Steric Hindrance of Primary Alcohols' Effect on Knoevenegal Condensation of Dimethyl Malonate

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ABSTRACT: We report a study in which the steric encumbrance of a primary alcohol was varied in a $HRu(bpi)(PPh_3)_2$-catalyzed Knoevenegal condensation with dimethyl malonate to assess yield. It was hypothesized that increased steric bulk of the substrate would correspond to higher yield of the malonate derivative that formed. Yield was observed but did not show a trend in relation to steric bulk of the alcohol.

Introduction

The ruthenium pincer-based catalyst $HRu(bMepi)(PPh_3)_2$ (bMepi = 1,3-bis(6'-methyl-2'pyridylimino)-isoindolate) has been studied extensively for its dehydrogenation capabilities. It has been observed to catalyze the oxidation of secondary alcohols to ketones[1] and the self-condensation of primary alcohols to form esters.[2] Alcohols as building blocks are inexpensive and readily available and can be utilized for the esterification of a range of prodrugs.[3]

In these catalytic conditions, C-C coupling proceeds from the oxidized C-O unit of primary alcohols.[4] Malonates are used as starting materials for various active pharmaceutical ingredients (APIs).[5] However, whether this C-C bond formation can be extended to malonate substrates remains understudied. Furthermore, the extent to which sterics of the alcohol influence the overall yield of malonate derivatives remains unexplored.

With this paper, we sought to evaluate if the catalyzed coupling reaction between primary alcohols and malonates occurs and the impact of sterics on yield. This was achieved by use of a $HRu(bpi)(PPh_3)_2$ catalyst in the presence of excess base to catalyze the Knoevenegal condensation between dimethyl malonate and a primary alcohol. Hexanol, 2-ethyl-1-butanol, benzyl alcohol, and 2-methyl benzyl alcohol were chosen due to the varying steric hindrance present in each alcohol. Manipulating functional structures of compounds is integral to synthetic chemistry, facilitating the development of novel synthetic pathways.

Experimental

General Considerations

Calcium chloride, $RuCl_2(PPh_3)_3$, $NaPF_6$, 2-ethyl-1-butanol, 2-methylbenzyl alcohol, and potassium tert-butoxide were purchased from Sigma. Aminopyridine was purchased from Tokyo Chemical and pthalonitrile was purchased fom Acros. Hexanol was purchased from Alfa Aeser and benzyl alcohol was purchased from Fischer Scientific. Anhydrous Tetrahydrofuran was purchased from Sigma Aldrich. 100 MHz NMR was performed on a Nanalysis 100 Pro NMR machine while Varian NMR machine. FT-IR spectra were collected using an Alpha-P-Bruker FT-IR.

Synthesis and Characterization of Hbpi

Reaction mixtures were prepared in two separate 25 mL round bottom flasks containing 1035 mg aminopyridine (11 mmol, 22 eq.), 640 mg phtalonitrile (5 mmol, 10 eq.), and 55.5 mg calcium chloride (0.5 mmol, 1 eq.). 15 mL hexanol was added to each mixture, and the flasks were equipped with a Teflon stir bar and a reflux condenser. The flasks were flushed with nitrogen and heated to reflux for two days while stirring. The reaction mixtures were cooled to room temperature and combined. The resulting brown solid was collected on a glass frit, washed with 10 mL of water, and then with 10 mL of chloroform. Solvent was removed from the filtrate by rotary evaporation to yield a yellow-brown solid which was filtered with hexanes through a glass frit to yield 1.234g of yellow-brown product at 41% yield. 100 MHz ^{1}H NMR in $CDCl_3$ and IR were both taken of the ligand, presenting a broad stretch at 3199 cm^{-1} and yielding ^{1}H NMR peaks 8.58 – 7.10 (m, 1H).

Synthesis and Characterization of $HRu(bpi)(PPh_3)_2$

55.5 mg Hbpi (0.20 mmol, 1 eq.), 192 mg $RuCl_2(PPh_3)$ (0.20 mmol, 1 eq.), 35 mg $NaPF_6$ (0.20 mmol, 1 eq.), and a stir bar were added to a 100 mL Schlenk flask and subjected to three evacuation and nitrogen fill cycles. 17.5 mL anhydrous THF was added through a syringe and the mixture was stirred at 70°C for 60 minutes under a nitrogen atmosphere. The mixture was then cooled to room temperature and solvent was removed by rotary evaporation to afford a black solid which was washed with 10 mL of dichloromethane over a glass frit, leaving behind a thin layer of sodium chloride. The filtrate was subjected to rotary evaporation again to yield a black solid that was washed over a glass frit with diethyl ether (4x20 mL) and hexanes (4x20 mL) to yield 0.799g of purple solid. 400 MHZ ^{31}P and ^{1}H NMR were taken of the product, as well as an IR. ^{31}P NMR yielded a single peak at 21.6 ppm and ^{1}H NMR yielded peaks of 8.05 – 6.49 (m, 1H), 1.27 (d, J = 7.5 Hz, 1H),

0.86 (dt, J = 12.4, 7.1 Hz, 1H). IR presented a weak stretch at 3342 cm^{-1}.

Primary Alcohol Esterification General Protocol

For each reaction, 2 mL of toluene, 5 mg of Ru catalyst complex (0.00538 mmol, 0.0108 eq.), 60 mg of potassium tert butoxide (0.54 mmol, 1.08 eq.), 101 µL of cyclohexene (1 mmol, 2 eq.), 0.5 mmol of alcohol (1 eq.), and a stir bar were added to an 8 mL vial. The vial was then purged with nitrogen gas and was heated to reflux at 110°C while stirring at approximately 1500 rpm for 60 minutes. The mixture was then cooled to room temperature and 2 mL of diethyl ether was added. Excess solvent was then removed by rotary evaporation, and a Q-NMR sample was prepared by adding a weighing a drop of HDMSO as an internal standard. The sample was then suspended in $CDCl_3$ and assessed by 400 MHz ^{1}H-NMR. The selected alcohols were hexanol, 2-ethyl-1-butanol, 2-methylbenzyl alcohol, and benzyl alcohol. The relevant peaks for each esterification product are presented here. Hexanol: 3.97 (q, J = 6.9 Hz, 1H), 2-ethyl-1-butanol: 3.97 (m, 1H), benzyl alcohol: 10.02 (s, 0H), 5.13 (s, 0H), 2-methylbenzyl alcohol: 10.22 (s, 1H), 5.84 (t, J = 1.6 Hz, 50H).

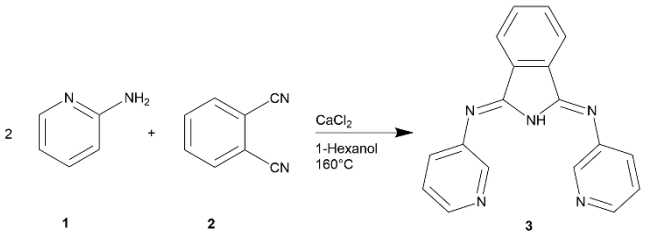
Koevenegal Condensation of Primary Alcohols General Protocol

For each reaction, 2 mL of toluene, 5 mg of Ru catalyst complex (0.00538 mmol, 0.0108 eq.), 120 mg of potassium tert-butoxide (1.08 mmol, 2.16 eq.), 0.5 mmol of alcohol (1 eq.), 286 µL of dimethyl malonate (2.5 mmol, 5 eq.), and a stir bar were added to an 8 mL vial. The procedure for the rest of the reaction follows the same reaction conditions as the esterification protocol, and the final mixture was assessed by 400 MHz ^{1}H-NMR. The relevant peaks for each Koevenegal condensation products are presented here. Hexanol: 4.21 (t, J = 6.9 Hz, 1H), 3.89 (s, 0H), 2-ethyl-1-butanol: 3.99 (dd, J = 5.8, 1.7 Hz, 1H), 0.76 (m, 6H), benzyl alcohol: 5.08 (d, J = 6.4 Hz, 21H), 3.99 (s, 0H), 2-methylbenzyl alcohol: 5.29 (s, 1H), 3.83 (s, 1H).

Controls for both the esterification and Koevenegal condensation reactions were run with a hexanol substrate under each of the following conditions: no catalyst, no base, and no catalyst and no base.

Results and Discussion

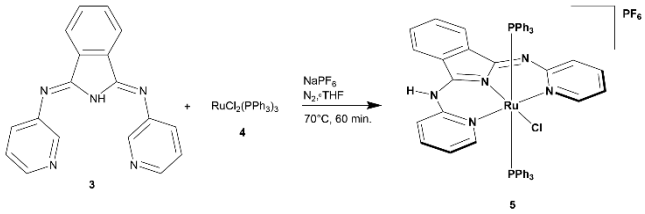
Aminopyridine **(1)** underwent a condensation reaction with pthalonitrile **(2)** facilitated by $CaCl_2$ in 1-hexanol to form 1,3-bis(pyridylamino)isoindoline (Hbpi) **(3)** (Scheme 1).



Scheme 1. Synthesis of Hbpi

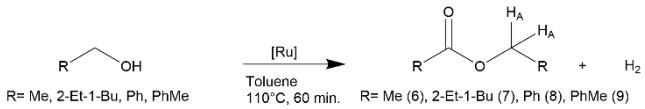
The crude product was worked up as previously described and afforded a yellow-brown solid in 41% yield. 100 MHZ ^{1}H NMR in $CDCl_3$ and IR were taken of the product. A multiplet at 7.10 - 8.58 ppm confirmed the presence of the aromatic hydrogens on the product, which is consistent with previously published shifts[4] FTIR presented a broad stretch at 3199 cm^{-1} corresponding to the nitrogen-hydrogen bond of the ligand, and no peaks were found around 2250 cm^{-1} where we would expect to see the nitriles corresponding to the pthalonitrile structure.

Metalation of **(2)** with a $RuCl_2(PPh_3)_3$ **(4)** complex was performed under an inert atmosphere in anhydrous THF solvent with $NaPF_6$ as the counter ion to form the $HRu(bpi)(PPh_3)_2$ catalyst (Scheme 2). The crude product was worked up, affording 0.799g of purple solid in 120% yield. ^{1}H NMR presented peaks at 8.05 – 6.49 (m, 1H), which correspond to the aromatic hydrogens on the ligand, which have been shifted upfield due to their proximity to the ruthenium. However, ^{31}P NMR presented a singular peak at 21.6 ppm, which is not consistent with the literature value of 39.2 ppm.[6] The lack of a matching peak can be attributed to error in preparing the sample, as experimental data confirmed the formation of product, which would not be possible without the correct catalytic conditions. The FTIR spectrum of the catalyst saw the peak at 3199 cm^{-1} of the ligand corresponding to the nitrogen-hydrogen bond disappear, and a new weak stretch appeared at 3342 cm^{-1}, consistent with the new nitrogen-hydrogen bond of the pincer ligand complexed with the ruthenium metal center.



Scheme 2. Metalation of Hbpi with Ruthenium Complex

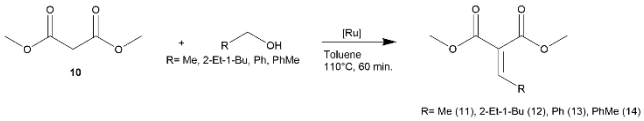
Esterification of primary alcohols is a reaction that is known to proceed through the use of this ruthenium catalyst and was performed on a variety of alcohols to provide a baseline for our investigation of C-C bond formation in malonates. The alcohols of interest for this work were hexanol, 2-ethyl-1-butanol, benzyl alcohol, and 2-methylbenzyl alcohol for their differences in steric bulk. Furthermore, the selection of these alcohols allowed for steric comparisons between a set of aliphatic and aromatic alcohols. For each alcohol, an eight mL vial was prepared containing toluene, ruthenium catalyst, potassium tert-butoxide, alcohol, cyclohexene, and a stir bar. The vial was purged with nitrogen gas and the reaction proceeded as the vial was heated to reflux and was allowed to stir for 60 minutes (Scheme 3).



Scheme 3. Esterification of Primary Alcohols with Ruthenium Catalyst

The reaction mixture was cooled to room temperature, worked up as previously described, and was quantified via quantitative ^{1}H NMR in $CDCl_3$. The hexanol product was verified by the peak at 3.97 ppm corresponding to hydrogen A, as seen in Scheme 3, which is consistent with the spectrum found in the SDBS database.[7] 2-ethyl-1-butanol, benzyl alcohol, and methylbenzyl alcohol products were verified by peaks corresponding to hydrogen A at 3.97, 5.13, and 5.84 ppm respectively, which agree with spectra found in the literature.[8,9,10]

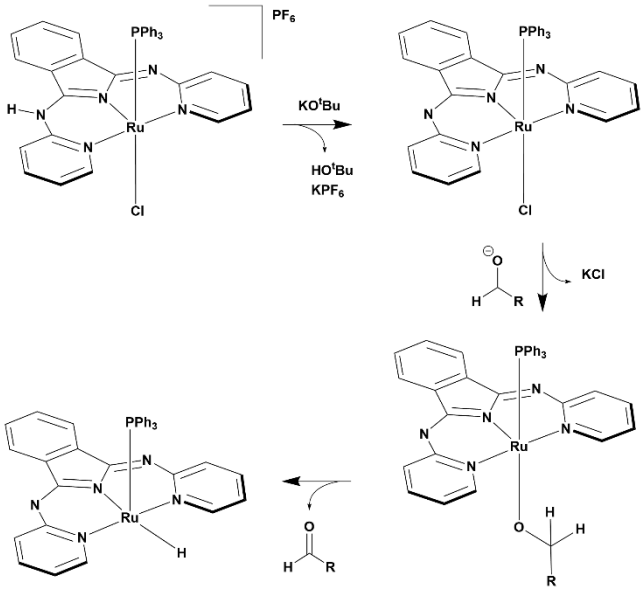
The Knoevenegal condensation of the primary alcohols of interest with dimethyl malonate was performed by adding toluene, ruthenium catalyst, potassium tert-butoxide, alcohol, and dimethyl malonate to an eight mL vial (Scheme 4).



Scheme 4. Koevenegal Condensation of Primary Alcohols with Dimethyl Malonate

The vial was then purged with nitrogen gas and allowed to stir for 60 minutes under reflux. The reaction mixture was cooled to room temperature and was worked up identically to the esterification trials and ^{1}H NMR was taken in the same manner. Product formation was verified by peaks at 3.89, 3.99, 3.99, and 3.83 ppm for hexanol, 2-ethyl-1-butanol, benzyl alcohol, and 2-methylbenzyl alcohol respectively. These peaks were upshifted relative to the methyl peaks from the dimethyl malonate starting material, indicative of the formation of the product, and are consistent with spectra found in the SDBS database and the literature.[11,12] The 2-ethyl-1-butanol spectrum was unable to be found in the literature, but the reported peak is consistent with where methyl peaks are expected to appear in spectra, and is upshifted relative to the methyl peak corresponding to the dimethyl malonate substrate.[13]

$HRu(bpi)(PPh_3)_2$ has been studied for its ability to dehydrogenate substrates. To accomplish this, it must first be activated by deprotonation of an alcohol to facilitate the coordination of a reactive hydrogen to the ruthenium metal center, as outlined in Scheme 5.[14]



Scheme 5. Current Accepted Mechanism for Activation of Ruthenium Catalyst Complex

The proposed mechanism for the dehydrogenation of primary alcohol substrates is shown in Scheme 6.[14] Due to the importance of the binding of the substrate to the ruthenium metal center in the mechanism, my group hypothesized that greater steric bulk would hinder the ability of the substrate to coordinate with the catalyst, thus decreasing the yield of the malonate derivative formed from the primary alcohol substrate if it formed. This steric-dependent hypothesis was extended to the well-established esterification of primary alcohols, as the only variation in the transition state between the reactions is the nucleophile bound to the coordinated aldehyde.

To test this hypothesis, hexanol, 2-ethyl-1-butanol, benzyl alcohol, and 2-methylbenzyl alcohol were selected as primary alcohols of interest due to their varying amounts of steric bulk, and the structure for each is shown in Figure 1. Hexanol and 2-ethyl-1-butanol have an identical number of carbons but vary in terms of structure, with hexanol being a straight chain, whereas 2-ethyl-1-butanol is a branched chain. Benzyl alcohol and 2-methylbenzyl alcohol were selected to provide insight into how aromatic compounds with differing sterics interacted with the catalyst to form the malonate derivative product.

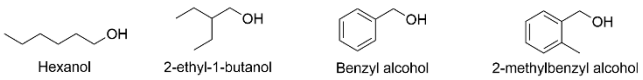


Figure 1. Structure of Primary Alcohols

The impact of sterics on the esterification of primary alcohols was investigated as a baseline to extend to the proposed Knoevenegal condensation with dimethyl malonate. The percent yield data collected from this reaction is presented in Table 1.

Table 1. Yield for Esterification of Primary Alcohols

Entry	Alcohol	Expected Product	Average Yield (n = 3)
1	Hexanol	6	3.8 ± 3%
2	2-ethyl-1-butanol	7	0.80 ± 0.5%
3	Benzyl alcohol	8	0.36 ± 0.5%
4	2-methylbenzyl alcohol	9	0.49 ± 0.3%

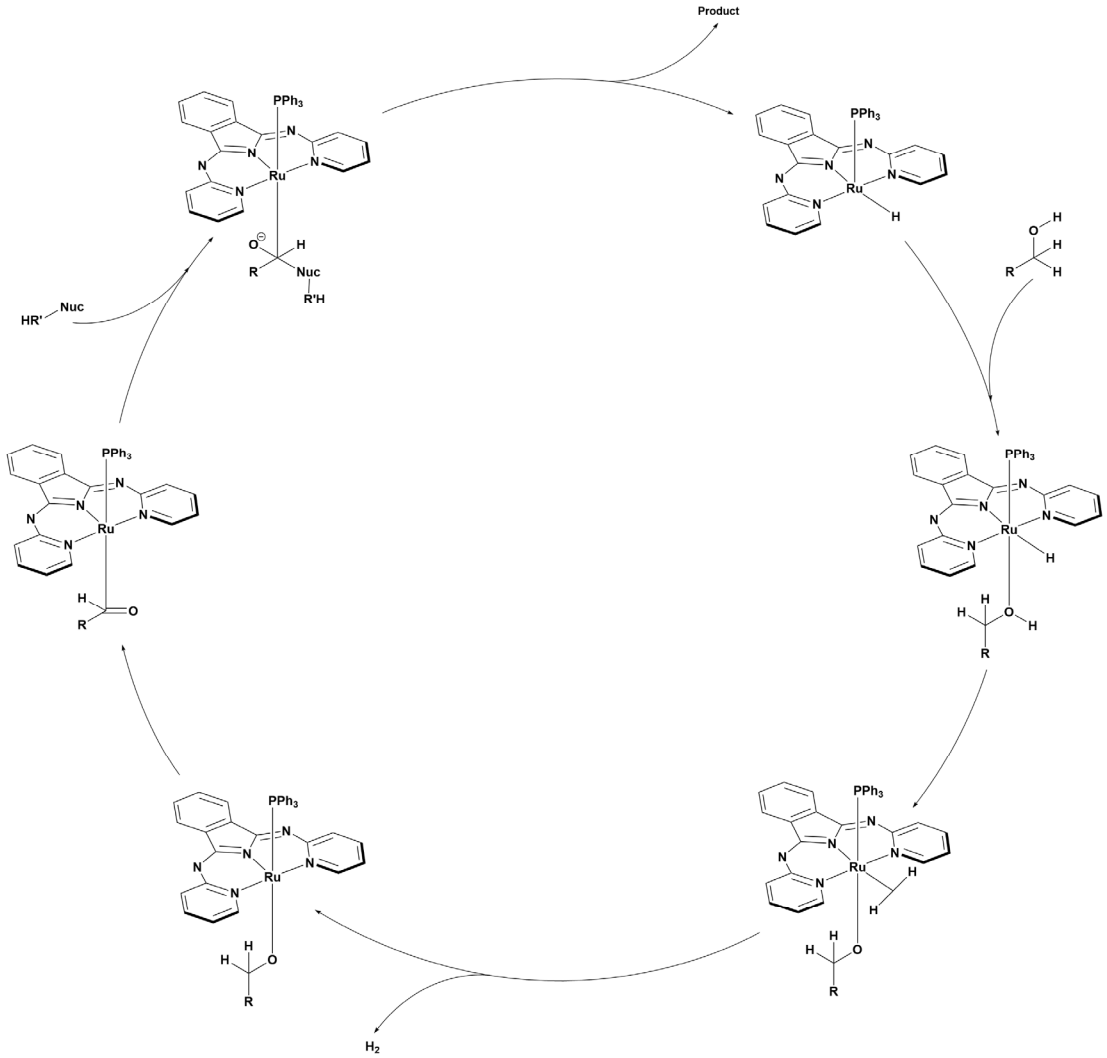
Hexanol has a higher yield than 2-ethyl-1-butanol, which supports our hypothesis as hexanol has a straight-chain structure while 2-ethyl-1-butanol has a branched chain. However, the aromatic alcohols show the opposite trend, where the less sterically hindered benzyl alcohol presented a lower yield than the more sterically hindered methylbenzyl alcohol. Additionally, all of the standard deviations of the three trials averaged together overlap with each other, so no trend exists between steric hindrance and yield. This data refutes our hypothesis that the yield of the product is correlated to the steric bulk of the alcohol substrate. This can be rationalized when inspecting the mechanism through which the reaction is believed to proceed. Because the pincer ligand is 90 degrees from the coordination site that the oxygen binds to, it is likely that the alcohol is not close enough in physical space to the pincer ligand for steric hindrance to have any effect on the alcohol's ability to coordinate.

Percent conversion as well as identification and quantification of side products was analyzed. This data is reported in Table 2.

Table 2. Conversion and Side Product Formation for Esterification of Primary Alcohols

Entry	Alcohol	Average Percent Conversion (n = 3)	Average Percent Yield of Aldehyde Side Product (n = 3)
1	Hexanol	88 ± 10%	N/A
2	2-ethyl-1-butanol	91 ± 4%	N/A
3	Benzyl alcohol	65 ± 30%	5.3 ± 4%
4	2-methylbenzyl alcohol	70 ± 10%	6.3 ± 7%

Specific side products were unable to be identified for hexanol and 2-ethyl-1-butanol due to their complicated spectra contributing to overlapping peaks, but an aldehyde side product was identified in the benzyl alcohol and 2-methylbenzyl alcohol reaction mixtures. This aldehyde formation is supported by the presence of ^{1}H NMR peaks at 10.02 and 10.22 ppm for benzyl alcohol and 2-methylbenzyl alcohol respectively, which is reflected by shifts reported in the SDBS database.[15,16] For these alcohols, the aldehyde side product constituted only a small portion of the overall conversion, which would typically indicate the presence of other many other unidentified side products. However, the ^{1}H NMR spectra corresponding to the reaction mixtures of each alcohol were missing peaks with high enough integrations to compensate for the hydrogens converted from the starting material. This observation can be rationalized when considering the rotary evaporation protocol followed during the experiment. Time constraints forced the need for quick solvent removal, which led to aggressive evaporation of solvent at low pressures, which could have removed a percentage of the primary alcohol. This explanation is further supported by seeing that percent conversion is inversely correlated to boiling point in our data, with benzyl alcohol having the lowest conversion and 2-ethyl-1-butanol having the highest. In the future, the time spent on solvent evaporation should be increased to ensure toluene is the only chemical being removed from the mixture. Because conversion was potentially much lower than we calculated due to this error, we are unable to draw conclusions about the selectivity of either reaction for the intended product.



Scheme 6. General Accepted Mechanism for Dehydrogenation of Alcohols by Ruthenium Catalyst Complex

Although our hypothesis was refuted by the data from the esterification reaction, the Knoevenegal condensation was still investigated. The data for this reaction is presented in Table 3.

Table 3. Yield for Knoevenegal Condensation of Primary Alcohols with Dimethyl Malonate

Entry	Alcohol	Expected Product	Average Yield (n = 3)
1	Hexanol	11	0.89 ± 0.1%
2	2-ethyl-1-butanol	12	2.2 ± 0.1%
3	Benzyl alcohol	13	0.91 ± 1%
4	2-methylbenzyl alcohol	14	0.95 ± 0.4%

The Knoevenegal condensation provided similar results as the preliminary esterification reaction, affording low yields and relatively large standard deviations. Products were identified as outlined previously. We see the opposite trend of what would be expected from our hypothesis for both aliphatic and aromatic alcohols, as the alcohol with the greater degree of steric hindrance provided larger yields. This data again refutes our hypothesis and points to the absence of a relationship between steric hindrance and yield.

Both results corresponding to the aromatic alcohols are within a standard deviation of each other, so no credible conclusion can be made. However, 2-ethyl-1-butanol has a higher percent yield than hexanol with no overlap between the standard deviations. This suggests the relationship predicted by our hypothesis but is discredited by the absence of a relationship in the esterification data and by the overall low yields indicating either an error within the experimental protocol or a poorly optimized reaction. This experimental error could have arisen from the experimental design allowing for the removal of starting material or solvent impurities within the catalyst, which was collected at 120% yield. Additionally, 2-ethyl-1-butanol had a larger yield than either aromatic alcohol, which refutes our hypothesis further because the benzene ring of each aromatic alcohol has a greater contribution to steric bulk than the branched chain of 2-ethyl-1-butanol.

The Knoevenegal condensation reaction generally had a high conversion, but this can be attributed to the same sources of error discussed in the esterification section, as side product formation remained much less than the overall conversion. Data pertaining to percent conversion and side product formation is shown in Table 4.

Table 4. Conversion and Side Product Formation for Koevenegal Condensation of Primary Alcohols with Dimethyl Malonate

Entry	Alcohol	Average Percent Conversion (n = 3)	Average Percent Yield of Ester Side Product (n = 3)
1	Hexanol	86 ± 20%	11 ± 10%
2	2-ethyl-1-butanol	84 ± 4%	4 ± 7%
3	Benzyl alcohol	89 ± 8%	39 ± 30%
4	2-methylbenzyl alcohol	85 ± 4%	32 ± 20%

The primary side product that was able to be identified was the ester product presented in Scheme 3 and that was previously investigated in this work. These ester products are verified by peaks at 3.89, 3.99, 5.08, and 5.29 ppm for hexanol, 2-ethyl-1-butanol, benzyl alcohol, and 2-methylbenzyl alcohol respectively, which are consistent with the shifts of hydrogen A in Scheme 3 found in the SDBS database.[11,12,13] Because overall conversion was high while the percent yield of the side product was relatively low, it is likely that the alcohol was removed during rotary evaporation as well.

Despite the large range associated with the standard deviations of the ester side products, the magnitude of the yield was much greater than in the trials where the ester was the intended product. This can be attributed to the reaction conditions, as two equivalents of potassium tert-butoxide were added in the condensation reaction, as opposed to one equivalent in the original esterification trials. This result supports the proposed mechanism in Scheme 5, which illustrates the dependence of the catalyst activation on the presence of base. However, this result suggests that the esterification is kinetically more favorable than the Knoevenegal condensation due to the disparity between the yield of esters and malonate derivatives in the condensation trials.

Despite low yields seen throughout both reactions, the success of the catalyst can be reinforced by the data collected from our control reactions. For both reactions, a control was run under each of the following conditions with a hexanol substrate: no catalyst, no base, no catalyst or base. The data for these controls is presented in Table 5.

Table 5. Yield of Intended Product for Control Reactions

Reaction	Condition	Average Yield (n = 3)
Esterification	No catalyst	0%
Esterification	No base	0%
Esterification	No catalyst, no base	0%
Condensation	No catalyst	0%
Condensation	No base	0%
Condensation	No catalyst, no base	0%

No yield of any product was collected for any of the control trials. This validates the synthesis of the catalyst, as no product can form without the presence of the catalyst complex. It also verifies the dependence of the mechanism on the presence of a base in solution, which is consistent with Scheme 5, consequently promoting the reactivity shown in Scheme 6.

No other groups within chemistry 482 tested the Knoevenegal condensation. However, we can extrapolate our hypothesis to others' data by investigating the formation of products that proceed through a ruthenium-coordinated transition state similar to our reactions and examining the impact of the steric encumbrance of the substrate on yield.

Group 2 from section 101 investigated the oxidation of secondary alcohols by means of $HRu(bpi)(PPh_3)_2$-facilitated dehydrogenation. Their data is provided in Table 6.

Alcohol	Average Percent Yield (n = 3)
2-hexanol	110 ± 80%
1-phenylethanol	90 ± 20%

Benzhydrol	50 ± 10%

Table 6. Experimental Data – Group 2, Section 101

The data for 2-hexanol falls within a standard deviation of each of the other alcohols, pointing to errors within group 2's experimental procedure, but conclusions can be drawn from the comparison of benzhydrol and 1-phenylethanol. This comparison supports the argument that increasing sterics negatively affects yield, as the less sterically hindered 1-phenylethanol saw a greater yield than the more sterically encumbered benzhydrol. This indicates that there is an inverse relationship between steric bulk and product yield of secondary alcohols that proceed through this mechanism. However, because the alcohols in this study were not primarily substituted, this trend cannot be extended to support our hypothesis. An explanation as to why this trend exists for secondary alcohols and not primary alcohols could be that secondary alcohols have a greater degree of localized steric bulk around the nucleophilic alkoxide that forms, so decreasing the steric hindrance of a secondary alcohol has a much greater effect on coordination efficiency than decreasing the steric hindrance of an already less sterically hindered primary alcohol.

Conclusions

From the data collected in this experiment, we can reject the hypothesis that steric hindrance alone drives overall yield in both the esterification and Knoevenegal condensation of primary alcohol substrates. No trend between steric encumbrance and yield was observed. Multiple sources of error including starting material evaporation and catalyst impurities led to low yields in all data sets despite high conversion of starting material. The disparity between conversion and side product formation points to experimental error and prevents the formation of any conclusions relating to the selectivity of the reaction for the desired product. By examining the collected data, the argument can be made that other factors like nucleophilicity of the alcohol or dipole moment play a role in the overall yield.

Our group was able to verify the formation of malonate derivatives from the Koevenegal condensation of primary alcohol substrate with dimethyl malonate. Additionally, the data we collected relating to ester side product formation in the condensation reaction suggests the kinetic favorability of the esterification over the condensation. The necessity of base and catalyst for formation of product were proved by our controls, and the base-dependent activation of the catalyst was verified, as doubling the amount of base in the reaction increased ester yield.

Future studies should repeat this experiment on a larger scale with extended reaction times. This would ameliorate the issue of low yields while providing greater insight into if a trend exists and would result in more precise data as competency is gained with more exposure to the experimental protocol. Solvent removal time should be greatly increased, as to avoid the removal of starting material, so selectivity of both reactions can be properly assessed. If no trend arises between sterics and yield, secondary alcohols could be investigated, as preliminary data collected by group 2 of section 101 suggests a trend exists between the two.

Acknowledgement

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