Final Progress Report : Green and Effective Continuous Multi-Step Synthesis of Ring-Fused Heteroaromatics

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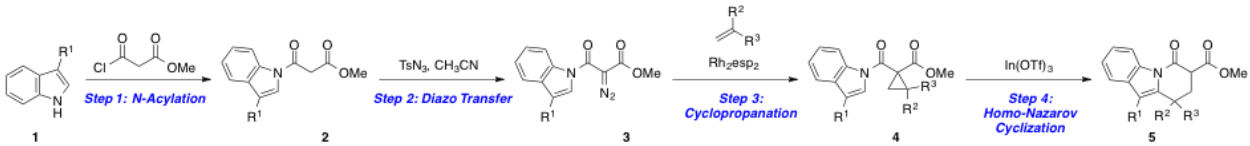
I. Objective:

Develop a new, economic, and environmentally-beneficial multi-step continuous flow protocol for the synthesis of hydropyrido[1,2-*a*]indoles and heteroaryl-fused cyclohexanones via Lewis acid-catalyzed homo-Nazarov cyclization of donor-acceptor cyclopropanes.

II. Abstract:

Historically, batch processing has been the major strategy in the synthesis of complex molecules, especially molecules of pharmaceutical interest. In general, this approach has been fraught with high cost, excessive time for scale-up, and waste issues. In order to address these issues, continuous flow technology has been identified as an alternative production vehicle since it has both environmental and economic advantages. Continuous flow technology offers superior mass and heat transfer, and lower production costs when compared with the traditional batch technology. Technological transfer from batch to continuous flow maximizes performance in terms of product yield and selectivity while minimizing solvent and catalyst needs thereby lowering production costs. In addition, continuous flow processes can be "scaled out" in contrast to batch processes that must be "scaled up." In this research project, we take advantage of continuous flow technology to conduct the multi-step synthesis shown in Scheme 1.



Scheme 1. Multi-step synthesis of the model hydropyrido[1,2-*a*]indole.

III. Summary of Project Aims and Progress:

Aim 1: Optimize Lewis acid-catalyzed heteroaromatic homo-Nazarov cyclization to produce hydropyrido[1,2-a]indole **5** in both batch and continuous flow reactions.

Aim 2: Optimize production of amidoester **2**, diazoester **3**, and cyclopropane **4** in both batch and continuous flow mode.

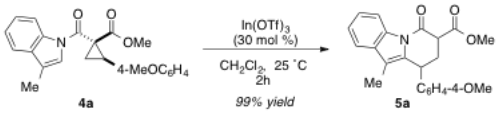
Aim 3: Develop a strategy that enables the multi-step process shown in Scheme 1 to be conducted in continuous flow mode.

Aim 4: Develop a strategy that enables an efficient one-pot tandem cyclopropanation/homo-Nazarov cyclization reaction (**NEW AIM**)

IV. Results:

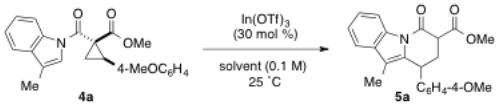
Aim 1: Optimize Lewis acid-catalyzed heteroaromatic homo-Nazarov cyclization to produce hydropyrido[1,2-*a*]indole **5** in both batch and continuous flow reactions.

A. Batch Optimization:



(1)

Inspired by the literature procedure reported by France and coworkers,[1] cyclopropane **4a** was chosen as the model system for the batch optimization studies based on its efficient conversion to hydropyrido[1,2-*a*]indole 5a in >99% yield in dichloromethane in the presence of 30 mol % $In(OTf)_3$ in under 2 h (eq 1). Cyclopropane **4a** was synthesized on a large scale (55 g) and subsequently used for reaction optimization in terms of solvent and catalyst loading (Tables 1 and 2). All experiments were carried out in oven-dried glassware under N_2 atmosphere and care was taken to keep moisture out of the reaction vessel. Cyclopropane **4a** and indium (III) trifluoromethanesulfonate ($In(OTf)_3$, 0.5 to 30 mol%) in a given solvent were stirred at the indicated temperature. The reactions were monitored by thin layer chromatography (TLC) every 15 minutes until the starting material could no longer be detected. The reaction was then quenched with 1.0 mL of water and the ^{1}H-NMR acquired. The conversion of the cyclopropane **4a** was calculated from the crude reaction mixture using ^{1}H-NMR. The ratio of the 3-methylindole peak of the hydropyrido[1,2-a]indole **5a** (1.70 and 1.94 ppm in Figure 2, as diastereomers) to the 3-methylindole peak of the cyclopropane **4a** in the crude reaction mixture was used as an approximate measure of conversion. This standard batch procedure, analysis, and calculation of the conversion remained consistent during the investigations to optimize solvent and catalyst loadings. Given that the original reaction was complete with 15 min, we were determined to maintain that time marker in the transfer from batch to flow. **Thus, in all experiments, the reactions that were the deemed most successful, were ones that gave complete conversion within a 15 min timeframe**. This context is central to understanding the decisions made throughout the optimization studies.



entry	solvent	time[b]
1	DCM	15 min
2	THF	12 h
3	MTBE	9 h
4	MeOH	--[c]
5	iPrOH	--[c]
6	**CH_3CN**	**15 min**
7	$PhCH_3$	15 min
8	Acetone	30 min
9	EtOAc	15-30 min

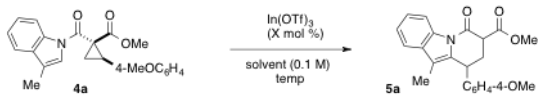
[a] Reactions were run with **4a** and $In(OTf)_3$ in the indicated solvent (0.1 M). [b] Time at which full conversion is observed by crude ^{1}H-NMR. [c] No reaction observed after 24 h.

Table 1. Solvent Optimization

The solvent study for the homo-Nazarov cyclization step was accomplished utilizing the different pharmaceutically- and/or industrially-suitable solvents listed in Table 1. Solvents such as acetonitrile (CH_3CN, entry 6), toluene ($PhCH_3$, entry 7), acetone, and ethyl acetate (EtOAc, entry 9) gave conversions comparable to those observed in dichloromethane (DCM, entry 1). Solvents containing an ether moiety, such as tetrahydrofuran (THF, entry 2) or methyl *tert*-butyl ether (MTBE, entry 3), were excluded from further studies due to long reaction times even when

high catalyst loadings were used. Alcohols (entries 4 and 5) were also excluded because no reaction was observed in these solvents within a 24 hour time frame. This lack of reactivity could be attributed to the insolubility of both the $In(OTf)_3$ and cyclopropane **4a** as well as a potential interaction between the solvent and Lewis acid. Based upon these results, an effort was made to optimize reaction temperature and catalyst loadings in the optimal solvents of CH_3CN, EtOAc and toluene.

Next, various reaction temperatures and catalyst loadings in CH_3CN, EtOAc and toluene were explored in an effort to optimize the reaction (Table 2). At room temperature in CH_3CN, the catalyst loading could be readily reduced to 10 or 5 mol % to give full conversion within 15 min (entries 1 and 2). At 1 or 0.5 mol % loadings, full conversion was not achieved within the 15 min window (entries 3 and 4). Similarly, heating the reaction with 1 mol % catalyst at 80 ˚C failed to give full conversion within 15 min (entry 5). In comparison, EtOAc resulted in higher reaction times at higher loadings (entries 6-9). Toluene also failed to provide good conversions as compared to CH_3CN (entry 10). Thus, for **4a**, the **optimized batch conditions selected for technology transfer to continuous flow were 5 mol % $In(OTf)_3$ in CH_3CN (0.1 M) at room temperature for ~15 min**.



entry	catalyst loading (mol %)	solvent	temperature (˚C)	time	conversion[b] (%)
1	10	CH_3CN	20	15 min	100
2	**5**	**CH_3CN**	**20**	**15 min**	**100**
3	1	CH_3CN	20	20-30 min	95
4	0.5	CH_3CN	20	18 h	90
5	1	CH_3CN	80	15 min	95
6	10	EtOAc	20	12 h	90
7	5	EtOAc	20	24 h	<10[b]
8	10	EtOAc	77	20-30 min	100
9	5	EtOAc	77	30-40 min	95
10	5	$PhCH_3$	20	18 h	95

[a] Reactions were run with X and $In(OTf)_3$. [b]Reaction stopped at 24 h.

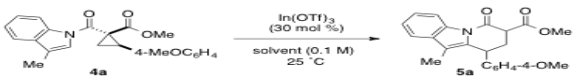
Table 2. Catalyst Loading Optimization

With a working substrate in hand, we were interested in exploring the generality of the optimized conditions for other cyclopropane substrates that would ultimately be amenable to flow conditions. Cyclopropanes **4b**-**4d** were prepared and examined for compatibility (Figure 1). Cyclopropane **4b** contains different functionality on the indole moiety at the 3-position as compared to **4a** (methyl acetate vs methyl). **4c** (derived from alpha-methyl styrene) contains two geminal donor groups on the cyclopropane. The product from this substrate would contain a quaternary center. Finally, **4d** replaces the 4-methoxy phenyl group with a 2-furyl moiety.

Figure 1. Expanding scope of optimized reaction

According to previous work carried out by the France lab, cyclopropane **4b** cyclizes in the presence of 30 mol% $In(OTf)_3$ in dichloromethane (DCM) to give **5b** in a 88% yield after 3 h.[1] In order to make this transformation pharmaceutically attractive and amenable to flow, we

explored the use of the CH_3CN and toluene as solvents for the reaction (Table 3). CH_3CN worked very well whereas toluene (entry 5) did not work within the desired timeframe. Gratifyingly, the same optimized conditions worked for **4b** as did for **4a** (entry 2). **Using 5 mol % $In(OTf)_3$ in CH_3CN at room temp, a 90% yield of hydropyrido[1,2-*a*]indole 5b was obtained**.

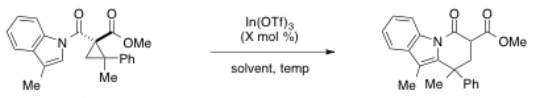


entry	solvent	time[b]
1	DCM	15 min
2	THF	12 h
3	MTBE	9 h
4	MeOH	---[c]
5	iPrOH	---[c]
6	**CH_3CN**	**15 min**
7	$PhCH_3$	15 min
8	Acetone	30 min
9	EtOAc	15-30 min

[a] Reactions were run with **4a** and $In(OTf)_3$ in the indicated solvent (0.1 M). [b] Time at which full conversion is observed by crude ^{1}H-NMR. [c] No reaction observed after 24 h.

Table 3. Batch optimization of cyclopropane **4b**.

Cyclopropane **4c** has been previously shown to provide its product **5c** in 94% yield after in 2 h when using 30 mol % $In(OTf)_3$ in DCM. To make 4c amenable to flow, we looked to optimization the formation of hydroprido[1,2-a]indole **5c** in CH_3CN or toluene (Table 4). At a cyclopropane concentration of 0.2 M and a catalyst loading of 5 mol%, the reaction was slow and failed to reach >50% conversion even after 3 h in CH_3CN (entry 1). In toluene, the reaction did not proceed at all after 30 h (entry 2). Therefore, only CH_3CN was used in further studies. Increases in both reaction concentration and catalyst loading led to increased yields, with the highest yield (67.2%) obtained at a concentration of **4b** of 1.0 M with a catalyst loading of 15 mol% after 2.5 h (entry 8). Interestingly, when the reaction was quenched at 20 minutes, a 62.9 % yield was obtained which is comparable to the 2.5 h reaction under the same reaction conditions (entry 7). The reason for this is due to the formation of a side product (observed by TLC) as the reaction progressed past the 1 h mark. Isolation and identification of the side products are ongoing. Given concerns about the potential for product precipitation at high concentrations (>0.5 M), we focused our efforts on a concentration of 0.1 M. We anticipated that an increase in temperature could help the overall reactivity. Given that 15 mol % loading of $In(OTf)_3$ gave a good yield at room temp, we heated **4c** at 50 ˚C with the same loading but at a concentration of 0.1 M (entry 10). We were pleased to find that **product 5c was obtained in quantitative yield after 15 min**.

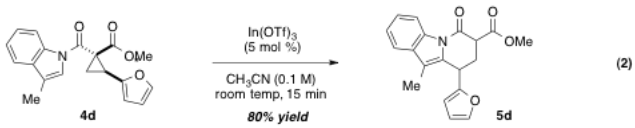


entry[a]	catalyst loading (mol %)	solvent	Concentration (M)	T (°C)	time (min)	yield (%)[b]
1	5	CH_3CN	0.2	23	>120	...[c]
2	5	$PhCH_3$	0.2	23	>>120	...[d]
3	10	CH_3CN	0.2	23	15	24
4	10	CH_3CN	0.2	23	20	32
5	15	CH_3CN	0.2	23	20	46
6	15	CH_3CN	0.5	23	20	42
7	15	CH_3CN	1.0	23	20	63
8	15	CH_3CN	1.0	23	150	67
9	30	CH_3CN	0.1	23	20	44
10	**15**	**CH_3CN**	**0.1**	**50**	**10**	**>99**

[a] Reactions were run with **4c** and $In(OTf)_3$ according to the conditions above. [b] Isolated yield after column chromatography. [c] Product not isolated. [d] No reaction observed.

Table 4. Batch optimization of cyclopropane **4c.**

Finally, the optimization of cyclopropane **4d** required minimal effort as **4d** readily gave **5d** in 80% isolated yield in 10-15 min using the same conditions (5 mol % $In(OTf)_3$, CH_3CN (0.1 M)), that worked for **4a** and **4b** (eq 2). With four optimized substrates in hand, we next focused our efforts on the transfer from batch to continuous flow. We synthesized ~15-30 g of each cyclopropane.



(2)

B. Flow Optimization:

A simple plug flow reactor was used to conduct homo-Nazarov cyclizations at batch-optimized conditions (Figure 2). Two Eldex series 2000 ReciPro reciprocating pumps feed stock solutions of desired cyclopropane **4** and indium triflate catalyst. The solutions mix and begin reacting at a 1/16" tee-joint where they proceed into the reactor tract. The system pressure and temperature are measured prior to entering the main body of the reactor. The main body of the reactor consists of a coil of ¼" stainless steel tubing extending for a final reaction volume of 29.5 mL. The reactor is heated (when necessary) with heating tape controlled by a Eutech Instruments Digi-Sense temperature controller. The reactor effluent temperature is measured before emptying into a collection flask for analysis.

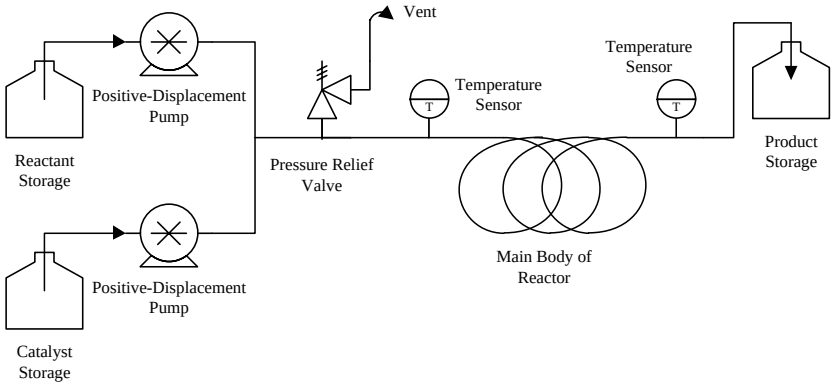


Figure 2. Schematic of the continuous flow reactor.

The homo-Nazarov cyclizations were performed as follows: a 0.2 M solution of cyclopropane in acetonitrile was mixed with a 0.01 M solution of $In(OTf)_3$ in acetonitrile. Each reciprocating pump was set to 0.984 mL/min in order to yield a total flow rate 1.968 mL/min and a residence time of 15 minutes. The resulting reaction stream composition was 0.1 M in cyclopropane and 0.005 M indium triflate. The composition and flow rates were chosen to directly mimic conditions and reaction time of batch reactions. Samples were taken at residence time intervals (~every 15 min) to establish equilibrium composition and yield. Reactor effluent was collected with water in order to quench further reaction. Samples were extracted with dichloromethane, washed with water and evaporated to dryness with a rotary evaporator. Yield was calculated by weighing solid residue and performing ^{1}H-NMR analysis using a Bruker 400 MHz NMR spectrometer.

The results of a number of continuous homo-Nazarov cyclization experiments are shown below in Figure 3. The first continuous flow reaction was performed with cyclopropane **4a** at ambient temperatures (~18°C) and reached full conversion to **5a** (i.e., no starting material was detected by HPLC nor by NMR) after one residence time (~15 minutes). Two or three additional samples were collected from the reactor at residence times two (30 min), three (45 min), and four (60 min). Initial concentrations of cyclopropane **4a** and $In(OTf)_3$ upon mixing were 0.1 M and 0.005 M, respectively. The lactam **5a** was isolated (extracted twice into dichloromethane, washed twice with water, dried over $MgSO_4$, and solvent removed by rotary evaporation) and was found to have **yields of 82%, 99%, 99% and 99%** at residence times one, two, three and four, respectively.

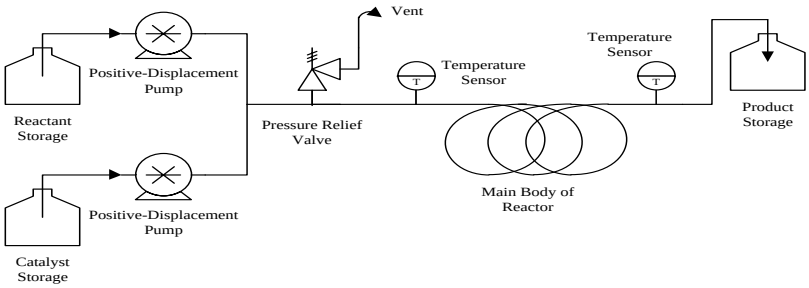
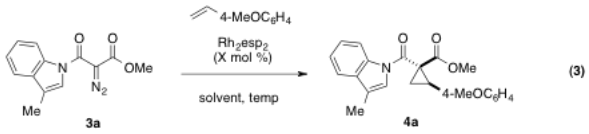


Figure 3. Continuous flow results for products **5a**-**5d**.

Cyclopropanes **4b** and **4d** similarly transferred well to the continuous flow reactor at room temperature and achieved near-quantitative yield within two residence times (Figure 3). **4b** provided its product **5b** in 66%, 96%, 96%, and 95% yields at residence times one, two, three and four, respectively. 76%, 98%, 93% and 91% yields were obtained for hydropyrido[1,2-*a*]indole **5d** at the respective four residence times. In contrast, the methyl-phenyl cyclopropane **4c** reached an equilibrium yield of ~26% within two residence times at room temperature. This result matches well with the batch result given that full conversion within 15 min is not achieved. Inspired by the batch optimization study, we ran the flow reactor while heating the system to 50 ˚C. We were pleased to find that the yields dramatically increased to near-quantitative yields (65%, 94%, and 93% yields for residence times one, two and three, respectively) by raising the temperature.

With the successful batch to flow transfer of four representative homo-Nazarov substrates, we have successfully completed Aim 1. Building upon this success, we have subsequently started a series of experiments aimed at addressing the goals of Aim 2.

Aim 2: Optimize production of amidoester **2**, diazoester **3**, and cyclopropane **4** in both batch and continuous flow mode.

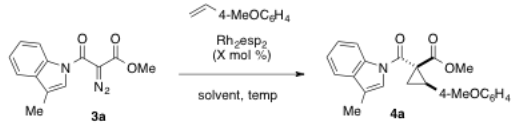


(3)

*Optimize production of cyclopropane **4** in both batch and continuous flow mode*. With a working homo-Nazarov cyclization (Step 4), we next decided to work on the batch optimization of the cyclopropanation reaction (Step 3, eq 3). Following the procedure reported by France and coworkers,[1] large scale batch reactions were performed to synthesize 20 g of diazoester **3a.** The cyclopropanation reaction to form **4a** was optimized for batch operation prior to the transfer to continuous operation. All reactions were carried out under anhydrous conditions. 0.1 mol% of bis[rhodium(α,α,α′,α′-tetramethyl-1,3-benzenedipropionic acid)] ($Rh_2(esp)_2$) was dissolved in solvent and then 4-vinylanisole (1.0 equiv) was added to the solution. Next, diazoester **3a** (1.1 equiv) was added to the reaction mixture and allowed to stir at ambient temperature. The reactions were monitored via TLC every 5 minutes until the starting material could no longer be detected. The original protocol calls for dichloromethane as the solvent; however, as we proposed to move away from chlorinated solvents and optimize a multi-step continuous synthesis, we optimized the reaction conditions with acetonitrile and toluene as solvents (EtOAc was not examined due to the undesired reactivity between ethyl acetate and the putative carbenoid species).

In anticipation of the development of a multistep synthesis in flow, we focused our studies on obtaining a final reaction concentration of 0.2 M, which direcly matches with the 0.2 M cyclopropane solution that was employed for the optimized continuous flow homo-Nazarov cyclizations. This study investigated both the solvent employed in the reaction (acetonitrile vs. toluene) as well as the catalyst loading. The results are ~~as~~ summarized in Table 5. At loadings of

0.1, 0.5 and 1.0 mol % Rh_2esp_2, the reactions in acetonitrile at 23 °C require more than 2 hours to achieve completion (entries 1-3). Just as a marker point, the reaction at 1 mol % in CH_3CN was quantified after it reached completion. An 82% yield of cyclopropane **4a** was observed (entry 3). An increase in the reaction rate was observed when the reaction was heated to 50 °C and the reaction reached completion in ~15 min (entry 4). The product **4a** was observed in 73% yield. Raising the temperature to reflux (~82 ˚C) further increased the reaciton rates and allowed for lowered catalyst loadings (entries 5-7). Toluene was also tested as a reaction solvent. The observed rates were faster as compared to acetonitrile at 23 °C.



entry[a]	catalyst loading (mol %)	solvent	temperature (˚C)	time	conversion (%)	yield (%)[b]
1	0.1	CH_3CN	23	>24 h	40-50	--[c]
2	0.5	CH_3CN	23	>2 h	90-95	--[c]
3	1.0	CH_3CN	23	>2 h	100	82
4	1.0	CH_3CN	50	15 min	100	73
5	0.1	CH_3CN	82	15-20 min	90	--[c]
6	0.5	CH_3CN	82	< 5 min	100	--[c]
7	1.0	CH_3CN	82	< 5 min	100	77
8	0.1	$PhCH_3$	23	15-20 min	100	--[c]
9	0.5	$PhCH_3$	23	< 5 min	100	--[c]
10	1.0	$PhCH_3$	23	< 5 min	100	86

[a] Reactions were run with **3a** and Rh_2eps_2 in indicated conditions. [b] Isolated yield after column chromatography. [c] Product not isolated

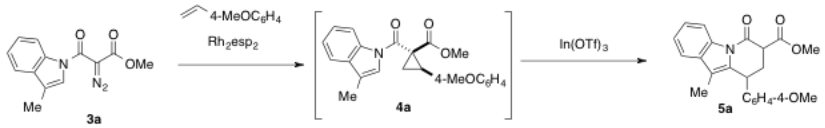
Table 5. Solvent and catalyst loading study for the rhodium(II)-catalyzed cyclopropanation.

In summary, we have **successfully optimized the batch mode Rh(II)-catalyzed cylopropanation** reaction to perform efficienty in two greener solvents as compared to DCM. The reaction in CH_3CN was designed to be completely compatible with the optimized homo-Nazarov cyclization. Our next major endeavor is to run the cyclopropanation in flow and, once successful, perform the tandem cyclopropanation/homo-Nazarov cyclization in flow.

***Flow Optimization*:**

Given the results from the cyclopropanation studies, we are preparing to transfer the technology from batch to continuous flow. We have already synthesized ~25 g of diazo compound **3a**. We are currently planning to perform two separate continuous flow reaction conditions (Scheme 2). The first flow reaction will be performed with **3a** (1.1 equiv), 4-methoxystyrene (1.0 equiv) and Rh_2esp_2 (1.0 mol %) in CH_3CN (0.2 M) at 50 ˚C. The second flow reaction will be performed with **3a** (1.1 equiv), 4-methoxystyrene (1.0 equiv) and Rh_2esp_2 (0.1 mol %) in toluene (0.2 M) at room temperature.

Aim 3: Develop a strategy that enables the multi-step process shown in Scheme 1 to be conducted in continuous flow mode.



Scheme 2. Tandem cyclopropanation/homo-Nazarov cyclization protocol

The batch cyclopropanation procedure (Step 3) makes use of a rhodium(II) catalyst which is typically quenched with saturated thiourea. Translating this quenching procedure to the continuous flow reactor would add an additional complicated separation. For this reason, we began exploring a tandem batch protocol in which the homo-Nazarov cyclization is performed immediately after the cyclopropanation without quenching or removing the rhodium catalyst (Scheme 2). The choice of conditions was totally based on the outcomes of the optimization reaction for the individual cyclopropanation and homo-Nazarov cyclization steps. In this protocol, the cyclopropanation reaction was set up and outlined in the previous section. Next, $In(OTf)_3$ (5 mol %) was added to the reaction mixture once the diazoester was completely consumed (as determined by TLC monitoring every 5 minutes). Table 6 summarizes the preliminary data for the tandem protocol.

Solvent	Cyclopropanation Conditions[a]	Time[b]	Cyclization Conditions[c]	Time[d]	Yield[e] (%)
CH_3CN	82°C, 0.5 mol%	≤5 min	23°C, 5 mol%	1 hr	42.6
CH_3CN	50°C, 0.5 mol%	40 min	50°C, 5 mol%	10 min	65.0
$PhCH_3$	23°C, 0.5 mol%	≤5 min	23°C, 5 mol%	>1 hr	64.1

Table 6. Tandem protocol for the synthesis of the model heteroaryl-fused cyclohexanone starting from the diazoester compound **3**. [a]Temperature and loading of $Rh_2(esp)_2$, [b]Time for complete consumption of diazoester **3**, [c]Temperature and loading of $In(OTf)_3$, [d]Time for complete consumption of cyclopropane **4,** [e]Isolated yield.

When the cyclopropanation was performed in CH_3CN at 82 °C, the diazo compound was completely consumed in less than 5 minutes. The reaction mixture was cooled to 23 °C and $In(OTf)_3$ was added to the reaction. Complete consumption of the cyclopropane was observed after 1 hour and the product was isolated in 43% yield. The tandem reaction protocol was then performed at 50 °C (without cooling between reaction steps) in order to decrease the reaction time for the homo-Nazarov cyclization. The cyclopropanation took 40 minutes to reach completion and the cyclization step took 10 minutes (isolated hydropyrido[1,2-*a*]indole **5a** yield of 65%). The next planned reaction involves the use of 1 mol % of Rh_2esp_2 under similar reaction conditions (50 ˚C for both steps). We anticipate that these conditions will provide enable both steps to be individually complete within 15 min. Toluene was also used for the tandem protocol since the cyclopropanation requires shorter reaction times and lower loading of the catalyst in toluene. When the $In(OTf)_3$ was added to the reaction (once the diazo was completely consumed) the cyclization reaction took more than one hour for full completion (isolated yield of 64% for **5a**). Homo-Nazarov reactions at higher temperatures are underway in order to obtain a reasonable reaction time for the second step.

Aim 4: Develop a strategy that enables an efficient one-pot tandem cyclopropanation/homo-Nazarov cyclization reaction via cooperative catalysis

Based on the overwhelming successes of the batch optimization studies for the cyclopropanation and homo-Nazarov cyclization steps, we envisioned the development of a one pot, tandem reaction that would take advantage of cooperative catalysis. In sequential cooperative catalysis,[2] two catalysts, both present at the onset of the reaction, work in unison along a cascade pathway to generate a desired product (Figure 4). One catalyst promotes the formation of an intermediate and the second catalyst promotes the reaction of the intermediate into the product.

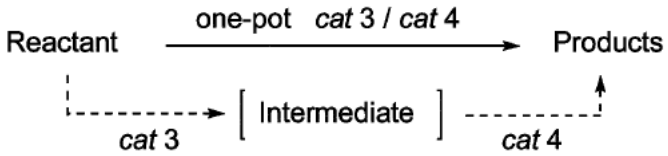
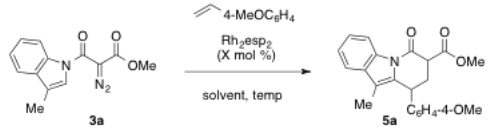


Figure 4. Sequential Cooperative Catalysis

The France group has previously reported an example of such a reaction for the heteroaromatic homo-Nazarov cyclization.[3] However, only one or two examples provided results superior to the tandem or step-wise processes. This type of catalysis has not been applied to the N-acyl cyclopropane systems for homo-Nazarov reactions. We sought to explore the possibility for this reactivity based on the extensive optimization data that was generated (Table 7). The first conditions that were examined utilized CH_3CN as the solvent. With an eye ultimately on flow, we sought reactions that could be completed within a short time frame (<30 min). When diazo ester **3a** (1.1 equiv) in a solution of CH_3CN was added to a solution of 4-methoxystyrene (1.0 equiv), Rh_2esp_2 (1.0 mol %) and $In(OTf)_3$ (5 mol %), the reaction provided very low conversion to the desired products within 2-3 h. Various byproducts were observed for the reaction. We assume these byproducts are a combination of degradation/unwanted reaction of the carbenoid species and polymerization of the alkene. Adding credence to this hypothesis, when the reaction was heated to 50˚C, only degration products were observed. Regardless of whether the stoichiometries of the various compenents were changed, only low conversion (<30%) of product **5a** were observed.



entry[a]	Rh_2esp_2 (mol %)	$In(OTf)_3$ (mol %)	solvent	Conc. (M)	temperature (˚C)	time	yield (%)[b]
1	1.0	5.0	CH_3CN	0.2	23	2-3 h	--[c]
2	1.0	5.0	CH_3CN	0.2	50	15-20 min	--[d]
3	1.0	1.0	CH_3CN	0.2	50	20-30 min	--[d]
4	0.1	5.0	$PhCH_3$	0.2	23	15-20 min	28
5	0.2	5.0	$PhCH_3$	0.2	23	15-20 min	trace
6	0.1	10.0	$PhCH_3$	0.2	23	10-15 min	trace
7	0.05	2.5	$PhCH_3$	0.2	23	> 2 h	trace
8	0.1	2.5	$PhCH_3$	0.2	23	1 h	trace
9	0.1	5.0	$PhCH_3$	0.1	23	15 min	75 (71)[e]

[a] Reactions were run with **3a** and Rh_2eps_2 in indicated conditions [b] Isolated yield after column chromatography. [c] Product not isolated [d] Only degration products observed. [e] Number in parentheses represents the yield of a duplicate reaction.

Table 7. Sequential cooperative catalysis study for formation of **5a**

In contrast to CH_3CN, when toluene was employed as the solvent, some interesting results were obtained (entries 4-9). When the 0.1 mol % Rh_2esp_2 and 5.0 mol % $In(OTf)_3$ was employed in toluene at a concentration of 0.2 M, hydropyrido[1,2-*a*]indole **5a** was obtained in 28% yield (~52% yield/step) (entry 4). Changes to the loadings of rhodiumn or indium failed to provide any tangible amounts of product (5-8). Interestingly, when the concentration was changed to 0.1 M while keeping the rhodium and indium loadings the same in entry 4 (0.1 mol % Rh_2esp_2, 5.0 mol % $In(OTf)_3$), the desired product **5a** was obtained in 75% yield (~87% yield/step) (entry 9). When the reaction was repeated a second time, a 71% yield of **5a** was obtained, thus confirming the validity and consistency of the protocol. Thus, we have **laid the groundwork for the development of one pot cyclopropanation/homo-Nazarov cyclizations of alpha-diazoesters via sequential cooperative catalysis**. Although this result is highly encouraging in batch, there is a major limitation to the transfer to flow. For the optimized reaction conditions, $In(OTf)_3$ is not fully solubilized in toluene at the 0.1 M concentration. This poses a major problem/challenge for continuous flow due to the inability of most pumps to handle heterogeneous solutions. This is something that will be addressed by examining other more soluble In complexes or other soluble Lewis acid catalysts.

IV. <u>Future Directions</u>:

A. Homo-Nazarov Cyclization

With the homo-Nazarov cyclization reaction optimized and the continuous flow reaction demonstrated to be a viable method, additional continuous flow experiments will be performed to further investigate catalyst loadings, flow rates, and temperature effects. These additional reactions will provide significant amounts of kinetic information that will be used to aid process development of the continuous technology

B. Diazo Transfer and Cyclopropanation

The cyclopropanation reaction will be further investigated in order to optimize the reaction as well as the tandem protocol that will enable the facile transfer to continuous technology. The continuous flow reactor will be modified to allow for additional reaction steps by including additional pumps, safety measures, temperature sensors, heating capabilities, and sampling points. The cyclopropanation and tandem protocol (cyclopropanation + homo-Nazarov) will then be demonstrated respectively using the modified continuous flow reactor.

C. Sequential Cooperative Catalysis

The one pot reaction will be expanded in order to understand the scope and limitations of the protocol. Further optimization for other diazo substrates will be pursued.

V. Expected Outcomes (Publications)

I. We are currently in the process of preparing a manuscript for submission describing the batch to continuous flow transfer for both the cyclopropanation and the homo-Nazarov cyclization. **The manuscript will be submitted to Organic Letters before the end of Feb 2014**.

II. We plan to expand the substrate scope of the sequential dual catalytic one pot protocol. Once completed, **the manuscript will be submitted to the Journal of the American Chemical Society within the next two months**.

VI. <u>References</u>:

1. Patil, D. V.; Cavitt, M. A.; Grzybowski, P.; France, S. *Chem. Comm.*, **2011**, *47*, 10278.
2. Lee, J. M.; Na, Y.; Han, H.; Chang, S. *Chem. Soc. Rev*. **2004**, *33*, 302.
3. Phun, L. H.; Patil, D. V.; Cavitt, M. A. *Org. Lett*. **2011**, *13*, 1952.