general to the said process. Doing so ensures the general safety of everyone involved to a greater extent than simply managing the exposure and even if something goes wrong, an innocuous compound will remain an innocuous compound. One might ask: How does this apply to research? Paul T. Anastas

and John C. Warner laid down 12 fundamental rules or guidelines that chemists should keep in mind when designing new reactions:[2]

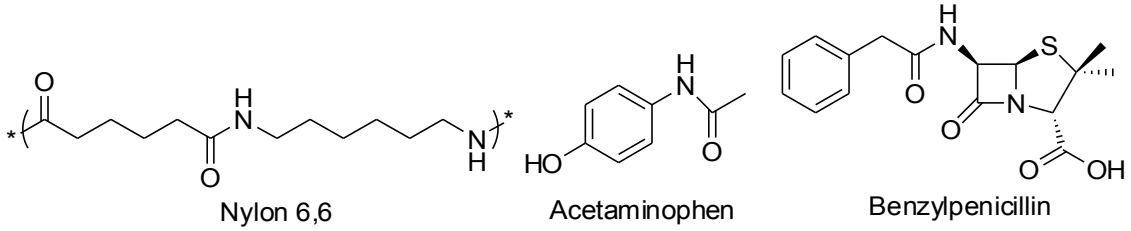
1) It is better to prevent waste than to treat or clean up waste after it is formed.
2) Synthetic methods should be designed to maximize the incorporation of all materials used in the process into the final product.
3) Wherever practicable, synthetic methodologies should be designed to use and generate substances that possess little or no toxicity to human health and the environment.
4) Chemical products should be designed to preserve efficacy of function while reducing toxicity.
5) The use of auxiliary substances (e.g. solvents, separation agents, etc.) should be made unnecessary wherever possible and, innocuous when used.
6) Energy requirements should be recognized for their environmental and economic impacts and should be minimized. Synthetic methods should be conducted at ambient temperature and pressure.
7) A raw material or feedstock should be renewable rather than depleting wherever technically and economically practicable.
8) Unnecessary derivatization (blocking group, protection/ deprotection, temporary modification of physical/chemical processes) should be avoided whenever possible.
9) Catalytic reagents (as selective as possible) are superior to stoichiometric reagents.

10) Chemical products should be designed so that at the end of their function they do not persist in the environment and break down into innocuous degradation products.
11) Analytical methodologies need to be further developed to allow for real-time, in-process monitoring and control prior to the formation of hazardous substances.
12) Substances and the form of a substance used in a chemical process should be chosen to minimize potential for chemical accidents, including releases, explosions, and fires.

These rules led to the creation of various indicators or green chemistry metrics such as: atom-economy, environmental factor (or E-factor), effective mass yield (EMY)[3] and others.

1.3 Importance of Amide Bond

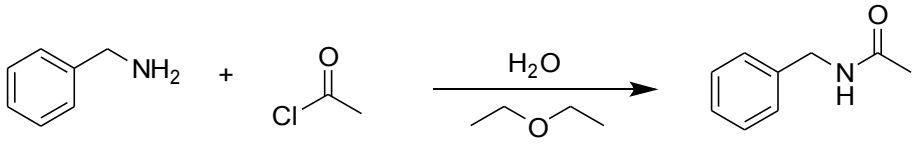
Amide-containing molecules are an essential component of modern life. They are key components of modern medicine (as in acetaminophen or benzylpenicilin to name only two), as well as man-made fabric such as Nylon 6,6 (Scheme 1) and they form the key linkage between amino acids in order to form peptides.



Scheme 1: Common amide-containing molecules

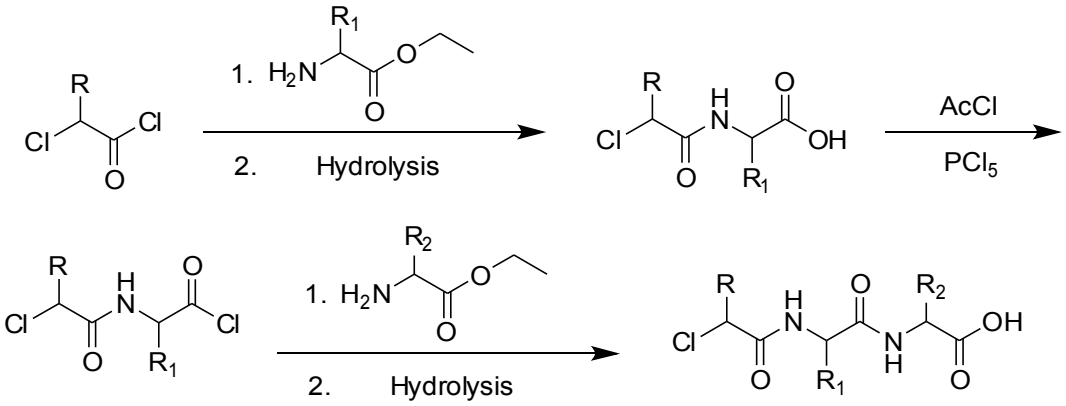
1.4 Classical Syntheses of Amides

Due to the their importance, it is not surprising that numerous methods have been developed in order to synthesize amides. One of the methodologies was developed by German chemists Carl Schotten[4] and Eugen Bauman (published in 1883) involving the condensation of an acid chloride with an amine (Scheme 2).



Scheme 2: Schotten-Bauman reaction

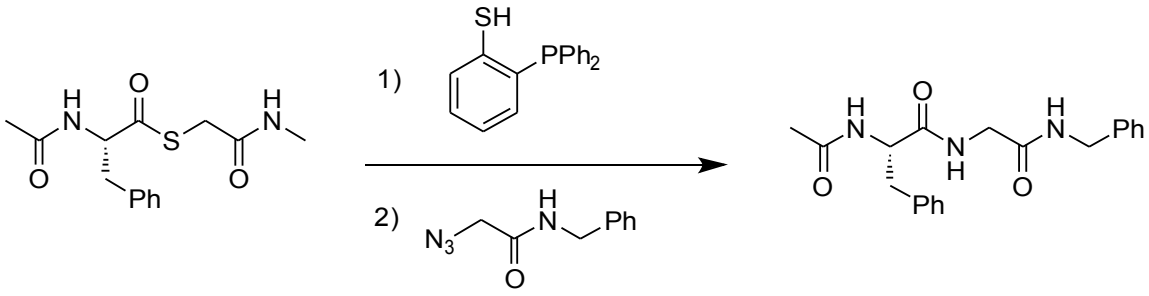
In the same vein, a successful peptide synthesis methodology was achieved by Emil Fisher in 1903[5], where an alpha-halo acid chloride is condensed with the ester of an amino acid, followed by hydrolysis in order to obtain the free peptide (Scheme 3).



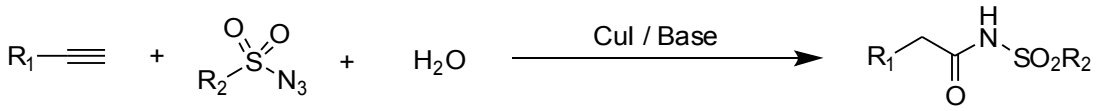
Scheme 3: Fischer peptide synthesis

From there, a myriad of synthetic methods came to light during the 20th century, most of them are based on the condensation of an activated carboxylic acid derivative with an amine. It is not the goal nor the point of this thesis to review those, so a few relevant examples will be presented in order to provide context and comparison to the original research detailed in this thesis. In the 21st century, other methodologies have

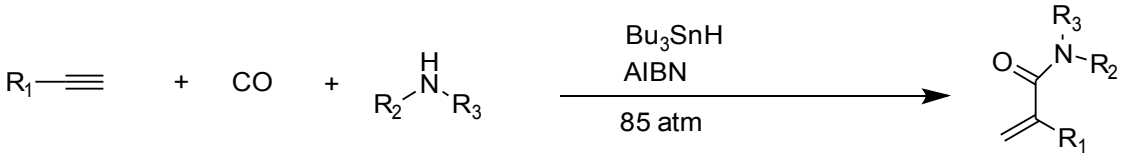
been developed: modified Staudinger reaction[6] using azide as a source of nitrogen (Scheme 4), thio acid/ester ligation,[7] hydrative amide synthesis with alkynes[8] (Scheme 5), transition-metal-catalyzed carbonylation of alkynes[9] (Scheme 6), alkenes and haloarenes.[10] Albeit succesful, many of the aforementioned methods have several weaknesses: sub-optimal atom-economy, low energy efficiency, use of hazardous chemicals (azide) or processes.



Scheme 4: Modified Staudinger reaction



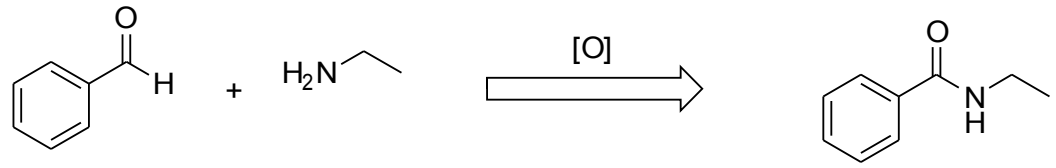
Scheme 5: Hydrative amide synthesis with alkynes



Scheme 6: Tin-catalyzed carbonylation of alkynes

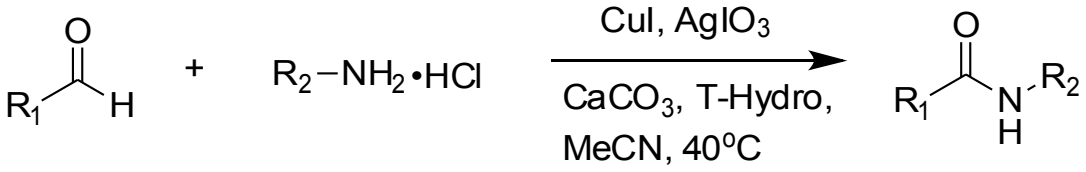
1.5 Oxidative Amidation of Aldehydes

A more efficient method would be to make use the acyl C-H of aromatic aldehyde under oxidative conditions, in other words, an oxidative amidation of an aldehyde in the presence of amine (Scheme 7).

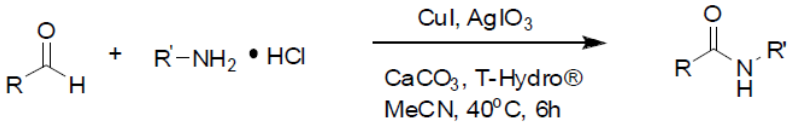


Scheme 7: General scheme of an oxidative amidation of aldehyde in presence of an amine

This methodology was developed by Yoo and Li,[11] it uses CuI as a catalyst and silver iodate as an additive (Scheme 8). This methodology requires the use of amine hydrochloride salts rather than the free amine. The amine is then deprotonated *in situ* by an insoluble base ($CaCO_3$). The protection of the amine is required since the free amine is vulnerable to oxidation. The reaction system was originally optimized using ethylamine and benzaldehyde.



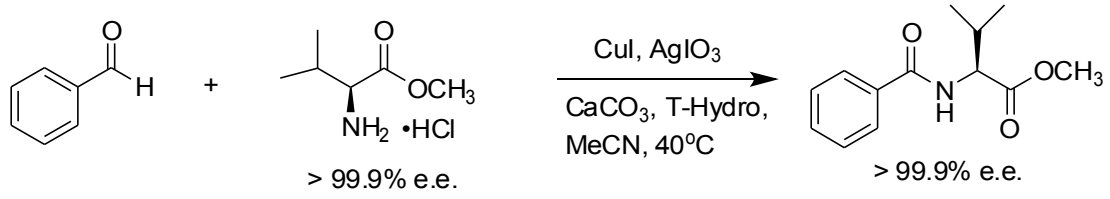
Scheme 8: Copper-catalyzed oxidative amidation of aldehyde in the presence of amine hydrochloride salts



Entry	R	R'	Isolated yield (%)
1	Ph	Et	91
2	Ph	Bn	71
3	Ph	CH_2Bn	89
4	Ph	cyclohexyl	73
5	Ph	^tBu	39
6	Ph	CH_2CH_2Cl	89
7	Ph	CH_2COOEt	91
8	4-Me-C_6H_4	CH_2COOEt	91
9	4-MeO-C_6H_4	CH_2COOEt	78
10	4-Cl-C_6H_4	CH_2COOEt	81
11	4-NO_2-C_6H_4	CH_2COOEt	49
12	cyclohexyl	CH_2COOEt	39

Table 1: Initial scope of the copper-catalyzed oxidative amidation

The oxidative amidation of benzaldehyde and electron-rich aromatic aldehydes was proven to be successful, however this was not the case when an electron-withdrawing group or an aliphatic aldehyde was used. Concerning the choice of amine hydrochloride salts, the reaction was tolerant of other electrophiles (such as ester or alkyl chloride). The reaction was also proven to be successful with L-valine methyl ester hydrochloride, both in term of yield and retention of stereochemistry (Scheme 9).



Scheme 9: Oxidative amidation of benzaldehyde with L-valine methyl ester hydrochloride

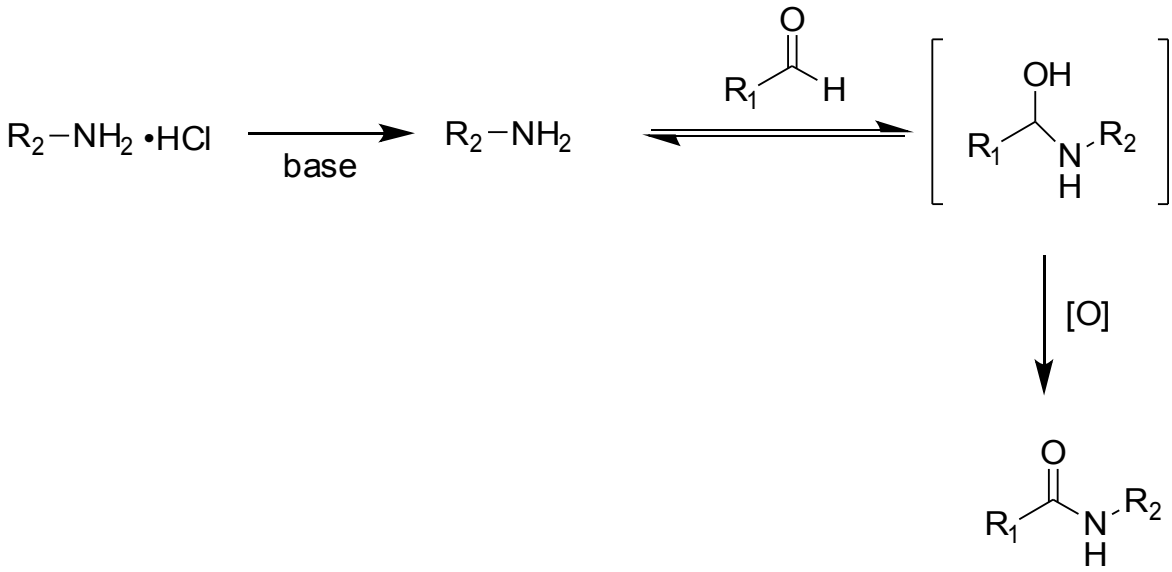
1.6 Large-Scale Optimization and Plausible Mechanism

This reaction was first done on a 200 mg scale, one of the later goals was to scale-up and optimize this reaction to a 5 gram scale. Another goal was to expand this methodology to short peptide synthesis or modification.

An excess of the amine hydrochloride salts (1.5:1 ratio) was found to improve the yield significantly. The amount of solvent was also a key issue in the process. This oxidative amidation reaction was found to give a higher yield with a lower amount of solvent. Nevertheless, a sufficient amount of solvent needs to be added to make sure that all the amine is dissolved and that all the reactants are in solution. The reaction was originally carried out under argon atmosphere, but it was later found that the reaction could run in air unimpeded. In order to obtain an efficient stirring, a mechanical stir paddle had to be used (as opposed to the usual magnetic stirrer) due to the large amount

of solids, especially the insoluble base. The said insoluble base ($CaCO_3$) is also another key aspect since it is necessary to deprotect the amine, but a more soluble base like $NaHCO_3$ yields some undesired side products. Acetonitrile is the solvent of choice for this reaction, since it has proven to give significantly higher yields than other solvents in the previous optimization. Due to its immiscibility with alkanes, using a tert-butyl hydroperoxide solution in decane was not an optimal choice. By using a tert-butyl hydroperoxide solution in water (T-Hydro®), we benefit from the miscibility between water and acetonitrile, thus making the oxidant much more available to the reaction mixture. This observation had already been made by Yoo and Li,[12] so the same oxidant and solvent were used.

The reaction is thought to go through the following mechanism (Scheme 10); where the first step is a deprotonation of the amine hydrochloride salt by the $CaCO_3$, followed by the nucleophilic addition of the free amine to the aldehyde to generate a carbinol amine intermediate. Meanwhile, Cu(I) present in solution is most likely oxidized to Cu(II) by the tert-butyl hydroperoxide, the silver iodate and the oxygen if present. The Cu(II) can then oxidize the carbinolamine to the amide in a subsequent step.



Scheme 10: Plausible mechanism for the oxidative amidation of aldehydes with amine hydrochloride salts

Another possibility would be a transamidation reaction with a carboxylic acid derived from the oxidation of the aldehyde. This possibility is less likely since if we replace benzaldehyde by benzoic acid, the expected amide product is not observed.

Different methods of purification were also analyzed: extraction followed by recrystallization, column chromatography with or without prior extraction. Recrystallization might be considered to be an ideal mean of purification on large scale since it is more easily applied to large quantities, it is faster and less solvent intensive than column chromatography. Extraction followed by recrystallization was proven to be an effective purification method if coupled with a filtration on silica gel since the metal catalysts were not removed otherwise. Nevertheless, the yield (41%) was too low to be considered an efficient method. The best results were obtained by using extraction followed by column chromatography, where an 83% yield was obtained.

The purity of the resulting product was assessed by various methods: ^{1}H-NMR, ^{13}C-NMR, infrared spectroscopy, elemental analysis, mass spectrometry and chiral high-performance liquid chromatography (to assess the enantiomeric excess).

The specific rotation of the compound was also evaluated and reported for the first time. Getting an accurate and reproducible measurement has proven to be a challenge in that case. Samples of various concentrations were prepared and analyzed more than 10 times each (with some as high as 50 times) and the average was taken. The main issue being a low precision, when the same sample is analyzed repeatedly.

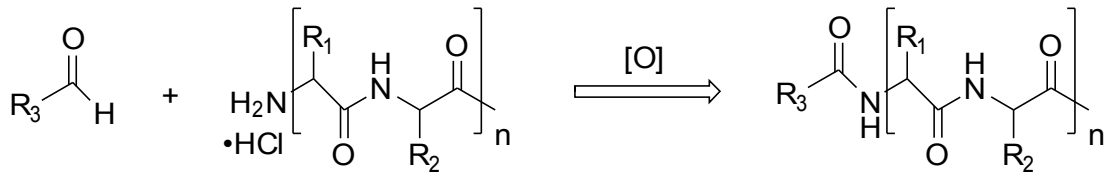
$$[\alpha]_{20}^{D} = \frac{\alpha}{l\,x\,d}$$

Equation 2 : Equation describing the specific rotation of a compound in solution

Where [α] is the specific rotation of the compound when it is irradiated at 589 nm (sodium D line) at 20°C, α is the optical rotation, c is the concentration (g/100ml), l is the path length (dm)

1.7 Amino Acids and Short Peptides as Substrates

Following the large-scale optimization, we wanted to expand the scope of the copper-catalyzed oxidation to functionalization of short peptides. As shown in the scheme below, the proposal would be that an aromatic aldehyde would undergo oxidative amidation in the presence of the amine hydrochloride salt of a peptide to give the amide product (Scheme 11).

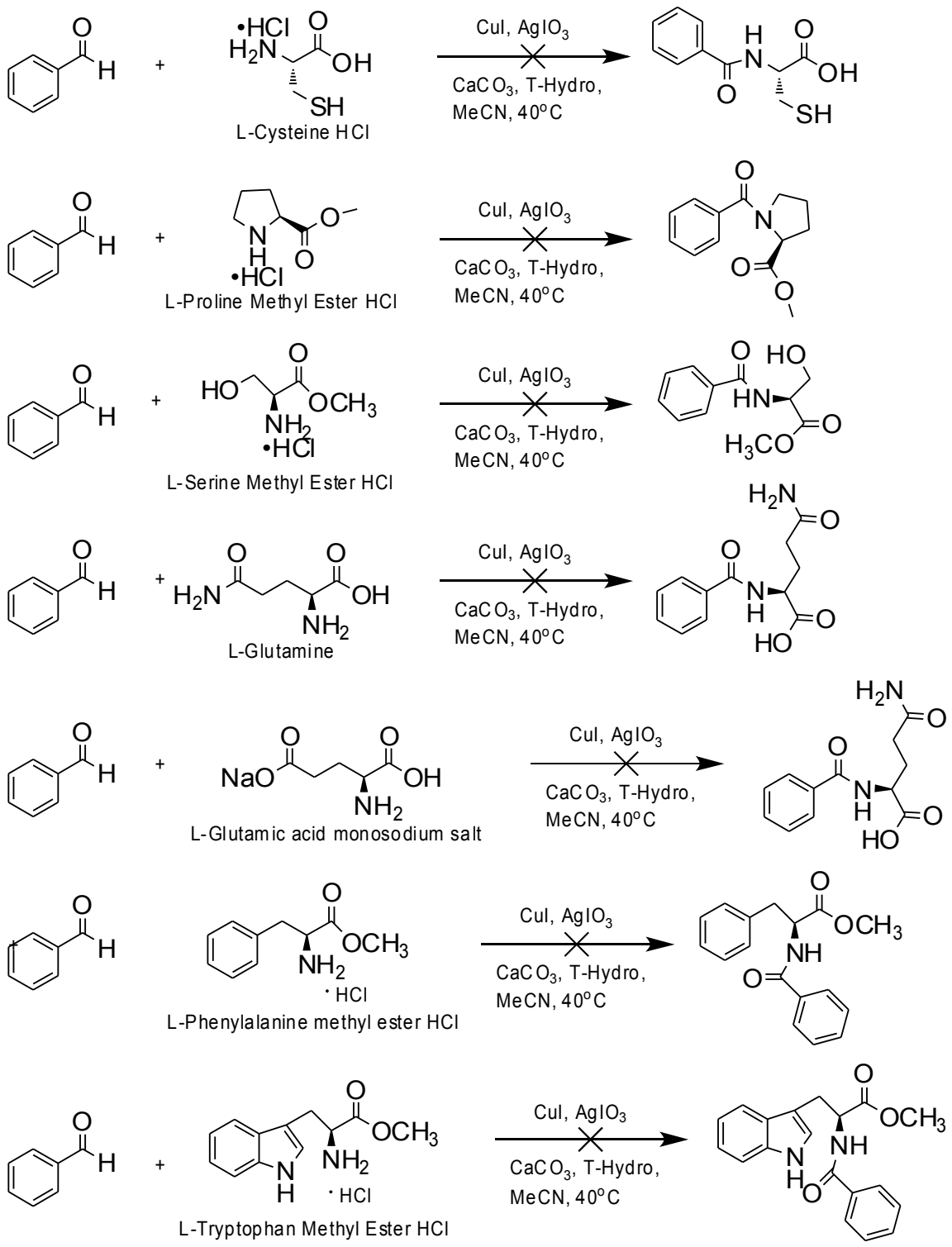


Scheme 11: Possible application of the oxidative amidation methodology to peptides

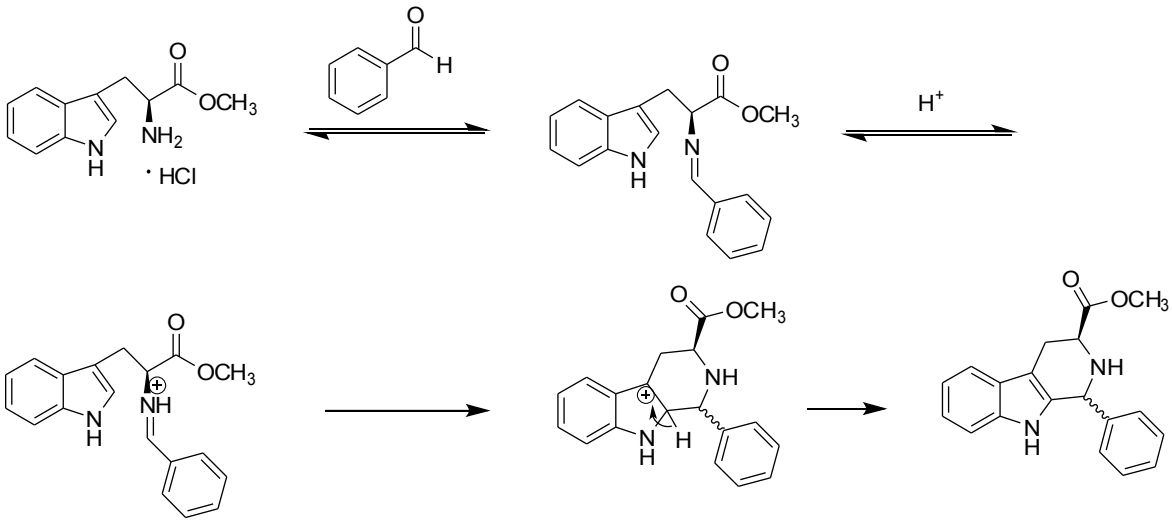
The first step in this process was to screen various amino acids and amino acids derivatives in order to find those that were compatible with the already established reactions conditions. The following schemes present a sampling of the amino acids / derivatives that were tried. Amino acids containing carboxylic acids prevented the desired reaction from occurring. This also occured with alcohol/thiol containing moiety. Samples of these reactions are shown in Scheme 12.

For these reasons, serine, cysteine, glutamine and glutamic acid derivatives had to be excluded. It was also found that secondary amines do not yield the desired product either, so proline derivatives had to be excluded. This left us with 6 amino acid candidates: glycine esters, tryptophan esters, phenylalanine esters, alanine esters, leucine esters and isoleucine esters.

Since the tryptophan esters and the phenylalanine esters were not yielding the desired product at the usual reaction temperature (40^{o}C), we decided to increase the temperature in order to promote a reaction. This increase in temperature promoted an undesired albeit well known reaction: the Pictet-Spengler reaction. In the following example (Scheme 13), the amine first condenses with the aldehyde to form the imine. The imine is then protonated to the iminium form, which is followed by an electrophilic substitution and ring closure to form a tetra-hydro-β-carboline derivative. This reaction is highly favoured at high temperature and does not require any catalyst. This reaction is also in agreement with Baldwin's rules for ring closure since it is a 6-endo-trig process, which is favoured.



Scheme 12: Amino acid screening as substrates for the oxidative amidation reaction



Scheme 13: Prevalent side-reaction with tryptophan derivatives: the Pictet-Spengler reaction

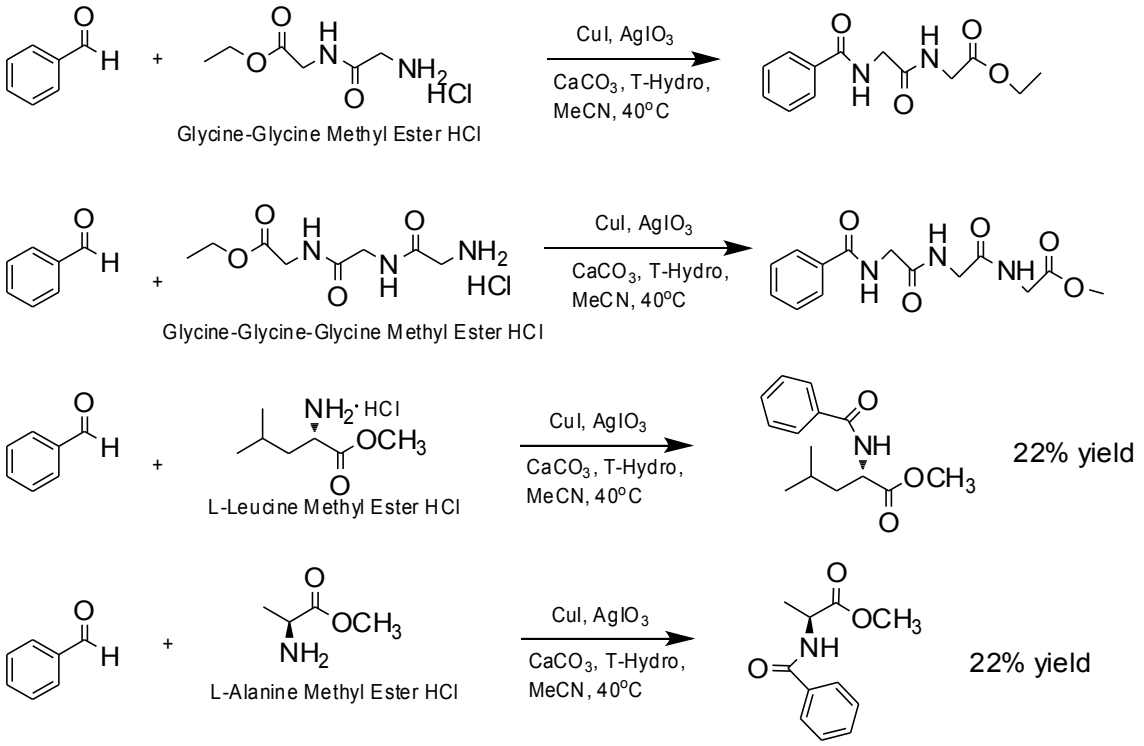
The use of glycine-glycine (Gly-Gly) methyl ester hydrochloride was more successful and yielded the desired product, albeit in low yield. Once again, various reaction parameters were modified: use of different inorganic bases (Cs_2CO_3, $NaHCO_3$), solvents (chlorobenzene, water), temperature and ratio of starting materials. When chlorobenzene was used as a solvent, the tert-butyl hydroperoxide was used as a solution in decane as opposed to water to improve its solubility. Nevertheless, the yield could not be improved significantly.

Gly-Gly-Gly methyl ester hydrochloride was also investigated as a possible substrate. The addition of another amino acid unit might have decreased the solubility of the amine in organic solvents, so an hybrid solvent system (various ratios of MeCN-H_2O) was investigated as well as using pure water. We were also faced with another problem: the characterization of the desired product using ^{1}H-NMR had proven to be difficult due to the overlap of numerous peaks.

If another glycine unit is added, the solubility in organic solvents becomes a major

issue and water has to be used.

Other amino acid derivatives such as L-leucine methyl ester HCl and L-alanine methyl ester HCl yielded the desired product as expected (see Scheme 14), but in both cases, 22% was the best yield obtained.



Scheme 14: Amino acids derivatives yielding the desired product

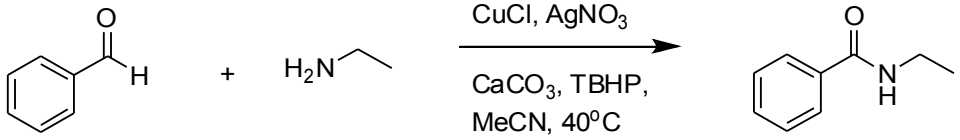
A possible improvement to the hybrid solvent system or pure water conditions would be the addition of a surfactant (sodium dodecyl sulfate for example). By setting the concentration of the surfactant below the critical micelle concentration (CMC), we could improve the solubility of the reagents by lowering the surface tension of water. If we set the concentration higher than the CMC (> 8.3×10^{-3} M in pure H_2O at room temperature for SDS[13]), micelles would form and would most likely encapsulate hydrophobic material, hence artificially increasing the relative concentration of the reactants.

Other possible improvements include: using isoleucine (since its structure would most likely be compatible with this methodology) and small peptides containing valine, alanine, leucine or glycine moieties as substrates for the oxidative amidation since those were successful substrates and one could hope to expand their reactivity to homodimers and heterodimers.

1.8 Environmental Impact of Oxidative Amidation

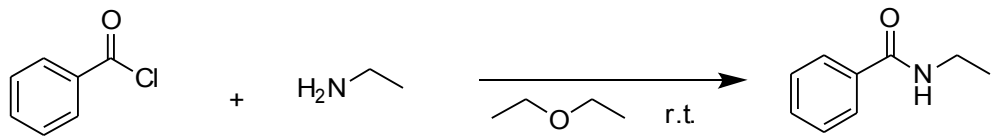
Our initial goals were not only to create an amide synthesis methodology but also to create one that would be environmentally benign, this is why we decided to include a small analysis of our methodology from a green chemistry perspective.

We chose to use the newly developed tool called iSustain™ Green Chemistry Index tool V. 2.0 which analyzes a chemical process based on the 12 principles of green chemistry. We decided to use the synthesis of N-ethylbenzamide (on a 5 gram scale) as our typical reaction. Two modifications were made due to the limitations of the software. CuI was replaced by CuCl in this simulation since the former was not part of the software database and $AgIO_3$ was replaced by $AgNO_3$ (as shown on Scheme 15).



Scheme 15: Oxidative amidation of benzaldehyde with ethylamine yielding N-ethylbenzamide

This reaction was compared to the following reaction (see Scheme 16) with the assumption that the yield for both reactions would be comparable.



Scheme 16: Schotten-Bauman reaction of benzoyl chloride and ethylamine yielding N-ethylbenzamide[14]

In both cases, all the steps involved in the reaction (including work-up and purification) were inputted.

According to this analysis (see Figure 1 and 2), the oxidative amidation proves itself superior in term of atom-economy (since chlorine is lost in the Schotten-Bauman reaction), safe raw materials (since benzoyl chloride poses reactivity and toxicity risks) and catalysis. On the other hand, the Scotten-Bauman reaction proves itself superior in term of energy efficiency (since the reaction is done at room temperature as opposed to 40°C for the oxidative amidation) and process complexity (due to its smaller number of components and additions).

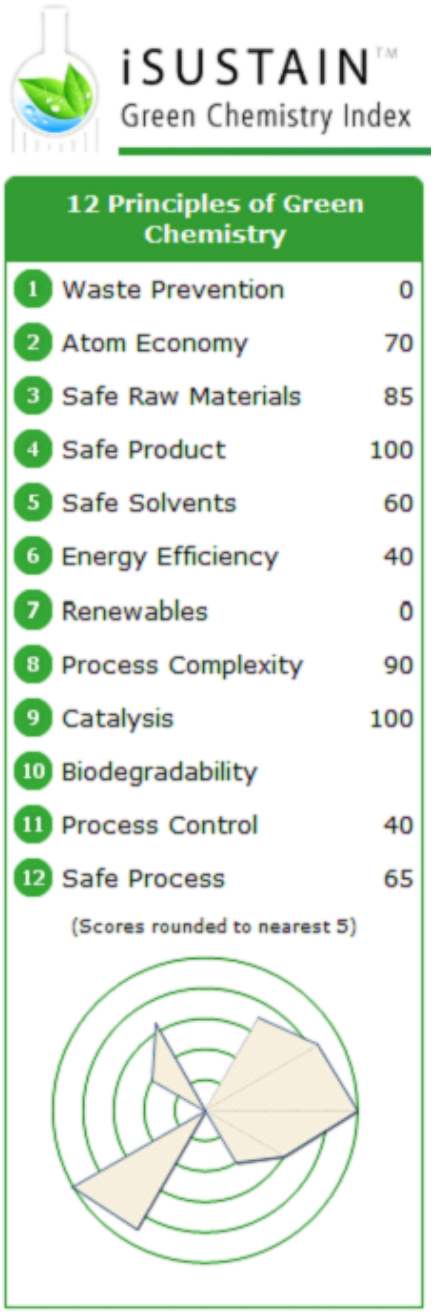


Figure 1: Score for the oxidative amidation

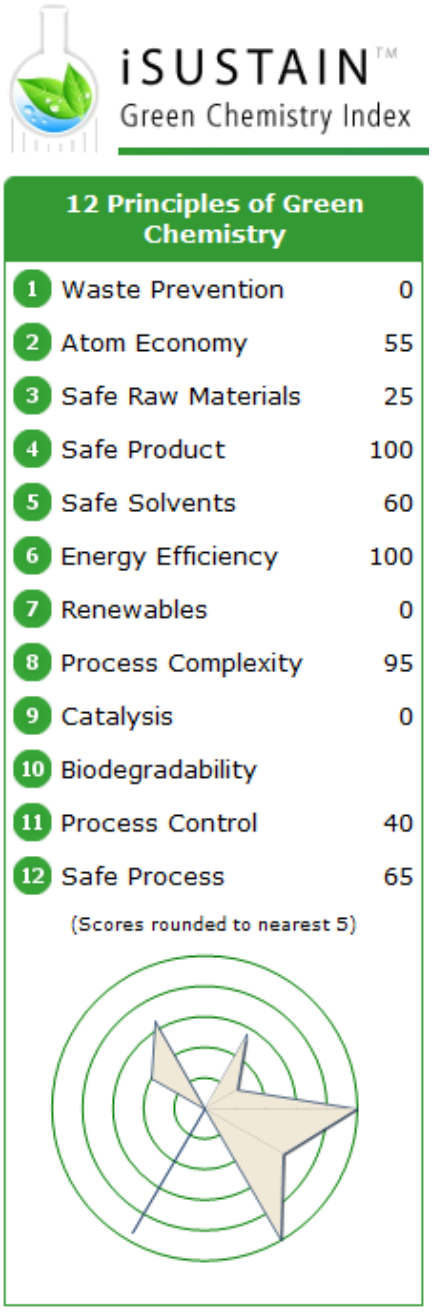


Figure 2: Score for the Schotten-Bauman reaction

Overall, this analysis agrees with our finding that the oxidative amidation method is a greener approach than others, but it also shows that it is not without its flaws. The major drawback for both these methods in term of "green chemistry" is the amount of

organic solvent that is used in the purification process, especially when column chromatography is involved. In order to propose a truly green synthesis, better purification methods and/or significant solvent recycling would have to be used.

1.9 Conclusion

The method of oxidative amidation of aldehydes in presence of amine hydrochloride salts developed by Li was optimized for a large scale (5 grams) synthesis using L-valine methyl ester hydrochloride as a substrate yielding (S)-methyl-2-benzamido-3-methylbutanoate as product without racemization and in good yield (83%). Hoping to apply this method to small peptides, various amino acids and their derivatives were analyzed as possible substrates for the reaction. Unfortunately, most of these substrates had proven to be non-compatible with the necessary reaction conditions to undergo oxidative amidation, either due to lack of reactivity or due to competing and prevalent side reactions. Nevertheless, the scope of the reaction was broadened to include multiple glycine units, leucine and alanine derivatives. Finally, a short comparative study was done using the newly developed iSustain™ tool in order to evaluate how "green" the oxidative amidation reaction is, as opposed to a more classic synthesis.

1.10 Experimental

General

^{1}H-NMR spectra were recorded using a Varian 400 MHz spectrometer. ^{13}C-NMR were recorded using a Varian 300 MHz spectrometer. The chemical shifts are reported in part per million (δ) and either deuterated chloroform or deuterated-DMSO were used as a solvent. One equivalent of CH_2Cl_2 is normally used as the internal standard when an NMR yield is given. The silica gel used for the purification is SiliaFlash F60 from Silicycle company. Unless otherwise specified, the chemicals used were purchased and used as such from Sigma-Aldrich. All reagents were weighted and handled in air at room temperature.

1.10.1 Large-Scale Oxidative Amidation of Benzaldehyde with L-Valine Methyl Ester Hydrochloride

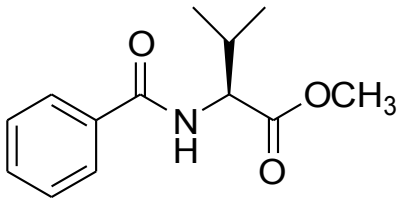
Procedure

A mechanical stir paddle was fitted to an oven-dried 100 mL round-bottomed flask (24/40 joint). CuI (0.0470 g, 0.246 mmol, 0.01 equiv) , $AgIO_3$ (0.070 g, 0.25 mmol, 0.01 equiv), L-valine methyl ester hydrochloride (6.19 g, 36.9 mmol, 1.5 equiv) and $CaCO_3$ (2.10 g, 21.0 mmol, 0.9 equiv) were added sequentially to the 100 mL round-bottomed flask and stirred at 230 rpm. Acetonitrile (5.5 mL) was added in one portion using a syringe under constant stirring. A white opaque solution was obtained at the end of this step. Benzaldehyde (2.5 mL, 24.6 mmol, 1.0 equiv) was added using a syringe under constant stirring. Upon addition, the reaction mixture changed to a yellow opaque solution. A *tert*-butyl hydroperoxide solution (4.0 mL, 28.0 mmol, 1.1 equiv) was added using a syringe under constant stirring. The solution then turned green. The plastic septum

attached to the mechanical stir paddle was lowered to cover the reaction flask and prevent excess evaporation of the solvent. The reaction flask was then put in an oil bath at 40°C for 6 hours.

After being put in the oil bath, the reaction mixture gradually became a clear orange-gold solution. After being taken out of the oil bath, the reaction flask was put in an ice-bath. Upon cooling, the solution became a thick mustard-yellow opaque mixture. Hydrochloric acid (1.6 M, 7.5 mL) was added dropwise (ca. 4 drops per second) under constant stirring. Upon neutralization, the reaction mixture turned green. The reaction flask was taken out of the ice-bath and ethyl acetate (25 mL) and distilled water (20 mL) were added. The organic layer was light green and the aqueous layer was white-blue and opaque. If left overnight at room temperature, the organic layer may turn orange. The reaction mixture was transferred to a 250 mL separatory funnel. The 100 mL round-bottomed flask was rinsed with ethyl acetate (15 mL) and distilled water (15 mL). The rinsings were transferred to the separatory funnel. Brine (15 mL) was added to the separatory funnel to obtain a better phase separation. The two layers were separated and were each poured in a 250 mL Erlenmeyer flask. The aqueous layer was then put back in the 250 mL separatory funnel and extracted with three portions of ethyl acetate (3x 25 mL). Brine (3x 15 mL) was added with every extraction. The organic layers were then combined and washed using a saturated solution of $NaHCO_3$ (25 mL) using the same 250 mL separatory funnel and poured in a 250 mL Erlenmeyer flask. Anhydrous magnesium sulfate (4.0 g) was then added. The solution was filtered under vacuum using 30 mL suction funnel equipped with a medium porosity fritted-disc into an oven-dried 500 mL round-bottomed flask (14/20 joint). The anhydrous magnesium sulfate accumulated in the

fritted glass filter was washed with two portions of ethyl acetate (2 x 10 mL) into the 500 mL round-bottomed flask. The solution was evaporated to dryness under vacuum and a white-beige solid was obtained. Dichloromethane (20 mL) was added to the round-bottomed flask. The flask was then sonicated for 30 seconds resulting in a green brown solution. Silica gel (5.0 g) was added to the flask and the solvent was evaporated using a rotary evaporator at 55-60^{o}C (21 mm Hg). Flash column chromatography was performed using a 5-cm-wide, 45-cm-high column packed with 230 g of silica gel. The column was packed with silica gel and flushed with 1000 mL of the eluent (hexanes: ethyl acetate = 3:2). The eluent level was adjusted to the upper level of the silica gel. The silica gel containing the compound was then loaded on the column and column chromatography was performed (1.7 L of eluent was used). The collected fractions (15 mL each) were analysed using TLC (eluting with hexanes: ethyl acetate =3:2) and the spots were visualized using a UV lamp (254 nm). The fractions (41 to 92) containing the desired compound (Rf= 0.45) were combined and evaporated to dryness using a rotary evaporator. The product was further dried under reduced pressure (0.01 mm Hg) for 2 hours to give (S)-methyl-2-benzamido-3-methylbutanoate (4.84 g, 20.6 mmol, 83% yield).



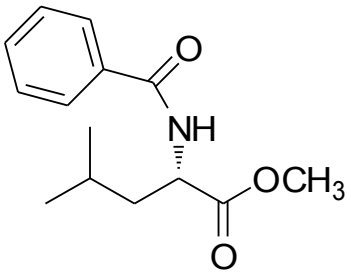
The product is obtained as a white (slightly yellow) flaky solid and had the

following physical and spectroscopic properties: Melting point: 104.5-106°C, IR (neat): 3345, 2966, 1736, 1640, 1516, 1489, 1201, 1150, 993, 692 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.78 (dm, J= 6.7 Hz, 2H), 7.77 (m, 1H), 7.47 (m, 1 H), 7.38 (m, 2 H), 6.75 (d, J = 8.4 Hz, 1H), 4.74 (dd, J= 5.2, 8.8 Hz, 1H), 3.72 (s, 3H), 2.23 (m, 1H), 0.96 (m, 6H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 172.7, 167.3, 134.1, 131.7, 128.5, 127.1, 57.5, 52.2, 31.5, 19.0, 18.0. MS (EI) m/z 235 (M^+). HPLC (Daicel Chiral AD-H, hexanes/isopropanol=95:5, flow rate 0.5 mL/min) t_R = 29.203 min, >99.9 % Ee, $[\alpha]_D^{21.6}$ = + 32.9° in dichloromethane (Average of 50 trials), c = 0.001082 g/ml

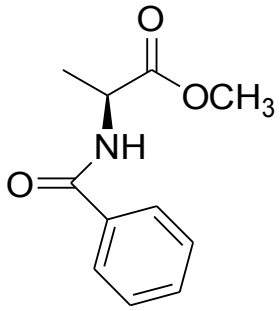
1.10.2 Small-Scale Oxidative Amidation of Benzaldehyde with Amino Acid Ester Hydrochloride Salts

CuI (0.0018 g), $AgIO_3$ (0.0020 g), amino acid ester hydrochloride salt (1.5 equiv., 0.3 mmol) and $CaCO_3$ were added to a round-bottom microwave tube containing a magnetic stir bar. Acetonitrile (1.5 mL) was then added. Benzaldehyde (1 equiv., 20 μL, 0.0212 g, 0.2 mmol) and T-Hydro®(1.05 equiv., 30 μL, 0.210 mmol) were successively added while stirring. The reaction was heated in an oil bath under stirring at 80°C for 24 hours. The reaction mixture was then separated by column chromatography using an hexanes:ethyl acetate mixture (3:2) as eluent.

(S)-Methyl 2-benzamido-4-methylpentanoate



^{1}H-NMR δ (400 MHz, $CDCl_3$) 7.80 (d, J= 7.60, Ar, 2H), 7.42-7.52 (m, Ar, 3 H), 6.53 (br, d, J = 7.60, -NH, 1 H), 4.87 (m, 1 H), 3.77 (s, -OCH_3, 3H), 1.64-1.78 (m, 3H), 0.96-1.00 (m, 6 H), beige solid



(S)-Methyl 2-benzamidopropanoate

^{1}H-NMR δ (400 MHz, $CDCl_3$) 7.80 (d, J= 8.40, Ar, 2 H), 7.45-7.51 (m, Ar, 3H), 6.71 (br, NH, 1H) 4.78-4.85(m, 1H), 3.80 (s, OCH_3, 3H), 1.52-1.54 (d, J= 7.2 , 3H)

1.10.3 Esterification of Gly-Gly-Gly

A round-bottom flask containing 20 mL of absolute ethanol was put in an ice-bath (0^{o}C) and $SOCl_2$ (3 equiv., 8.5 mmol, 0.61 mL) was slowly added. The flask was taken out of the ice-bath and stirred for 10 minutes. Gly-Gly-Gly (1 equiv., 2.8 mmol, 0.53 g) was added to the flask under stirring and the reaction mixture was heated at 70^{o}C for 5 hours.

1.10.4 iSustain Tables

Table 2: Oxidative amidation reaction

iSUSTAIN™ Green Chemistry Index

Getting Started | Scenarios | Data Input | My Profile | Log Out

12 Principles of Green Chemistry	
1 Waste Prevention	0
2 Atom Economy	70
3 Safe Raw Materials	85
4 Safe Product	100
5 Safe Solvents	60
6 Energy Efficiency	40
7 Renewables	0
8 Process Complexity	90
9 Catalysis	100
10 Biodegradability	
11 Process Control	40
12 Safe Process	65

(Scores rounded to nearest 5)

Data Input

Materials and process data may all be entered here for convenience, or in the separate Metrics pages.

Instructions

Bill of Materials In:

	Bill of Materials In	Type of Material	Wt/Batch	Est. % Recycle	% Renew.	Catalyst Mole %	Usage Wt/Wt	Safety	Health	Envir Impact	Regul Status	MatImp	% of Total	
	Benzaldehyde	Raw	2,604	0	0	0	0,538	100	80	100	100	93	1	
	Ethylamine	Raw	1,663	0	0	0	0,344	45	65	100	100	70	1	
	Copper chloride	Auxiliary	0	0	0	1	0,000	100	80	0	100	60	0	
	Silver nitrate	Auxiliary	0	0	0	1	0,000	100	55	0	100	51	0	
	Calcium carbonate	Auxiliary	2,1	0	0	0	0,434	100	55	100	100	85	1	
	Acetonitrile	Solvent	4,32	0	0	0	0,893	55	65	100	100	73	2	
	Water	Solvent	100	0	0	0	20,661	100	100	100	100	100	40	
	Butyl hydroperoxide, t-	Auxiliary	2,73	0	0	0	0,564	55	55	100	100	70	1	
	Ethyl acetate	Solvent	13,46	0	0	0	2,781	55	80	100	100	78	5	
	Hexane, n-	Solvent	124,32	0	0	0	25,686	55	55	35	50	24	49	

Add New

Bill of Materials Out:

	Bill of Materials Out	Type of Material	Wt/Batch	% Diluents	Wt times Severity	Aq.Tox.	Human Tox.	Ultimate Biodeg.	
	N-ethylbenzamide	Product	3,0462	0		Low	Low		
	Hex/EtOac	Waste Class 2	138		552				

Add New

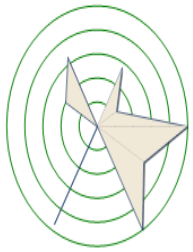
Table 3: Schotten-Bauman reaction

iSUSTAIN™ Green Chemistry Index

Getting Started | Scenarios | Data Input | My Profile | Log Out

12 Principles of Green Chemistry	
1 Waste Prevention	0
2 Atom Economy	55
3 Safe Raw Materials	25
4 Safe Product	100
5 Safe Solvents	60
6 Energy Efficiency	100
7 Renewables	0
8 Process Complexity	95
9 Catalysis	0
10 Biodegradability	
11 Process Control	40
12 Safe Process	65

(Scores rounded to nearest 5)



Data Input

Materials and process data may all be entered here for convenience, or in the separate Metrics pages.
Instructions

Bill of Materials In:

Bill of Materials In	Type of Material	Wt/Batch	Est. % Recycle	% Renew.	Catalyst Mole %	Usage Wt/Wt	Safety	Health	Envir Impact	Regul Status	MatImp	% of Total
Ethylamine	Raw	2,218	0	0	0	0,728	45	65	100	100	70	1
Water	Solvent	100	0	0	0	32,828	100	100	100	100	100	40
Ethyl acetate	Solvent	13,46	0	0	0	4,419	55	80	100	100	78	5
Hexane, n-	Solvent	124,32	0	0	0	40,812	55	55	35	50	24	50
Benzoyl chloride	Raw	3,458	0	0	0	1,135	100	55	100	0	0	1
Diethyl ether	Solvent	3,924	0	0	0	1,288	15	80	100	100	65	2

Add New

Bill of Materials Out:

Bill of Materials Out	Type of Material	Wt/Batch	% Diluents	Wt times Severity	Aq.Tox.	Human Tox.	Ultimate Biodeg.
N-ethylbenzamide	Product	3,0462	0		Low	Low	
Hex/EtOac	Waste Class 2	138		552			

Add New

Chapter 2: Cobalt-Catalyzed Enantioselective A^3-Coupling

2.1 Synopsis

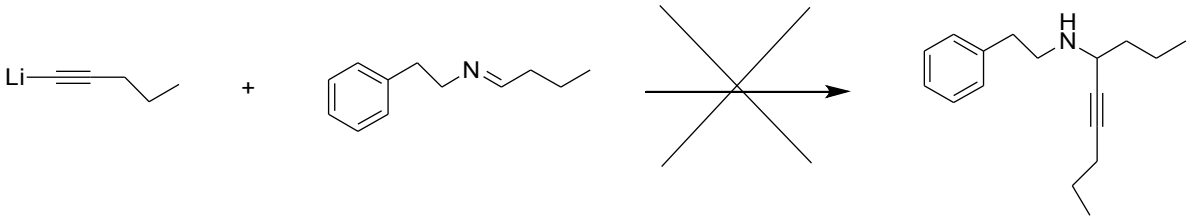
This chapter starts by highlighting various syntheses of propargyl amines. This is followed by a presentation on A^3-coupling and a more focused discussion on enantioselective cobalt-catalyzed A^3-coupling (impact of ligands, solvents, cobalts salts, etc.)

2.2 Importance of Propargyl Amines and their Synthesis

Nitrogen-bearing moieties are ubiquitous in natural products, bio-active compounds or polymers. Among those, propargyl amines struck our interest. They often are key intermediates in the synthesis of various drugs or target molecules.

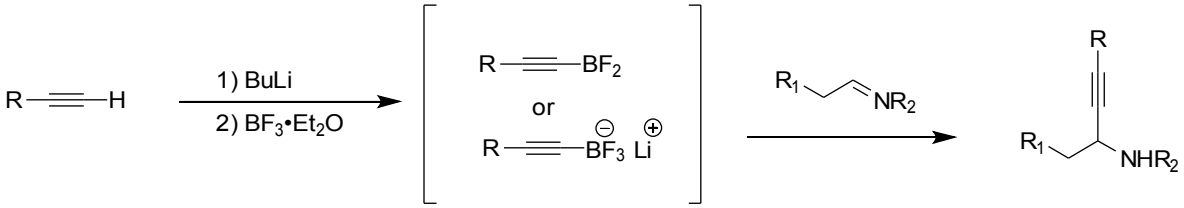
The addition of organometallic reagents to imines has been investigated by numerous groups and was initially faced with various problems, most of which were caused by the poor electrophilicity of the azomethine carbon.[15] For example, alkyl Grignard add poorly to imine and may lead to total enolization in refluxing THF.[16]

An approach to the synthesis of propargyl amines is the addition of lithium alkynide to imine. However, as Akiba[17] demonstrated, simple addition of lithium alkynide to imine will not yield the desired product (Scheme 17).



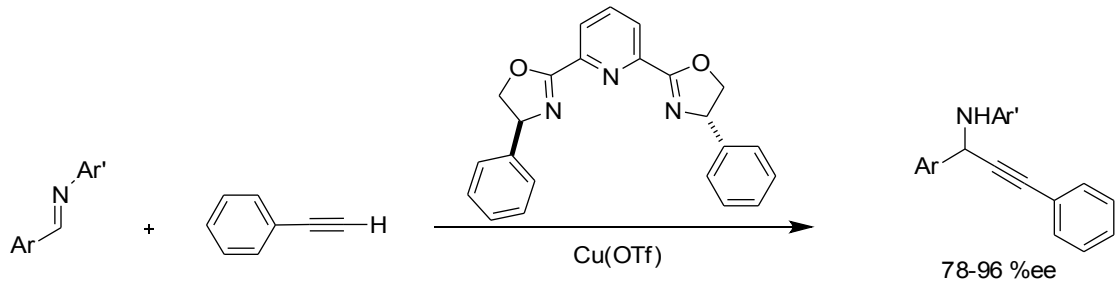
Scheme 17: Lithium alkynide addition to imine

Akiba solved this issue by adding boron trifluoride to the lithium alkynide, hence forming a boron-alkynide adduct (Scheme 18).

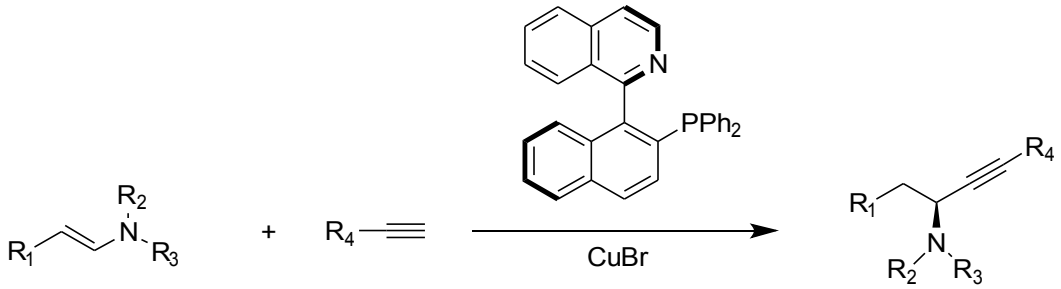


Scheme 18: Alkyne addition to imine using boron trifluoride

Another key improvement in the synthesis of propargyl amine is the enantioselective copper-catalyzed direct addition of terminal alkynes to imine (to generate secondary propargyl amines) first discovered by Li,[18] in which a tridentate bis(oxazolinyl)pyridine (commonly referred to as PyBOX) is used as a chiral ligand (Scheme 19). This was followed by the enantioselective copper-catalyzed addition of terminal alkynes to enamines to obtain tertiary propargyl amines published by Knochel.[19] In this case (Scheme 20), 1-(2-diphenylphosphino-1-naphthyl)isoquinoline is used as a chiral ligand (commonly referred to as QUINAP).



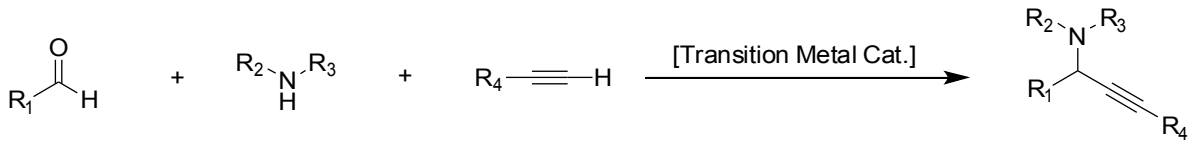
Scheme 19: Enantioselective copper-catalyzed alkyne addition to imine using PyBOX



Scheme 20: Enantioselective copper-catalyzed alkyne addition to enamine using QUINAP

2.3 A^3-Coupling

The next improvement to this method was to prepare the imine and iminium ion *in situ*, leading to a one-pot tandem reaction that was later coined as A^3-coupling (Aldehyde-Alkyne-Amine). This method presents the obvious advantages of being a one-step reaction and does not require strong organometallic reagents (Scheme 21). In fact, it can be catalyzed by various transition metal complexes (Cu(I)/Ru(III),[20] Ag(I),[21] Ir(I),[22] Fe(III),[23] Au(I)[24] for example) under mild reaction conditions and it is tolerant of air and water. The A^3-coupling reaction has a high atom economy; furthermore, the only byproduct is an innocuous substance: water. Depending on the reaction system, the reaction can be done neat, in water, in ionic liquids or in organic solvents.[25]

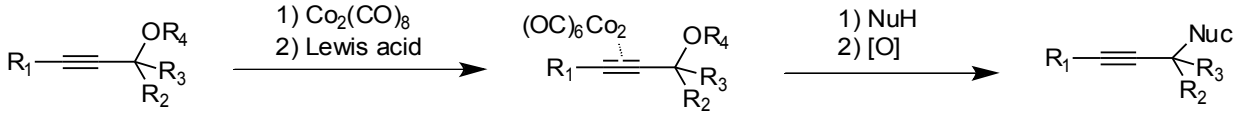


Scheme 21: Aldehyde-Alkyne-Amine (A^3) coupling reaction

The enantioselective version, AA^3 (Asymmetric Aldehyde-Alkyne-Amine-Coupling), was also developed using the same copper-pybox system and the copper-QUINAP system as mentioned for the alkyne addition to imine.

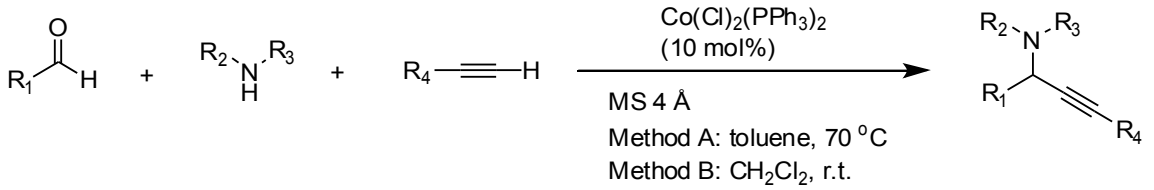
2.4 Enantioselective Cobalt-Catalyzed A^3-Coupling

A cobalt-catalyzed A^3-coupling was later investigated by Li.[26] Previously reported cobalt-catalyzed reaction, such as the Nicholas reaction (Scheme 22),[27] the Vollhardt [2+2+2] cyclization[28] or the Pauson-Khand reaction,[29] usually involves the η^2 interaction between the cobalt complex and the alkyne. Such reactions use high-field ligand (e.g. CO) on the cobalt center. Li proposed that if replacing the ligands by lower field ligands, hence decreasing the d_{Π}-d_{σ} crystal field energy gap, one could weaken the η^2 interaction and activate the C-H bond of a terminal alkyne.



Scheme 22: The Nicholas reaction

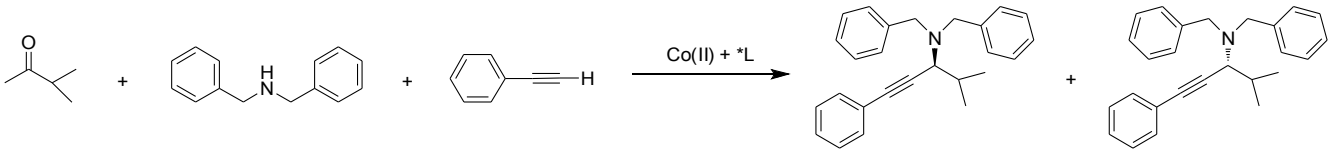
This was proven to be successful and they found two different reactions conditions that yielded really similar results. Both were using dichlorobis(triphenylphosphine)cobalt(II) as a catalyst and 4 Å molecular sieves as additives either in toluene at 70°C or at room temperature in dichloromethane (Scheme 23).



Scheme 23: Cobalt-catalyzed A^3-coupling

Good yields were obtained with aromatic or aliphatic aldehydes, secondary amines or alkynes as substrates.

Following this research, the next objective was to develop an enantioselective version of the cobalt-catalyzed A^3-coupling. The coupling of isobutyraldehyde, dibenzylamine and phenylacetylene (as illustrated on the following scheme) was chosen as the condition to be optimized.



Scheme 24: Selected reactants for the optimization of an enantioselective cobalt-catalyzed A^3-coupling methodology

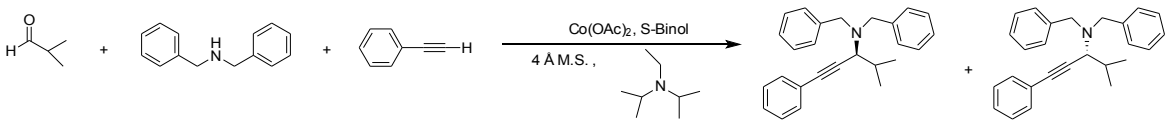
Part of the optimization was undergone by Dr Wen Wen Chen and I then took over the project after her departure from the group. The optimal ratio was found to be 1 equiv. of aldehyde to 1.2 equiv. of amine to 1.7 equiv. of alkyne. The typical reaction conditions involved the uses of a cobalt(II) salt and of a chiral ligand where the chiral transition metal complex was generated *in situ* (with addition of a base if necessary) prior to the addition of the starting materials. The reaction was then filtered on silica gel or separated directly using column chromatography. The isolated product was then analyzed by chiral normal-phase HPLC. The initial results were highly erratic and it was found that the presence of water significantly decreases, or if the concentration was high enough,

negates enantioselectivity. This became obvious after using freshly distilled dichloromethane as opposed to using dichloromethane that had been sitting in a bottle for days. As already mentioned, one equivalent of water was produced as a result of the A^3-coupling; in order to deal with that water, activated 4 angstrom molecular sieves were added. Furthermore confirming the impact of water in the reaction system, the enantioselectivity was found to decrease when using molecular sieves that had not been activated recently enough. We found that cobalt(II)-binol complex formed *in situ* in freshly distilled dichloromethane under an inert atmosphere were the optimal conditions fairly early on, this setup yielded a 31 % enantiomeric excess (e.e.) after 48 hours at room temperature. The enantiomeric excess was determined by subtracting the area of the second peak from the area of the first HPLC peak and dividing by their total area, this has been kept constant throughout this document, meaning that a positive value represents a 1st peak with a greater area than the 2nd, and a negative value represents the opposite.

$$Enantiomeric\,excess = \frac{Peak^1_{area} - Peak^2_{area}}{Peak^1_{area} + Peak^2_{area}} \times 100$$

Equation 3: Enantiomeric excess formula

Cobalt(II) acetate was used as the source of cobalt(II) and N,N-diisopropylethylamine (also known as Hunig's base) was used to deprotonate the binaphthol (Scheme 25).



Scheme 25: Enantioselective cobalt-catalyzed A^3-coupling

Various cobalt(II) salts (such as $CoCl_2$ and CoO) were investigated, but none of

them showed superior results compared to the cobalt(II) acetate. In all cases, the cobalt salts, the chiral ligand and the base were pre-stirred in the solvent for at least 30 minutes before addition of the starting material. The nature of the chiral ligand was also changed. The following figure shows a sampling of the ligands (using DCM as solvent) that were tried (the binaphthalene derivatives were synthesized and analyzed by Dr Wen-Wen Chen)

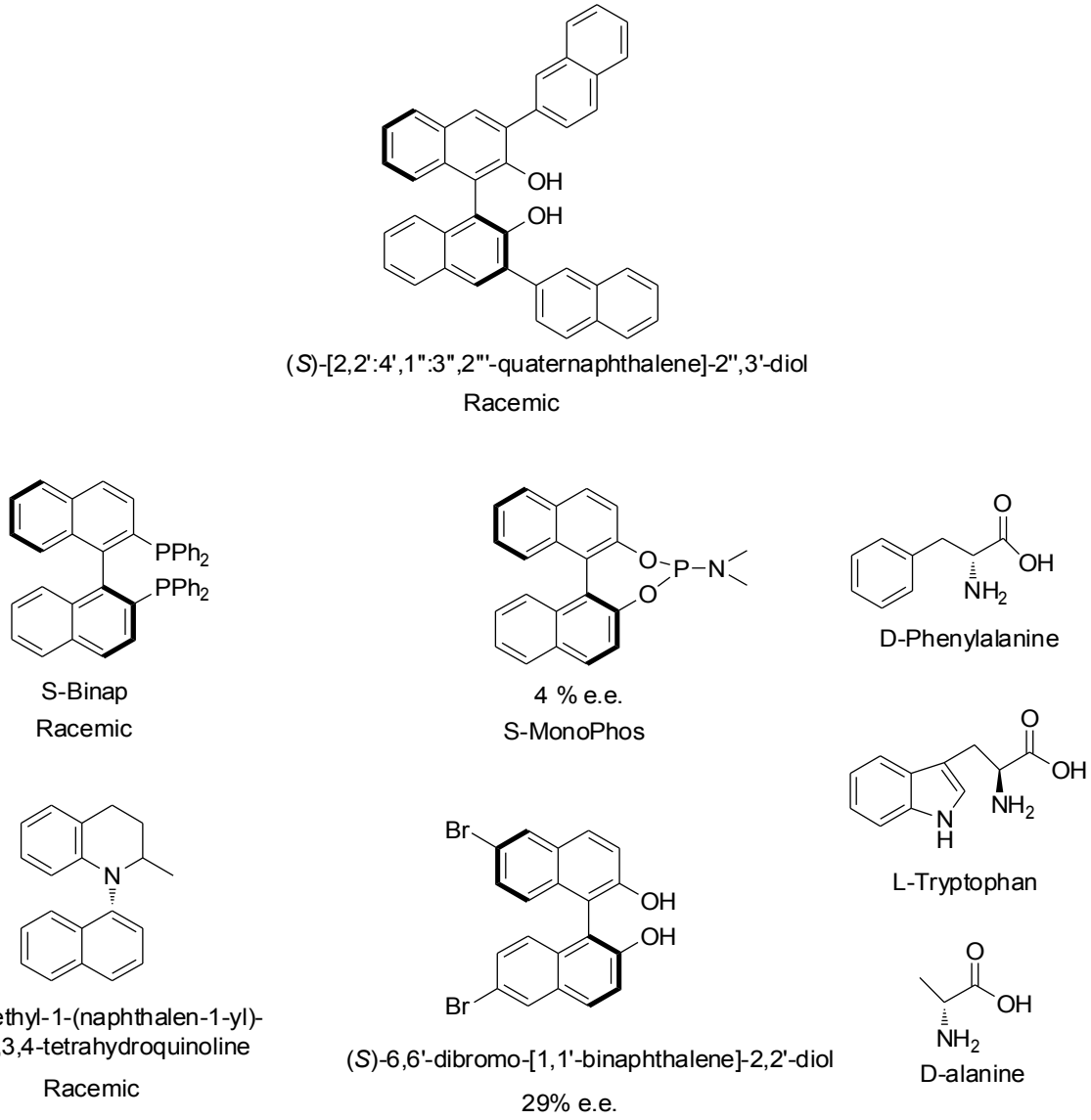


Figure 3: Binaphthalene derivatives and amino acids used as ligands

The (S)-6,6'-dibromo-[1,1'-binaphthalene]-2,2'-diol showed similar reactivity and selectivity to binol, whereas phosphorus containing ligand showed poor selectivity at best (4% e.e. for S-monophos). The 2-methyl-1-(naphthalen-1-yl)-1,2,3,4-tetraisoquinoline also only yielded a racemate. The use of chiral amino acids did not prove to be successful, it remains unknown whether or not the various amino acids were able to bind to the cobalt center *in situ* to form a catalyst. The presence of amine functionality in the ligand could also be problematic since the amine could be part of the A^3 coupling, although the pure amino acids that were used are not good substrates themselves for the A^3-coupling.

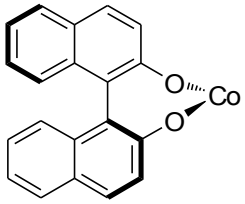


Figure 4: Cobalt-BINOL complex

The reaction was also tried using an isolated Co-BINOL complex (Figure 4) synthesized beforehand as opposed to an *in situ* synthesis. The initial results yielded a mostly racemic mixture. This was thought to be caused by the low purity of complex, hinting that some cobalt(II) salts not bound to the binaphthol ligands were still present. The complex proved to be challenging to be purified using recrystallization, so a mixed-solvent system was used initially comprising mostly of 1,4-dioxane and tetrahydrofuran. However, a ligand substitution by the 1,4-dioxane or the THF is a possibility since the cobalt-BINOL complex was subjected to relatively high temperature during the recrystallization; this would inherently diminish the efficiency of the catalyst (at least in term of enantioselectivity). The previously recrystallized complex was discarded and the crude Co-S-BINOL complex was recrystallized solely in acetonitrile to prevent a ligand

substitution. Nevertheless, this complex proved to be significantly less effective than the complex generated *in situ* since only a -5% e.e. was observed. A possible explanation is that, even after recrystallization, the complex still contained impurities.

It should be noted that even with dry solvent the enantiomeric excess was varying greatly between trials, even when they were seemingly under the same conditions. Minute differences in the experimental conditions might partially explain these discrepancies. One such discrepancy could be the oscillation in the actual room temperature, another one would be a partial exposure or total exposure of the reaction mixture to air since reusable teflon seals are used to cap the reaction vial and these seals are subject to wear from needle puncture. The seals used were purchased from 2 different companies and differ greatly in quality even though they are seemingly identical in appearance. Presence of trace amounts of transition-metal complex from previous reactions cannot be entirely be ruled out since the same vials and magnetic stir bars are being used over and over again.

The impact of the order of addition of the reagents was also analyzed. More specifically, whether adding the aldehyde and the amine first (hence letting the imine form), followed by addition of the alkyne as opposed to adding all the reagents at once. This impact was also evaluated over time as shown in the following table:

	Aldehyde, amine, added at same time			Aldehyde, amine first		
Reaction time	24h	43h	67h	24h	44h	68h
% e.e.	1.2	0.7	15.7	2.3	-0.3	14.8

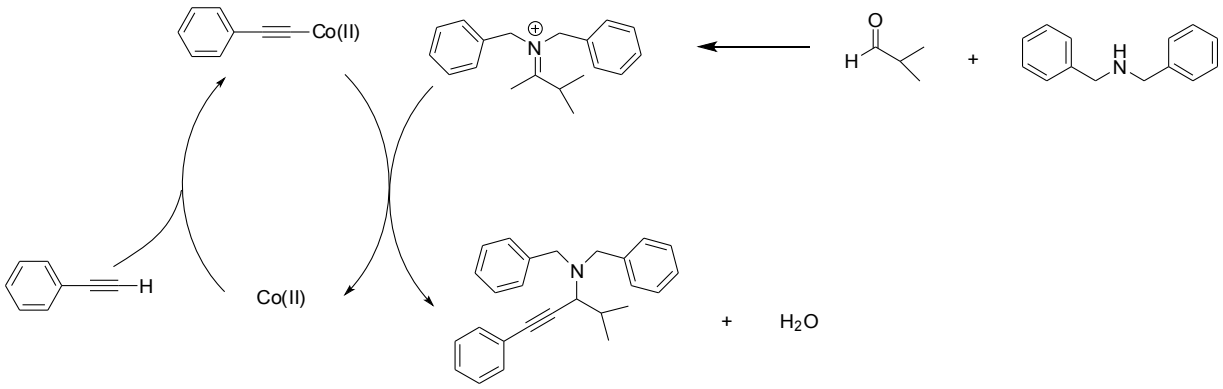
Table 4: Enantioselectivity of cobalt-catalyzed A^3-coupling over time

This example illustrates the lack of reproducibility of this reaction under seemingly identical conditions, nevertheless there does not seem to be a significant difference

between addition of the aldehyde, amine first, followed by addition of the alkyne or addition of the reagents at the same time.

2.5 Cobalt-Catalyzed A^3-Coupling Reaction Mechanism

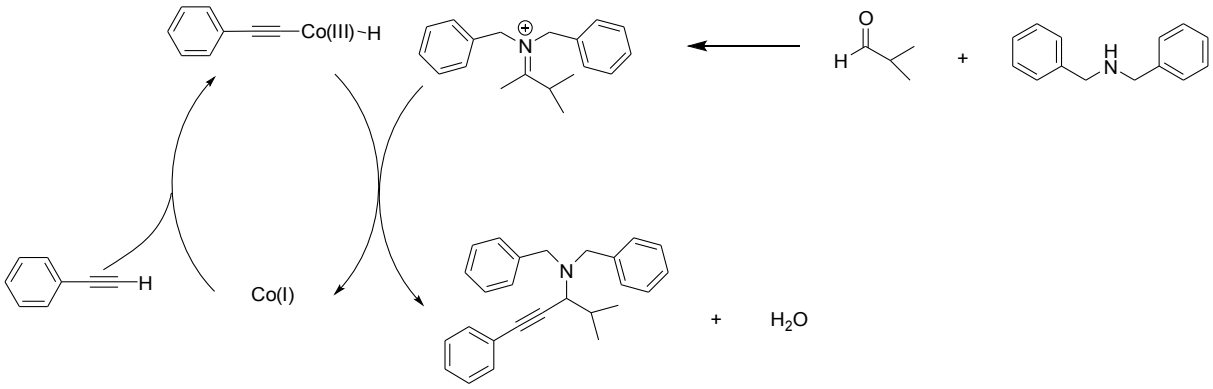
The following schemes show two tentative reaction mechanisms concerning the cobalt-catalyzed A^3-coupling reaction that was investigated. The first one (Scheme 26) involves a Co(II) catalytic cycle where the valency of the cobalt remains the same. The first step is the condensation of the aldehyde with the amine to form the iminium intermediate. The cobalt(II) then activates the terminal alkynes in the presence of a base (amine) to form the propargyl amine and regenerate the Co(II) catalyst.



Scheme 26: Plausible cobalt(II)-catalyzed A^3-coupling reaction mechanism

The second possible mechanism (Scheme 27) shares the same first step as the previously mentioned cycle where the aldehyde condenses with the amine to form the iminium intermediate. Co(I) undergoes oxidative addition to the terminal C-H bond of the acetylide to form a alkynyl-Co(III) hydride. This alkynyl-Co(III) hydride then adds to the iminium intermediate generating the propargyl amine and regenerates the Co(I) catalyst through reductive elimination.

It should be noted that cobalt(II) salts were used as catalyst in our experiments, these cobalt(II) salts could have been reduced to cobalt(I) by the alkyne. This could explain why 1.7 equivalent of alkyne showed the best results in the analyzed reaction.



Scheme 27: Plausible cobalt(I)-cobalt(III)-catalyzed A^3-coupling reaction mechanism

2.6 Impact of Solvent on Enantioselectivity

As mentioned earlier, dichloromethane is the optimal solvent for this reaction, but it is not the only one that can allow an enantiomeric excess. When freshly distilled tetrahydrofuran is used as a solvent, a modest enantiomeric excess (< 10 % e.e.) is observed. This led to the idea that 2-methyltetrahydrofuran could be an excellent solvent, even better than dichloromethane for this reaction.

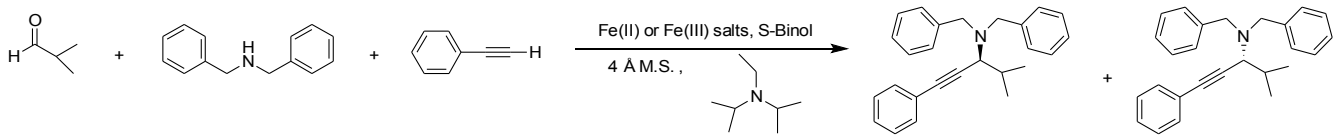
2-Methyltetrahydrofuran is an aprotic polar solvent derived from various agricultural by-products and has numerous advantages over THF. It has a higher boiling point (78-80°C), low miscibility with water and is less likely to form an emulsion with water (as opposed to THF and DCM). 2-Methyltetrahydrofuran is derived from biomass and as such has a low carbon footprint. THF on other hand, is derived from fossil fuels[30]

and therefore has a higher carbon footprint. Carbon footprint is defined as : “[a] measure [of] the total greenhouse gas emissions caused directly and indirectly by a person, organisation, event or product “.[31] The main drawback of 2-MeTHF for now is its significantly higher price than THF. It might be negligible on a lab scale, but would make a significant difference on an industrial one. Another limitation is that 2-methyltetrahydrofuran is (like THF) prone to peroxide formation (if not stabilized properly) and it can even form peroxides faster than THF under some specific conditions (if air is intensively mixed with the solvent for example).[32]

The key reason for trying 2-methyltetrahydrofuran is that it has drastically increased the enantioselectivity of reactions in some specific cases. For example, Hisashi Yamamoto's group published an article on cobalt-catalyzed asymmetric Nozaki-Hiyama propargylation of aldehydes[33] and 2-methyltetrahydrofuran showed superior selectivity than THF for some substrates.

In our case, 2-methyltetrahydrofuran showed a superior selectivity than tetrahydrofuran, but was nevertheless inferior to dichloromethane. We were unable to extract quantifiable enantiomeric excess when using 2-methyltetrahydrofuran as solvent due to a deterioration of the HPLC column used, for analysis.

2.7 Enantioselective Iron-Catalyzed A^3-Coupling



Scheme 28: Enantioselective iron-catalyzed A^3-coupling

The use of BINOL as a chiral ligand was also briefly investigated for iron-catalyzed enantioselective A^3-coupling using either Fe(II) or Fe(III) salts. $FeBr_2$, $FeCl_2$ and $Fe(acac)_3$ yielded the desired product but showed a really low selectivity. The procedure used was the same as the cobalt-catalyzed one.

	$FeBr_2$	$FeCl_2$	$Fe(acac)_3$
% ee	-1.9	-1.1	-2.9

Table 5: Enantiomeric excess using various iron sources

Possible future investigation could include addition of a small polar protic molecule like isopropanol to see if it interacts in a similar way to water and reduces the enantioselectivity or if it leaves the selectivity untouched. Relying on the fact that 2-MeTHF has a chiral center, using (R)- or (S)-2-methyltetrahydrofuran could also be an interesting experiment, analyzing whether or not the chirality of the Lewis base has an impact on the chirality of the product.

2.8 Conclusion

An enantioselective cobalt-catalyzed A^3-coupling using 1,1'-Bi-2,2'-naphthol as a chiral ligand was developed. This method presents the advantages of effectively synthesizing propargyl amines without using organometallic reagents such as butyl lithium. Unfortunately, the method is really water-sensitive and the enantioselectivity is poor at best. The enantioselectivity was capped at 31% e.e. and BINOL derivatives failed to increase that number. The same approach was also used briefly to investigate iron-catalyzed A^3-coupling using Fe(II) and Fe(III) salts, this yielded almost no enantioselectivity (at most -2.9% e.e.). Finally, other solvent systems, mainly the use of 2-methyltetrahydrofuran, were investigated alas, no significant improvements.

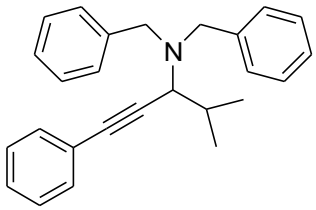
2.9 Experimental

General

^{1}H-NMR spectra were recorded using a Varian 400 MHz spectrometer. ^{13}C-NMR were recorded using a Varian 300 MHz spectrometer. The chemical shifts are reported in part per million (δ) and either deuterated chloroform or deuterated-DMSO was used as a solvent. Enantioselectivity was ascertained using an Daicel Chiral OD-H column using a heptane:isopropanol eluent (99:1) at a 0.5 ml/min flow rate. The silica gel used for the purification is SiliaFlash F60 from Silicycle company. Unless otherwise specified, the chemicals used were purchased and used as such from Sigma-Aldrich. All reagents were weighted and handled in air at room temperature.

Procedure

The enantioselective cobalt-catalyzed A^{3}-coupling was done on a 0.2 mmol scale with the aldehyde as the limiting reagent.



Synthesis of N,N-dibenzyl-4-methyl-1-phenylpent-1-yn-3-amine

Cobalt acetate (10 mol%, 0.02 mmol, 0.0035 g), S-BINOL (10 mol%, 0.02 mmol, 0.006 g) and activated 4Å molecular sieves (0.0090 g) were added to a conical vial containing a stir bar. The vial was then capped and put under argon. CH_2Cl_2 (0.25 mL, freshly

distilled) was added using a syringe followed by addition of iPr_2NEt (0.057 mmol, 10 μL). This mixture was left to stir at room temperature for at least 30 minutes. Isobutyraldehyde (1 equiv., 0.2 mmol, 17.6 μL), N.N-dibenzylamine (1.2 equiv., 0.24 mmol, 45 μL) and phenylacetylene (1.65 equiv., 0.32 mmol, 35 μL) were added successively using a microsyringe. The reaction was left to stir at room temperature for 48 hours. The reaction mixture was then separated using column chromatography. The product was then analyzed by HPLC (Daicel Chiral OD-H column using a heptane:isopropanol eluent (99:1) at a 0.5 mL/min flow rate), t_R = 21.5 min and 23.6 min. ^{1}H-NMR (400 MHz, $CDCl_3$): 7.53-7.51 (m, 2H), 7.43-7.41 (m, 4H), 7.36-7.30 (m, 7H), 7.23-7.21 (m, 2H), 3.88 (d, J= 13.6 Hz, 2H), 3.46 (d, J= 13.6 Hz, 2H), 3.11 (d, J= 10.4 Hz, 1H), 2.05-1.96 (m, 1H), 1.05-1.03 (m, 6H)

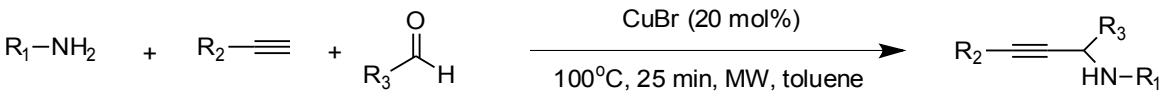
Chapter 3: Silver-Catalyzed Alkyne Addition to Iminoesters and Silver-Catalyzed A^3-Coupling

3.1 Synopsis

This chapter starts by presenting limitations of the A^3-coupling and by presenting a silver-catalyzed alkene addition to iminoesters. This leads to our research goals (enantioselective silver-catalyzed alkyne addition to imine) inspired by an article published by Zhou (Ref. 37).

3.2 A^3-Coupling Using Primary Amines

As previously stated the aldehyde-alkyne-amine coupling reaction presents numerous advantages over other syntheses of propargyl amines and can be catalyzed by various transition metals, Ag(I) being one of them. Nevertheless, in most those cases, no matter which transition metal is used, primary amines are considered to be tough substrates, hence limiting access to secondary propargylamines. An exception to the previous statement is the copper-catalyzed microwave-assisted A^3-coupling (Scheme 29) developed by Van der Eycken[34] where various primary amines are used as substrates yielding secondary propargyl amines with good to poor yields (Table 6).



Scheme 29: Copper-catalyzed and microwave-promoted A^3-coupling

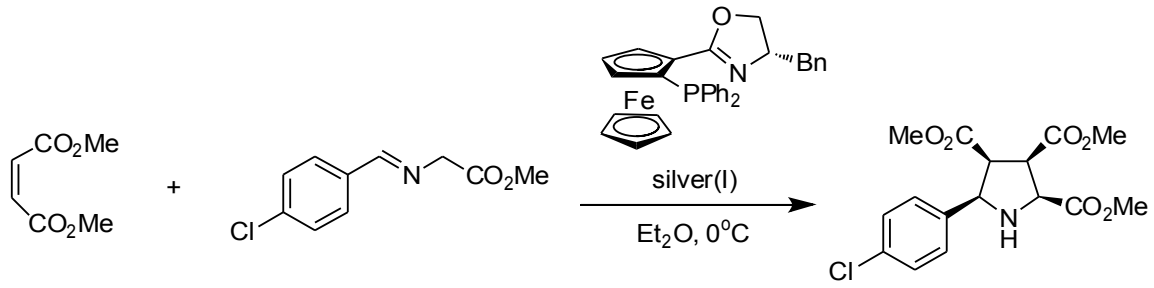
Entry	R^1	R^2	R^3	Yield [%][a]
1	Bn	Ph	*i*Pr	89
2	Bn	Ph	*p*-tolyl	85
3	Pr	Ph	*i*Bu	94
4	3-methoxyphenethyl	Ph	*i*Bu	66
5	*t*Bu	Ph	*i*Bu	73
6	cycloheptyl	Ph	*i*Bu	72
7	cyclododecyl	Ph	*i*Bu	68
8	*p*-methoxybenzyl	Ph	*i*Bu	60
9	*i*Bu	Ph	*i*Bu	67
10	dodecyl	Ph	*i*Bu	46
11	cyclooctyl	Ph	pentyl	83
12	Bn	*p*-tolyl	*i*Pr	69
13	*p*-methoxybenzyl	*p*-(*t*Bu)Ph	*p*-FPh	89
14	Bn	*p*-pentyloxyphenyl	*p*-tolyl	62
15	Bn	thiophene-3-yl	Ph	42
16	Bn	Bn	Ph	44
17	Bn	cyclopentyl	Ph	41
18	Bn	Ph	Et	86
19	Bn	Ph	Pr	73
20	Bn	Ph	Bu	65
21	Bn	Ph	*i*Bu	78
22	Bn	Ph	pentyl	77
23	Bn	Ph	octyl	83
24	Bn	Ph	decyl	75
25	Bn	Ph	cyclopropyl	64
26	Bn	Ph	cyclohexyl	85

Reaction conditions: alkyne (3.0 mmol), aldehyde (1.0 mmol), amine (1.5 mmol), CuBr (0.20 mmol, 57 mg), toluene (1.0mL), MW, 80 W, 100°C, 25 min; [a] Isolated after column chromatography.

Table 6: Scope of the copper-catalyzed and microwave-promoted A^3-coupling

The choice of solvent is a bit unexpected considering that toluene, having a dielectric constant of 2.38 at room temperature,[35] is a non-polar solvent and therefore is not an optimal choice for microwave irradiation. This might be partially offset by the high concentration of reactants in solution, which responds well to microwave energy. The

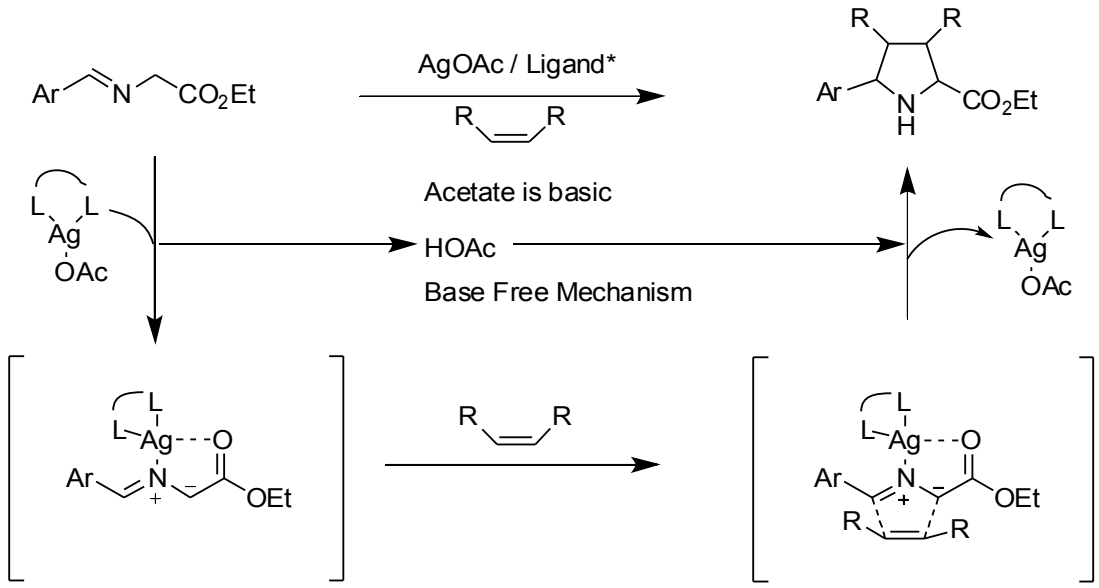
scope of reaction is limited to benzyl, aliphatic and cyclic amines; no other functional groups are present (Table 6).



Scheme 30 : Bifunctional AgOAc-catalyzed asymmetric reactions

3.3 Silver-Catalyzed Alkene Addition to Iminoesters

It has been shown that Ag(I) salts can catalyze the A^3-coupling in various solvents such as water or ionic liquids and do so with high efficiency.[36] Following an article by Zhou[37] on "bifunctional AgOAc-catalyzed asymmetric reactions", we had a new proposal concerning the synthesis of secondary propargyl amines. In the article published by Zhou, the authors showed that silver can catalyse the 1,3-dipolar cycloaddition of diethyl maleate to imino esters; moreover, when a chiral ligand is used, it can do so with high enantioselectivity (Scheme 30). Ferrocenyl-oxazolidine derivatives are the ligand that gave them the best selectivity.

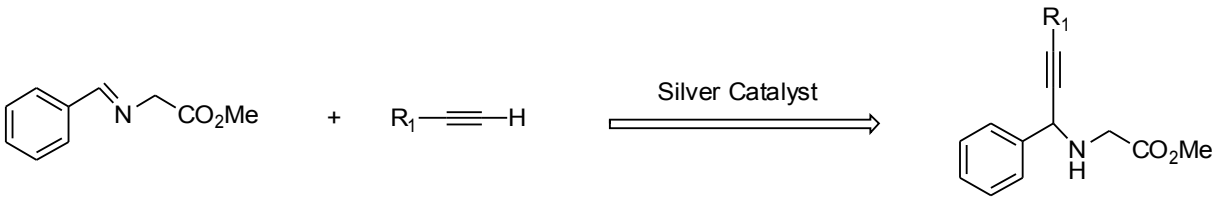


Scheme 31: Postulated reaction mechanism of 1,3-dipolar cycloaddition of diethyl maleate to iminoesters

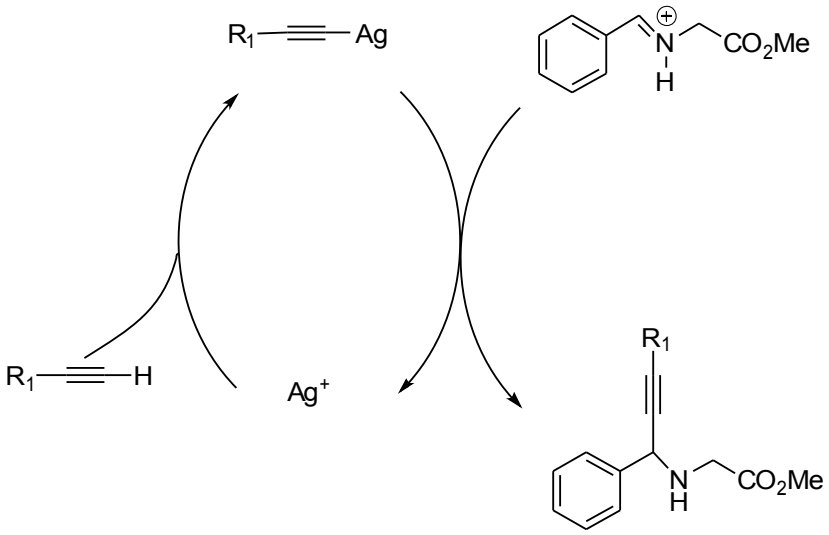
In the presence of the silver ferrocenyl-oxazolidine catalyst (Scheme 31), there is a deprotonation on the carbon adjacent to the nitrogen of the imino ester to form an azomethine ylide. This is possible due to the presence of an electron-withdrawing group adjacent to the nitrogen atom. By choosing the proper counter-ion (acetate in this case), this can be done without the use of additional base. The silver catalyst (being a Lewis acid) can then form an adduct with the azomethine ylide by coordinating with the nitrogen and the carbonyl group of the ester. This is followed by coordination of the dimethyl maleate to the azomethine ylide and then [3+2] cycloaddition to yield the substituted pyrrolidine and regenerate the silver catalyst.

3.4 Silver-Catalyzed Alkyne Addition to Iminoesters

Following the article by Zhou, we thought that by using terminal alkynes instead of alkenes we could obtain secondary propargyl amines (Scheme 32).

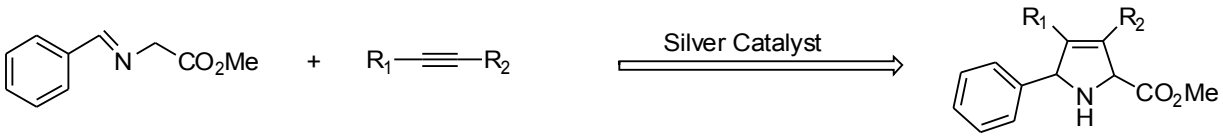


Scheme 32: Target synthesis involving the silver-catalyzed alkyne addition to iminoester



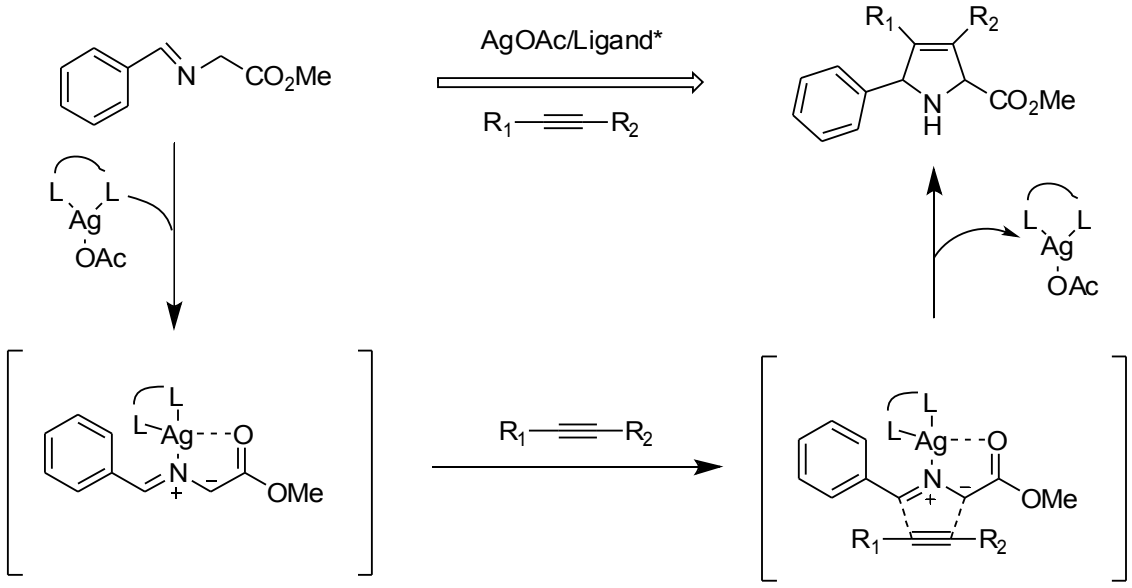
Scheme 33: Plausible silver-catalyzed A^3-coupling reaction mechanism

These secondary propargyl amines bearing an ester moiety could prove to be interesting and these type of molecules have not been reported in the literature as of now. This reaction could possibly occur through a mechanism (Scheme 33) similar to silver-catalyzed A^3-coupling with the exception that the iminoester is synthesized beforehand rather than *in situ*. Silver(I) could activate the terminal C-H bond of the alkyne and generate a silver-acetylide and then attack the azomethine carbon of the iminoester to generate the secondary propargyl amine and regenerate the catalyst. Another possibility would be to use disubstituted alkynes (Scheme 34) and hopefully obtain "pyrrolidine" derivatives.



Scheme 34: Desired reaction between iminoester and disubtitued alkyne

A possible reaction mechanism (Scheme 35) similar to the one proposed by Zhou has been postulated, where the activated azomethine ylide undergoes [3+2] cycloaddition with the disubtituted alkyne.

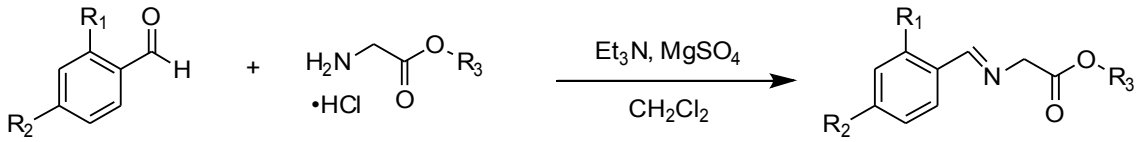


Scheme 35: Postulated reaction mechanism associated with our research goals

If we are able to obtain the aforementioned product, we could then try to form the imine *in situ* hence having an A^3-coupling rather than an alkyne addition to imine.

3.5 Synthesis of Starting Material

The first step of this project was to synthesize the necessary starting materials, namely the various iminoesters derived of glycine and benzaldehyde derivatives.



Scheme 36: Synthesis of iminoesters by condensation of an aldehyde with an α-aminoester

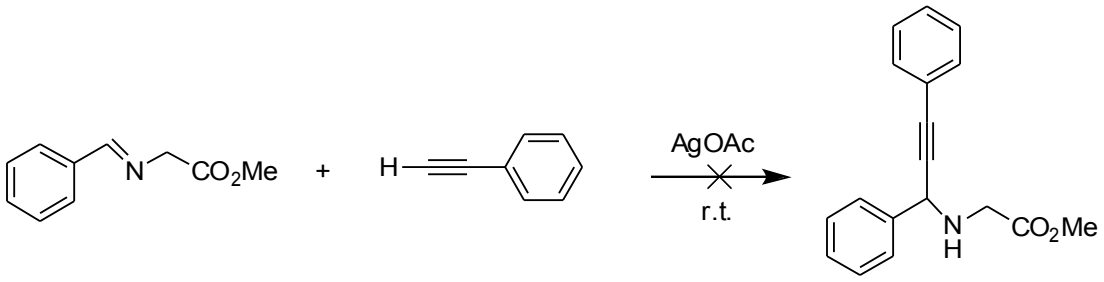
This was simply done by using a procedure developed by Carretero[38] and adapting it for substrates not covered by their procedure. This reaction involves the deprotection of the amine hydrochloride salt by triethylamine to yield the free amine followed by condensation of the aldehyde and the α-aminoester to form the desired α-iminoester. Magnesium sulfate had a twofold role in this case; it was added to the reaction mixture in order to bind the water molecule released from the dehydration reaction between the amine and the aldehyde and secondly it made sure that the solvent is dry. The absence of water pushed the reaction equilibrium toward the desired product.

Several substituents were used on the aromatic ring in order to hopefully tune the reactivity of the iminoester and provide a larger reaction scope if our endeavour proves itself successful. R_1 and R_2 are either a methyl (-CH_3), fluoro (-F), methoxy (-OMe) or hydrogen (-H) group. The carbon chain bonded to the oxygen of the ester was also slightly modified, in that case R_3 is either a methyl or an ethyl (-Et) group.

3.6 Terminal Alkyne Addition to Iminoesters

We tried to obtain the alkyne addition product using AgOAc at room temperature (Scheme 37). We hoped to achieve this reaction at room temperature since the true goal of

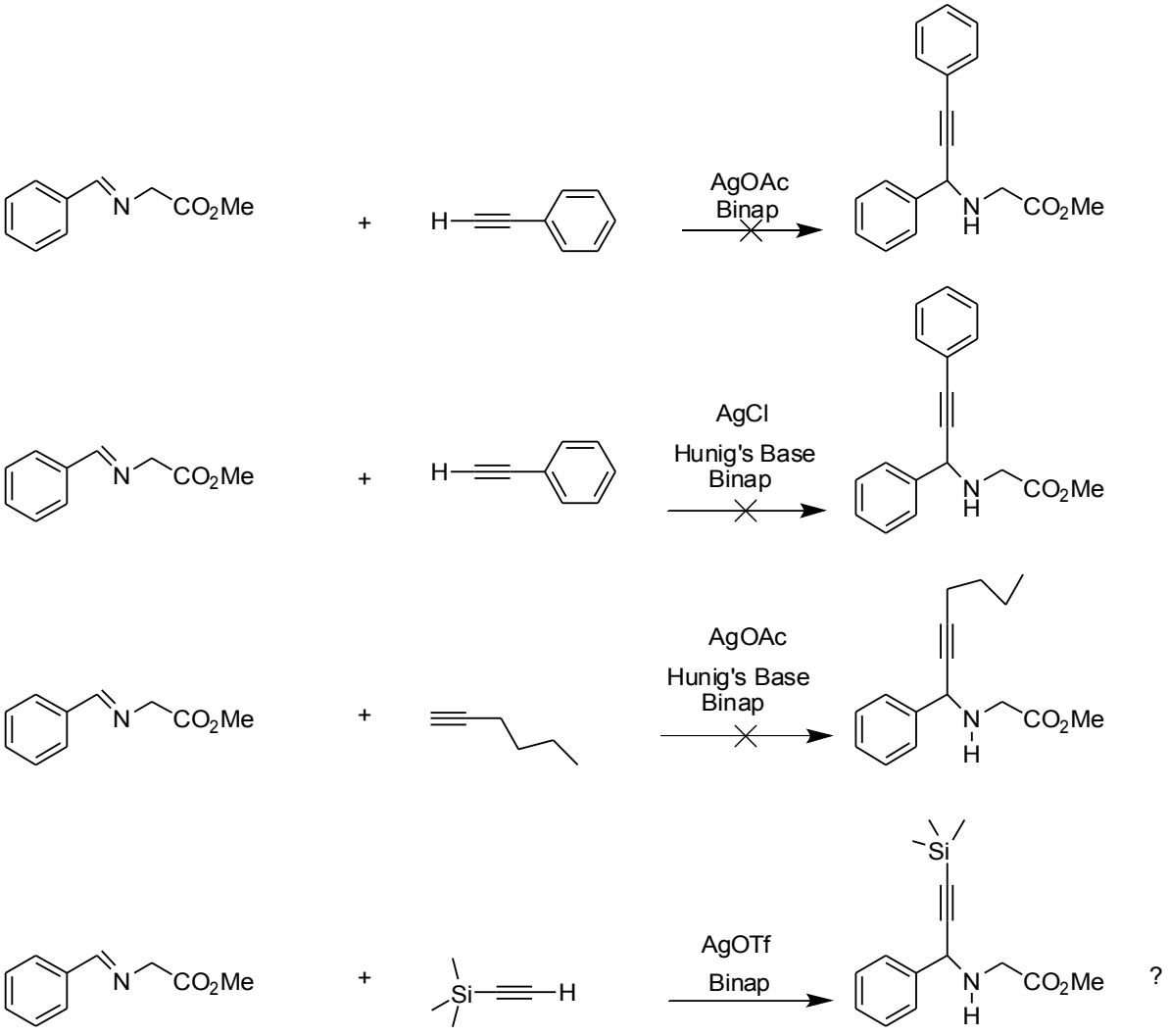
this methodology was to develop an enantioselective silver-catalyzed alkyne addition to imine (or A^3-coupling) and the use of higher temperature significantly reduces the odds of achieving an enantioselective process. Phenylacetylene was chosen as a good starting substrate since it had proven itself compatible with various A^3-coupling reactions. Various solvents were used including a more polar one, like THF and diethyl ether, that were favored by Zhou and a non-polar one like toluene which is more commonly used for A^3-coupling. None of those yielded the desired product. Our second guess was a simple silver salt would not be able to catalyze the reaction, so we decided to use 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (commonly referred to as BINAP) as a ligand. Zhou got the highest selectivity with phosphorus-containing ligands, so BINAP seemed to be a good starting point for our investigation.



Scheme 37: Initial attempt of silver-catalyzed alkyne addition to iminoester

Various counter-ions ($^-$Cl, $^-$OTf, $^-$OAc) were used in order to assess their impact on the reaction. The addition of an organic base (such as N,N-diisopropylethylamine) was also analyzed as well as the nature of the acetylene (aliphatic alkyne, aromatic alkyne or silyl alkyne). The reaction temperature was varied between room temperature and 100°C in order to promote a reaction. The following scheme shows a sampling of the reactions that we tried. It should be noted that all reaction vessels were shielded from light to

prevent degradation of the various silver complexes. No desired product was found when using phenylacetylene or 1-hexyne. The desired product was also not obtained when trimethylsilylacetylene was used, but a product was obtained. ^{1}H-NMR showed two product peaks (one at 5.8 ppm, the other at 6.5 ppm). The 5.8 ppm peak could be the proton peak indicator of a propargyl amine product (Figure 5), although it is lower than expected. The total absence of peaks around 0 ppm strongly suggests that no silyl group is present, hinting a possible hydrolysis of the silyl group.



Scheme 38: Silver-catalyzed alkyne addition to iminoester

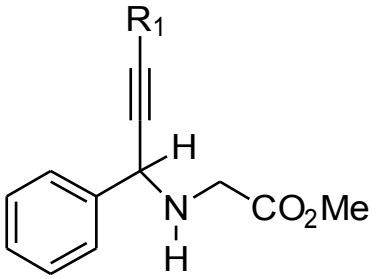
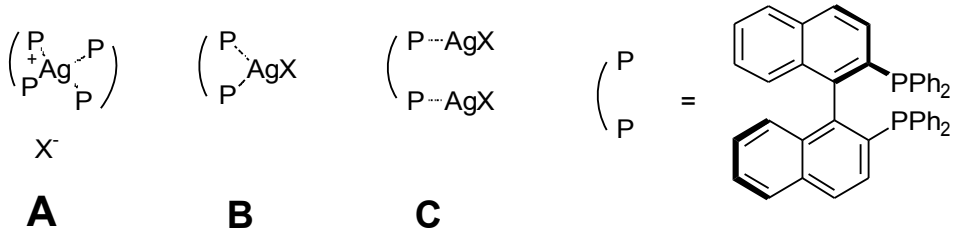


Figure 5: Characteristic hydrogen for identification

After reading an article published by Hisashi Yamamoto,[39] we realized that the stoichiometry or the ratio between the silver salt and the BINAP ligand could influence the nature of the silver-BINAP complex. As shown in table 7 (taken from Yamamoto), we can see that three different silver-BINAP complexes are possible depending on the stoichiometry. We then began to wonder if a certain complex could be more reactive than others.

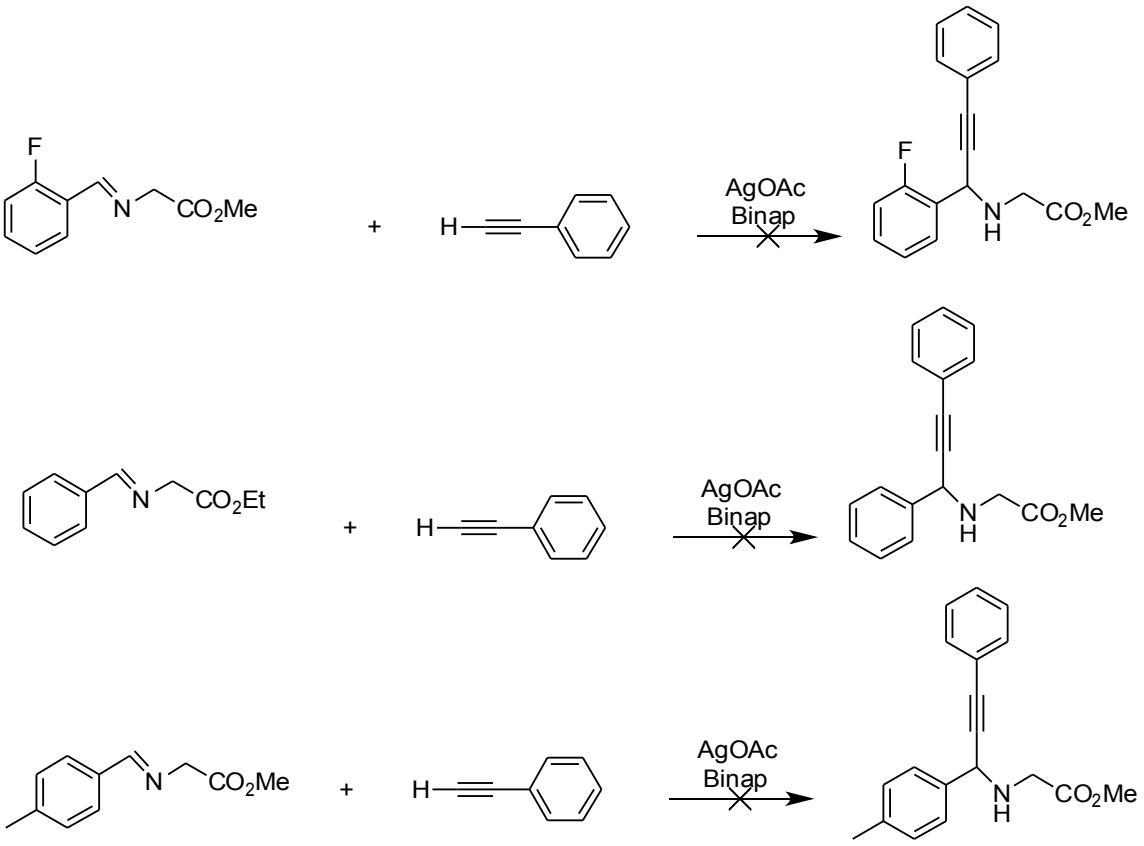


Silver salt (equiv.)	**A** / **B** / **C,** mol. ratio
AgOTf (0.4)	<1 / <1 / >99
AgOTf (0.5)	<1 / 19 / 81
AgOTf (0.6)	3 / 53 / 44
AgOTf (0.8)	17 / 65 / 18
AgOTf (1.0)	21 / 63 / 16
AgOTf (1.5)	69 / 31 / <1
AgOTf (2.0)	>99 / <1 / <1
AgOAc (1.0)	<1 / 93 / 7
$AgOCOCF_3$ (1.0)	29 / 71 / <1

Table 7: Various silver-BINAP complexes depending on the silver salt:BINAP ratio

For the sake of simplicity and expediency, we decided to use a higher catalyst loading

than usual (25 mol% rather than 10 mol%) and we used a 0.8 AgOTf:BINAP ratio ensuring us that the three silver-BINAP species would be present in solution at a relatively high concentration. This method didn't show any improvements.



Scheme 39: Effects of substituents on the reactivity of alkyne addition to iminoesters

Variations on the glycine-derived iminoester were also undergone as shown in Scheme 39. The presence of an electron-withdrawing group (-F) at the ortho position, or an electron-donating group (-Me) at the para position did not influence the reactivity of the imino ester. The carbon chain length of the ester was also slightly modified by adding an extra carbon, going from a methyl to an ethyl substituent. The end result was also the same for that modification: no desired product.

A common problem that was faced when using glycine-derived starting materials was their tendency to polymerize, a behaviour that has been reported in the literature.[40] This leads to the appearance of multiple peaks between 3 to 6 ppm and between 7 and 8 ppm on ^{1}H-NMR (using deuterated DMSO as solvent). We were able to partially overcome this issue by keeping the starting material at -20°C under an argon atmosphere.

We decided to explore other phosphorus-based ligands such as 1,2-bis(diphenylphosphino)ethane (dppe) and 1,2-bis(diphenylphosphino)butane (dppb) (Figure 6). We were hoping that the silver complex could still coordinate with the alkyne even though its coordination sites could be saturated and sterically shielded assuming a $[Ag(dppe)_2]OAc$ complex was formed.

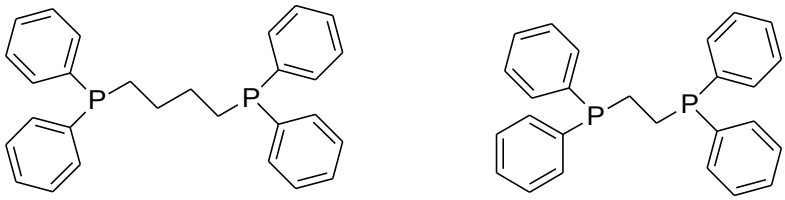
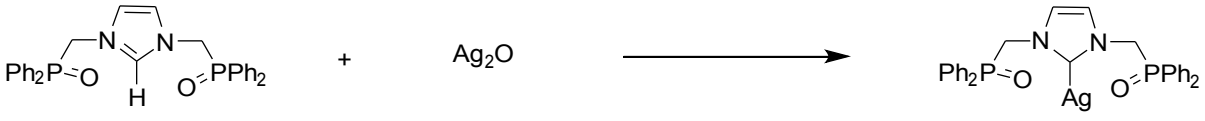
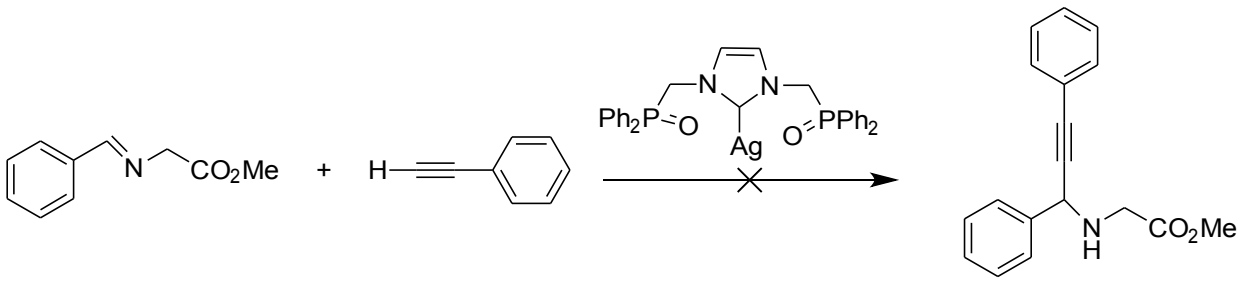


Figure 6: 1,4-Bis(diphenylphosphino)butane and 1,2-bis(diphenylphosphino)ethane ligands

A member of our research group (Leon Sun) had been working on heterocyclic carbenes as ligand, so we decided to investigate its use for our desired reaction. First the imidozolium oxide was reacted with silver oxide in the absence of light in freshly distilled CH_2Cl_2 under an argon atmosphere to yield the silver carbene (Scheme 40).



Scheme 40: Synthesis of silver-imidazolium carbene

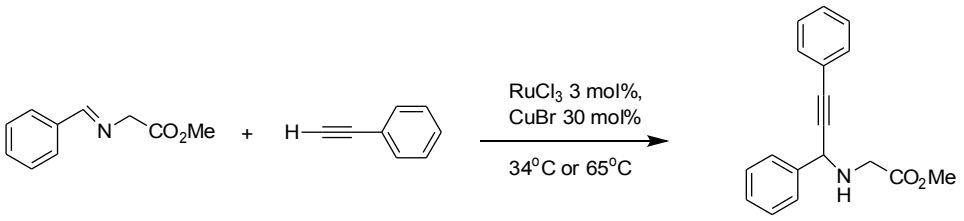


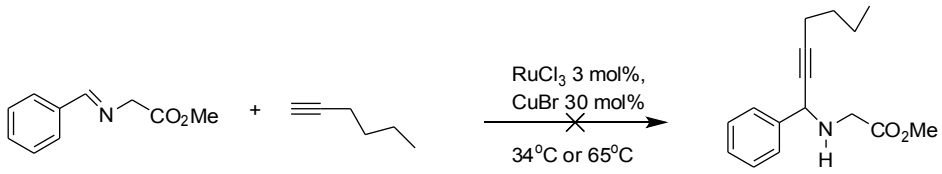
Scheme 41: Attempt at using the silver-carbene as a catalyst

The silver carbene was then tested using our standard conditions, using the methyl-iminoester and phenylacetylene as reactants (Scheme 41). Proton NMR revealed the possible formation of a product, but at best it would be in a really low yield, since the vast majority of the starting material seemed to not be consumed.

3.7 Cu/RuCatalyzed Alkyne Addition to Iminoesters

Faced with the difficulty of obtaining a clean sample of our desired product, we decided to use a methodology already developed by Li[41] to hopefully synthesize it. This method of alkyne addition to imine uses a copper(I)/ ruthenium(III) catalytic system and was highly efficient with a wide variety of substrates, including aniline. We used two types of alkynes: phenylacetylene and 1-hexyne and screened different solvents and temperatures in order to obtain the desired product. When THF was used as a solvent we were able to obtain the desired product (Scheme 42) in low yield.

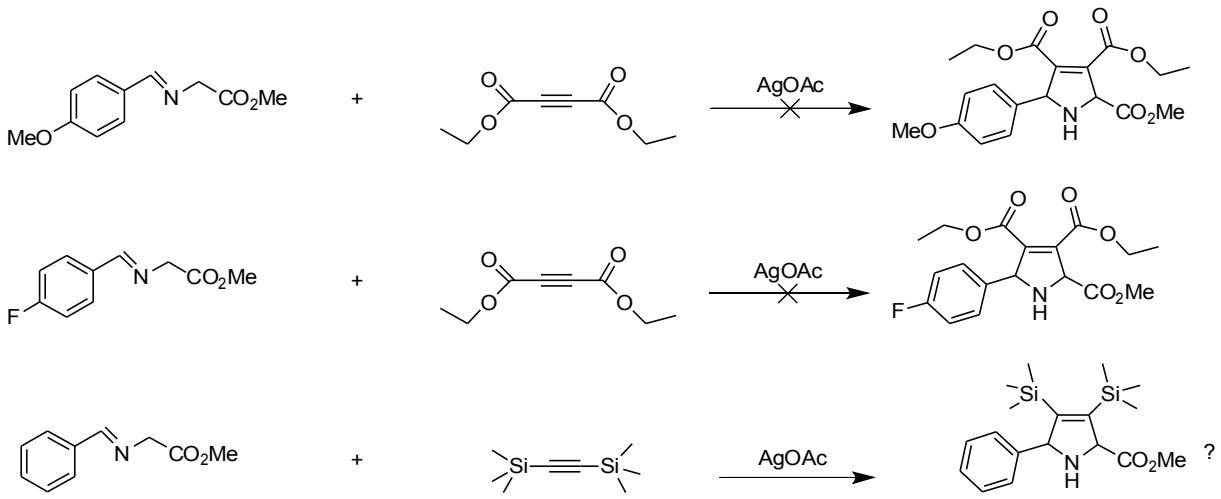




Scheme 42: Cu/Ru-catalyzed alkyne addition to iminoesters

3.8 Symmetrical Internal Alkyne Addition to Iminoesters

As mentioned earlier, the second part of the project involved the use of disubstituted alkynes instead of terminal alkynes. The following scheme shows a small sampling of the reaction conditions that were surveyed. We first used diethyl acetylenedicarboxylate as a alkyne in order to try the impact of an electrophilic alkyne. This did not yield the desired product, even if various substituents were present on the aromatic ring of the iminoester (-OMe, -F). We then decided to use electron-rich alkynes such as bis(trimethylsilyl)acetylene. A large amount of starting material seemed to be present after the reaction, but other peaks were present on ^{1}H-NMR which could be indicator (albeit in low yield) of the desired product.

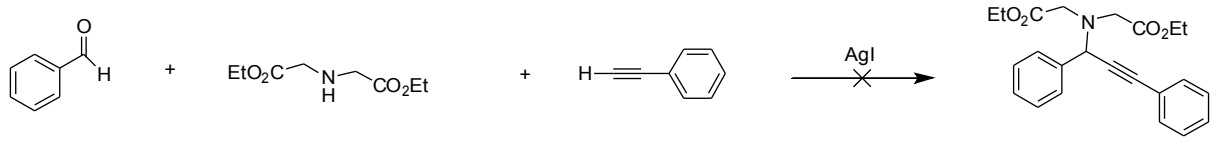


Scheme 43: Symmetrical internal alkyne addition to iminoesters

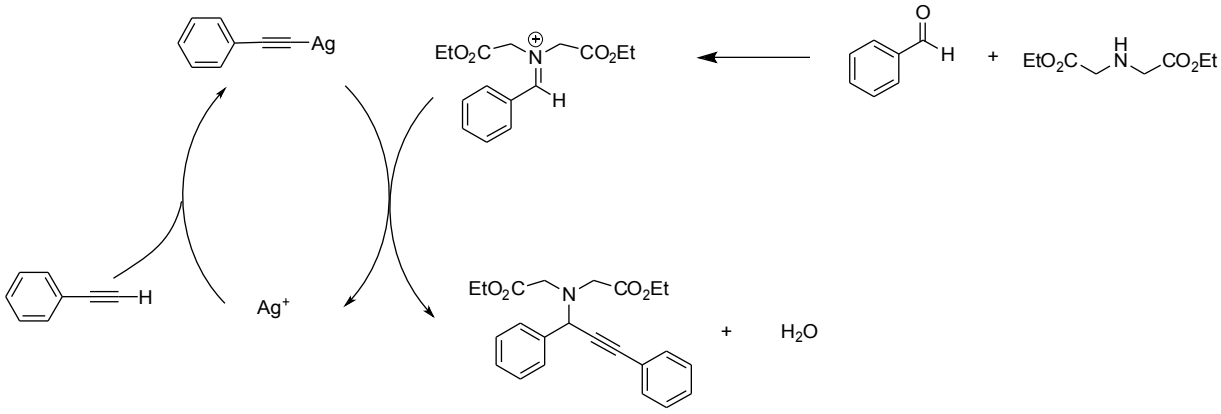
3.9 Silver-Catalyzed A^3-Coupling Using Secondary Amines

The main issue with the aforementioned project was the low reactivity of primary amines/primary amine-derived imino-esters toward A^3-coupling or alkyne addition to imine. Forced to see that this reactivity problem was not going to be solved by the reaction system that we were investigated, we decided to modify the equation by using secondary amines as substrates. Since we were interested in propargyl amines containing ester moieties as an product, we decided to use diethyl iminodiacetate as a substrate (Scheme 44). Once more, we did not obtain the desired product. A possible explanation is that the iminium intermediate (shown on Scheme 45) needed for the alkyne addition to proceed is highly unstable since the nitrogen center is deshielded by two electron-withdrawing groups (esters). We could get around that problem by increasing the temperature (previous reactions were at most at 60^{o}C) and/or increasing the concentration of the reactants, both measures would increase the number of collisions between the

amine and the aldehyde hence promoting the formation of the iminium intermediate.



Scheme 44: Silver-catalyzed A^3-coupling using diethyl iminodiacetate as substrate



Scheme 45: Plausible catalytic cycle of silver-catalyzed A^3-coupling using diethyl iminodiacetate as substrate

3.10 Conclusion

In retrospect, we were not able to establish a reliable synthetic method of silver-catalyzed alkyne addition to iminoester in order to obtain secondary propargyl amines. The lack of reactivity of primary amine-derived iminoester was most likely the key reason. Moreover, even when a secondary amine was used as a substrate, the desired product was not obtained. The use of either disubstituted alkynes or monosubstituted alkynes did not change the outcome, the same goes for the use of electron-withdrawing or electron-donating substituents on the alkyne.

3.11 Experimental

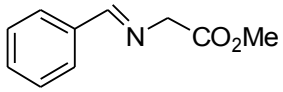
General

^{1}H-NMR spectra were recorded using a Varian 400 MHz spectrometer. ^{13}C-NMR were recorded using a Varian 300 MHz spectrometer. The chemical shifts are reported in part per million (δ) and either deuterated chloroform or deuterated-DMSO was used as a solvent. The silica gel used for the purification was SiliaFlash F60 from Silicycle company. Unless otherwise specified, the chemicals used were purchased and used as such from Sigma-Aldrich. All reagents were weighted and handled in air at room temperature.

Taken and adapted from Carretero[42] where all the ^{1}H-NMR match with previously reported spectroscopic data.

3.11.1 Synthesis of α-Iminoesters

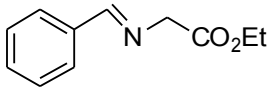
(E)-Methyl 2-(benzylideneamino)acetate



Glycine methyl ester HCl (1.9 g, 15 mmol), $MgSO_4$ (1.9 g, 16 mmol), Et_3N (2,1mL, 15 mmol) and freshly distilled CH_2Cl_2 (38 mL) were added sequentially to a 100 mL round-bottom flask and stirred heavily at room temperature for 1 hour. Benzaldehyde (1,1 mL, 11 mmol) was then added in 1 portion using a syringe. After 48 hours, the reaction mixture was filtered off and water was added (5 mL). The organic layer and the aqueous phase were separated. The aqueous phase was extracted 3 times with CH_2Cl_2 (10

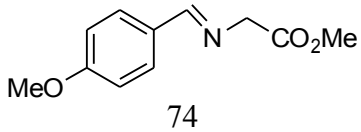
mL each time). The organic layers were then combined and washed with brine (15 mL) and dried over $MgSO_4$. The solvent was then evaporated *in vacuo* and yielded (E)-methyl 2-(benzylideneamino)acetate (1.94 g, 10.9 mmol, quantitative yield, yellow oil), ^{1}H-NMR (400 MHz,d-DMSO): δ = 8.35 (s, 1H), 7.77-7.74 (m, 2H), 7.47-7.42 (m, 3H), 4.42 (s, 2H), 3.66 (s, 3H)

(E)-Ethyl 2-(benzylideneamino)acetate



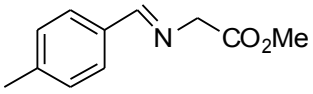
Glycine ethyl ester HCl (1.9 g, 15 mmol), $MgSO_4$ (1.9 g, 16 mmol), Et_3N (2.1mL, 15 mmol) and freshly distilled CH_2Cl_2 (36 mL) were added sequentially to a 100 mL round-bottom flask and stirred heavily at room temperature for 1 hour. Benzaldehyde (1.1 mL, 11 mmol) was then added in 1 portion using a syringe. After 48 hours, the reaction mixture was filtered off and water was added (5 mL). The organic layer and the aqueous phase were separated. The aqueous phase was extracted 3 times with CH_2Cl_2 (10 mL each time). The organic layers were then combined and washed with brine (15 mL) and dried over $MgSO_4$. The solvent was then evaporated *in vacuo* and yielded (E)-ethyl 2-(benzylideneamino)acetate (2.20 g, 11,5 mmol, quantitative yield, yellow oil), ^{1}H-NMR (400 MHz,d-DMSO): δ = 8.36 (s, 1H), 7.77-7.75 (m, 2 H), 7.48-7.41 (m, 3H), 4.40 (s, 2H), 1.20-1.16 (m, 3H)

(E)-Methyl 2-((4-methoxybenzylidene)amino)acetate



Glycine methyl ester HCl (1.9 g, 15 mmol), $MgSO_4$ (2.06 g, 17 mmol), Et_3N (2.1mL, 15 mmol) and freshly distilled CH_2Cl_2 (36 mL) were added sequentially to a 100 mL round-bottom flask and stirred heavily at room temperature for 1 hour. 4-Methoxybenzaldehyde (1.35 mL, 11 mmol) was then added in 1 portion using a syringe. After 48 hours, the reaction mixture was filtered off and water was added (5 mL). The organic layer and the aqueous phase were separated. The aqueous phase was extracted 3 times with CH_2Cl_2 (10 mL each time). The organic layers were then combined and washed with brine (15 mL) and dried over $MgSO_4$. The solvent was then evaporated *in vacuo* yielded (E)-methyl 2-((4-methoxybenzylidene)amino)acetate (2.41 g, 11.6 mmol, quantitative yield, yellow solid), ^{1}H-NMR (400 MHz,d-DMSO): δ = 8.27 (s, 1H), 7.69 (d, J= 8.80 Hz), 7.00 (d, 8.40 Hz), 4.36 (s, 2H), 3.79 (s, 3H), 3.65 (s, 3H)

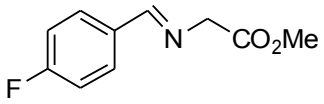
(E)-Methyl 2-((4-methylbenzylidene)amino)acetate



Glycine methyl ester HCl (1.6 g, 13 mmol), $MgSO_4$ (2.40 g, 20 mmol), Et_3N (2.1mL, 15 mmol) and CH_2Cl_2 (31 mL) were added sequentially to a 100 mL round-bottom flask and stirred heavily at room temperature for 1 hour. p-tolualdehyde (1.15 mL, 9.8 mmol) was then added in 1 portion using a syringe. After 48 hours, the reaction mixture was filtered off and water was added (5 mL). The organic layer and the aqueous phase were separated. The aqueous phase was extracted 3 times with CH_2Cl_2 (10 mL each time). The organic layers were then combined and washed with brine (15 mL) and dried over $MgSO_4$. The solvent was then evaporated *in vacuo* and yielded (E)-methyl 2-((4-

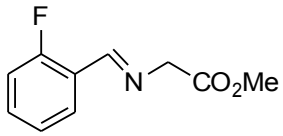
methylbenzylidene)amino)acetate. ^{1}H-NMR (400 MHz,d-DMSO): δ = 8.31 (s, 1H), 7.63 (d, J= 8.00 Hz, 2H), 7.25 (d, J= 8.00 Hz, 2H), 4.39 (s, 2H), 3.65 (s, 3H), 2.33 (s, 3H)

(E)-Methyl 2-((4-fluorobenzylidene)amino)acetate



Glycine methyl ester HCl (1.7 g, 14 mmol), $MgSO_4$ (2.48 g, 21 mmol), Et_3N (2.1mL, 15 mmol) and CH_2Cl_2 (34 mL) were added sequentially to a 100 mL round-bottom flask and stirred heavily at room temperature for 1 hour. 4-Fluorobenzaldehyde (0.75 mL, 7 mmol) was then added in 1 portion using a syringe. After 48 hours, the reaction mixture was filtered off and water was added (5 mL). The organic layer and the aqueous phase were separated. The aqueous phase was extracted 3 times with CH_2Cl_2 (10 mL each time). The organic layers were then combined and washed with brine (15 mL) and dried over $MgSO_4$. The solvent was then evaporated *in vacuo* and yielded (E)-methyl 2-((4-fluorobenzylidene)amino)acetate. ^{1}H-NMR (400 MHz,d-DMSO): δ = 8.35 (s, 1H), 7.82-7.79 (m, 2H), 7.28 (t, J= 8.80 Hz), 4.41 (s, 2H), 3.65 (s, 3H)

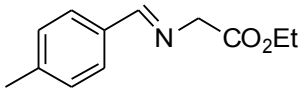
(E)-Methyl 2-((2-fluorobenzylidene)amino)acetate



Glycine methyl ester HCl (2.1 g, 17 mmol), $MgSO_4$ (2.25 g, 19 mmol), Et_3N (2.1mL, 15 mmol) and CH_2Cl_2 (36 mL) were added sequentially to a 100 mL round-

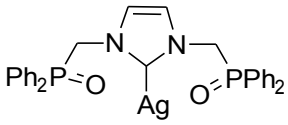
bottom flask and stirred heavily at room temperature for 1 hour. 2-fluorobenzaldehyde (0.75 mL, 7 mmol) was then added in 1 portion using a syringe. After 48 hours, the reaction mixture was filtered off and water was added (5 mL). The organic layer and the aqueous phase were separated. The aqueous phase was extracted 3 times with CH_2Cl_2 (10 mL each time). The organic layers were then combined and washed with brine (15 mL) and dried over $MgSO_4$. The solvent was then evaporated *in vacuo* and yielded (E)-methyl 2-((2-fluorobenzylidene)amino)acetate. ^{1}H-NMR (400 MHz,d-DMSO): δ = 8.60 (s, 1H), 7.92-7.89 (m, 1H), 7.57-7.51 (m, 1H), 7.31-7.25 (m, 2H), 4.49 (s, 2H), 3.66 (s, 3H)

(E)-Ethyl 2-((4-methylbenzylidene)amino)acetate



Glycine ethyl ester HCl (2.1 g, 15 mmol), $MgSO_4$ (2.50 g, 21 mmol), Et_3N (2.1 mL, 15 mmol) and CH_2Cl_2 (38 mL) were added sequentially to a 100 mL round-bottom flask and stirred heavily at room temperature for 1 hour. p-tolualdehyde (1.15 mL, 10 mmol) was then added in 1 portion using a syringe. After 48 hours, the reaction mixture was filtered off and water was added (5 mL). The organic layer and the aqueous phase were separated. The aqueous phase was extracted 3 times with CH_2Cl_2 (10 mL each time). The organic layers were then combined and washed with brine (15 mL) and dried over $MgSO_4$. The solvent was then evaporated *in vacuo* and yielded (E)-ethyl 2-((4-methylbenzylidene)amino)acetate. ^{1}H-NMR (400 MHz,d-DMSO): δ = 8.30 (s, 1H), 7.63 (d, J= 8.00 Hz, 2H), 7.26 (d, J= 8.00 Hz, 2H), 4.36 (s, 2H), 4.12-4.10 (m, 2H), 2.33 (s, 3H), 1.21-1.15 (m, 3H)

(1,3-Bis((diphenylphosphoryl)methyl)-2,3-dihydro-1H-imidazol-2-yl)silver



Imidozolium oxide (1 equiv., 0.013 g, 0.26 mmol) was added to a microwave reaction tube containing a magnetic stir bar. Ag_2O (0.5 equiv., 0.003 g, 0.13 mmol) was added, the reaction vessel was capped and put under an argon atmosphere. Freshly distilled CH_2Cl_2 (1,0 mL) was then added using a syringe and the reaction vessel was covered in aluminum foil in order to protect it from light. The reaction mixture was let to stir at room temperature for 24 hours. The solvent was then evaporated in vacuo yielding (1,3-bis((diphenylphosphoryl)methyl)-2,3-dihydro-1H-imidazol-2-yl)silver as a red-brown solid.

3.11.2 Alkyne Addition to Iminoesters

Typical procedure

AgOTf (0.0103 g, 0.04 mmol) and BINAP (0.0311 g, 0.05 mmol) were added successively to a microwave vial containing a magnetic stir bar. The vial were then capped and put under an argon atmosphere. Solvent (Toluene for example, 0.8 mL) was added in one portion using a syringe. The reaction vessel was then covered with aluminum foil and let to stit at room temperature for 30 minutes. (E)-methyl 2-(benzylideneamino)acetate (1 equiv., 0.033g, 0.2 mmol, ≈ 35 μL at R.T.) was added using a microsyringe followed by phenyl acetylene (1.2 equiv., 0.025 g, 0.024 mmol, ≈ 26 μL at R.T.). The reaction mixture was then stirred for 24 hours.

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Conclusions and Claims to the Original Knowledge

The method of oxidative amidation of aldehydes in presence of amine hydrochloride salts developed by Li was optimized for large scale synthesis of (S)-methyl-2-benzamido-3-methylbutanoate without racemization and in good yield using L-valine methyl ester hydrochloride as substrate. The scope of the reaction was expanded to include leucine and alanine derivatives as well as glycine-derived short peptides. Through the use of the iSustain™ Green Chemistry Index tool V. 2.0, we were able to demonstrate the "greenness" of our process.

This was followed by the development of an enantioselective cobalt-catalyzed A^{3-} coupling reaction namely through the investigation of a variety of binaphthyl ligands. We also gained insight on the reaction process by analyzing the impact of water on the enantioselectivity of the reaction.

Lastly, we tried to establish a silver-catalyzed alkyne addition to iminoesters methodology, but were faced with a lack of reactivity of the iminoester under the examined reaction conditions. This opened the way to future work with iminoesters using other transition metal catalysts.

The work produced from this thesis led to the following publication:

Giguère-Bisson, M.; Yoo, W-J.; Li, C-J, *Org. Synth.,* In Press.