**Integrating membrane separation with gold-catalyzed carboxylative cyclization of propargylamine and catalyst recovery via organic solvent nanofiltration**

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**ABSTRACT**

**Background**: Transition metal catalysis has, over recent decades, developed into one of the most important methods of constructing molecules. However, although efficient in the construction of complex molecules, these catalysts can be expensive as they are often based upon second and third row transition metals which have, for the most part, low terrestrial abundance. Present removal and recovery techniques of homogeneous catalysts tend, at best, to focus on recovering the metal center and to consider ligands as single use components. Whereas recovery of the whole catalyst would be more beneficial from an economic and environmental point of view.

**Results**: The integration of a membrane separation protocol with gold-catalyzed carboxylative cyclization of propargylamine (**PPA**) was investigated. Filtration conditions were identified in membrane screening experiments with the dinuclear catalyst [Au2Cl2(L)] **Au-1** and the mononuclear catalyst [Au(IPr)Cl] **Au-2**. Recovery of the whole catalyst was then investigated. Catalyst **Au-1** proved unstable and led to metal recovery for reprocessing upon completion of the process. However, the membrane methodology does allow recovery of the catalyst within the reaction mixture which increases its efficiency. On the other hand, catalyst **Au-2** proved more stable and can be recovered along with its ancillary ligands.

**Conclusion**: For both catalysts a membrane-based recovery protocol was successfully demonstrated. This protocol was either internal or external in that the Au complex along with its ligands can be recovered after reaction. This initial work shows the possibility that ligands do not always need to be considered as single use components.

The integration of a membrane separation protocol with gold-catalyzed carboxylative cyclization of propargylamine (**PPA**) was investigated. Filtration conditions were identified in membrane screening experiments with the dinuclear catalyst [Au2Cl2(L)] **Au-1** and the mononuclear catalyst [Au(IPr)Cl] **Au-2**. Catalyst **Au-1** proved unstable and led to metal recovery for reprocessing. On the other hand, catalyst **Au-2** proved more stable and was recovered in 50% yield without the need for any further treatment.

**Keywords:** OSN-homogenous catalysis-dinuclear gold catalyst-mononuclear gold catalyst-PPA-catalyst recovery-metal recovery

**INTRODUCTION**

Transition metal catalysis has, over recent decades, developed into one of the most important methods of constructing molecules; with the use of these catalysts ranging from research lab level up to large scale industrial applications.1-8 However, although efficient in the construction of complex molecules, these catalysts can be expensive as they are often based upon second and third row transition metals which have, for the most part, low terrestrial abundance.9, 10 Removal and recovery of the metals from reaction products has become important not only from a product purity point of view but also both economically and environmentally. This is especially the case with large scale industrial use.11,12 The use of heterogeneous catalysts can mitigate this problem as they are easily removed by filtration; however, this can lead to catalysts of lower efficiency at even greater cost. Alternatively, some of the issues associated with heterogeneous catalysts can be resolved by using their homogeneous equivalents.13-18 Removal of homogeneous catalysts or their degradation residues is however more complex. Therefore, efficient separation methods of homogeneous transition metal catalysts from reaction products is of fundamental importance.19, 20 Whereas there are several techniques that can efficiently remove and recover metals, the ligands in contrast, are often considered single use components. Ligands have a significant effect on the reaction outcome, but more importantly they largely contribute to cost and environmental impact of the catalyst, as a whole. If the complete catalyst, ligand and metal, can be recovered intact or at least reused continuously, it could facilitate the widespread application of that catalyzed synthetic route on larger scale. Such catalyst recovery/utilization can only be achieved if the catalyst itself is sufficiently stable. Notable examples of such catalysts are metal complexes bearing N-heterocyclic carbene (NHC) ligands. The strength of the metal-carbene bond has been repeatedly shown to be responsible for increasing the thermal and oxidative stability of NHC-based catalysts.21-24 Within the framework of our research directed towards N-heterocyclic gold complexes and their use in combination with membranes, we recently demonstrated that it was possible to recover the gold complex [Au(IPr)Cl] in moderate 44% yield at the end of another membrane integrated gold-catalyzed reaction.25 It should be noted that the recovered complex was not the initial catalyst added to the reaction; the starting catalyst being[Au(OTf)(IPr)]. It is however, the direct precursor of the latter as well as other gold(I)-NHC complexes bearing a variety of counterions. Furthermore, the [Au(Cl)(IPr)] complex that was isolated can itself be used as a catalyst. Indeed, gold complexes of this type have previously been used in other CO2-based transformations.26, 27

In the current report, we aimed to further investigate membrane integration and catalyst recovery in the carboxylative cyclization of propargylamine (PPA). To achieve catalyst recovery, efficient separation from the reaction product as well as stable and efficient catalysts are required.

***Process parameters measured in membrane filtration***

Process parameters can be defined in the context of membrane technology. Flux, permeability and retention are the ones most used in this report.

The flux, J, is an expression for the amount of volume (V) of a liquid feed that moves through a membrane surface area (A) at a certain pressure per unit of time (t), it is expressed as L. m−2. h−1. The equation can be found in equation 1.

$J=\frac{V}{At}$ (1)

Permeance is another parameter for the characterization of flow through a membrane. Flux does not take into account the pressure (P) used in a filtration system, whereas permeance does. The parameter is calculated according to equation 2. It is expressed in terms of L. m−2. h−1. bar−1 .

$ Permeance=\frac{J}{P}$ (2)

Another important aspect to consider upon performing OSN is the rejection profile of all reaction species. Membrane rejection is a function of the solute concentrations in the permeate Cp, and retentate Cr and is expressed as a percentage, see equation 3.

$R=\left(1-\frac{C\_{p}}{C\_{r}}\right)x 100$ (3)

where R is the rejection, Cp is the concentration of the solute in the permeate and Cr is the concentration of the solute in the retentate.

**MATERIALS AND METHODS**

**General information**

The solvents used in this study were methanol, ethanol, tetrahydrofuran (THF) and 2-methyltetrahydrofuran (Me-THF), all of technical grade purchased from VWR (Belgium) and used without prior purification. Commercially available membranes selected for this study were polymeric membranes with Borsig *oNF-1*, Borsig *oNF-2,* Borsig *oNF-3* purchased from (Borsig GmbH, Germany), Puramem selective Puramem 280 and Puramem performance from Evonik MET Ltd. (London, UK). All membrane experiments were performed in a cross-flow filtration unit made in-house, pressurized with nitrogen gas. Filtration experiments were performed with crossflow velocity of 0.3 m/s for polymeric membranes with a transmembrane pressure of 20 bar. Prior to use preconditioning of the membranes based on the manufactures recommendations was carried out. To this end the volume of solvent equivalent to 50L/m2 of membrane surface was permeated through the membrane, to simply ensure they were free of any residue remaining from the membrane preparation.

Samples of the carboxylation cyclization of propargylamine reaction were analyzed on a waters UPLC with a UV/Vis PDA detector. A Waters Acquity BEH C18 column with dimensions of 2.1 x 50 mm, 1.7µm and a gradient of water, acetonitrile buffered with 4mM ammonium acetate. The column temperature was 40°C and the detector was used at a wavelengths of 280 and 243 nm.

Analysis of Au species was carried out using inductively coupled plasma atomic emission spectroscopy (ICP-AES) and inductively coupled plasma mass spectrometry (ICP-MS). After evaporation of the solvent from the sample the residue was digested using *aqua regia* and diluted with deionized water to the required concentration range. The samples were then analysed for metal content.

The dinuclear gold catalyst **Au-1** and the mononuclear catalyst **Au-2** were prepared according to our previous published procedures.28, 29 *N*-benzylbut-2-yn-1-amine (**PPA-1**) substrate was prepared according to our previous procedure.28

**Experimental procedures**

**Off-line processing general procedure**

Each batch reaction was diluted to a volume of 500 mL with the corresponding organic solvent then the solution was inserted in the feed tank (B). The mixture inserted in the feed tank (B) was allowed to circulate via pump 1 (P1) under a pressure of 20 bar. The mixture that comes out through V1 is called the permeate phase and the mixture that remains in the unit is called the retentate phase. In Tables 1 and 3, screening tests were conducted while P2 is closed. In the case, where a diafiltration process is conducted (Tables 2 and 4), fresh solvent is added to the diafiltration tank (A), and on commencement of permeation, P2 starts to supply solvent from tank Aa a rate that is equivalent to the rate of permeation through the membrane, in order to wash out and permeate all the product remained in the retained phase, while keeping the volume constant in tank B (Figure 1).



**Figure 1.** Schematic setup of the OSN system used with off-line processing carried out for screening filtrations.



**Scheme 1.** Gold catalyzed carboxylative cyclization of **PPA-1**.

**General procedure for rejection profiling (screening filtrations) in solvents for catalyst (Au-1) used in carboxylative cyclization of PPA-1**

The solvent was purged for a few minutes with CO2 before use. A vial was charged with the **Au-1** (1 mol%, 0.05 mmol, 52 mg) and **PPA-1** (5 mmol,796 mg) in 4 mL MeOH under CO2 atmosphere (balloon of CO2). The reaction was allowed to stir for 24 hours at room temperature to yield the desired product **2** in 99% as indicated by UPLC analysis.

Each reaction mixture was then dissolved in 500 mL of solvent identified in the main text, Table 1 and the resulting solution was added to the filtration unit fitted with the required membrane and ready for use. The circulation pump was switched on, and the mixture circulated at a nitrogen pressure of 0.5 bar until the internal temperature was 25 °C. The pressure was increased to 20 bar with each polymeric membrane used. A dead permeation volume is first needed to achieve a stable flux (i.e., observed flux stops declining under operating conditions). This is due to membrane compaction caused by the applied pressure and is common with all pressure-driven filtrations using polymeric membranes. This compaction is highly dependent upon the membrane material and solvent used. In our case, and with all membrane/solvent combinations used in this work, a stable flux was attained in less than a minute. Afterwards, ~100 mL of solvent was allowed to permeate, and samples were taken from the retentate and permeate for both ICP and UPLC analysis.

**Downstream separation of catalyst (Au-1) from a 58 mmol scale reaction for catalyst recovery**

The solvent was purged for a few minutes with CO2 before use. A vial was charged with the **Au-1** (1 mol%, 0.58 mmol, 600 mg) and **PPA-1** (58 mmol, 9.2 g) in 46 mL MeOH under CO2 atmosphere (balloon of CO2). The reaction was allowed to stir for 24 hours at room temperature to yield the desired product **2** in 99% as indicated by UPLC analysis. MeOH was then evaporated and the crude was dissolved in 500 mL Me-THF. The mixture was inserted in the filtration unit and diverted over the Borsig *oNF-1* membrane and subjected to diafiltration with Me-THF at a flow of 45-52 Kg/h (0.3 m/s) in which 4 diafiltration volumes were washed over the membrane allowing the product to permeate through the membrane keeping only the solution of the catalyst in the retained phase. Regular sampling after each diafiltration volume was then taken from the retentate and permeate for both ICP and GC analysis.

Thereafter, the retained phase was evaporated to dryness to yield a decomposed gold species which was recovered for metal reprocessing.

**General procedure for rejection profiling (screening filtrations) in solvents for catalyst (Au-2) used in carboxylative cyclization of PPA-1**

The solvent was purged for a few minutes with CO2 before use. A vial was charged with catalyst **Au-2** (2 mol%, 0.1 mmol, 62 mg) and **PPA-1** (5 mmol,796 mg) in 4 mL MeOH under CO2 atmosphere (balloon of CO2). The reaction was allowed to stir for 38 hours at room temperature to yield the desired product **2** in 99% as indicated by UPLC analysis.

Each reaction mixture was then dissolved in 500 mL of solvent identified in the main text, Table 3 and the resulting solution was added to the filtration unit fitted with the required membrane and ready for use. The circulation pump was switched on, and the mixture circulated at a nitrogen pressure of 0.5 bar until the internal temperature was 25 °C. The pressure was increased to 20 bar with each polymeric membrane used. Once a stable flux had been reached around 100 mL of solvent was allowed to permeate. Sample were taken from the retentate and permeate for both ICP and UPLC analysis.

**Downstream separation of catalyst (Au-2) from a 48 mmol scale reaction for catalyst recovery**

The solvent was purged for a few minutes with CO2 before use. A vial was charged with the **Au-2** (2 mol%, 0.96 mmol, 600 mg) and **PPA-1** (48 mmol, 7.7 g) in 39 mL MeOH under CO2 atmosphere (balloon of CO2). The reaction was allowed to stir for 38 hours at room temperature to yield the desired product **2** in 99% as indicated by UPLC analysis. MeOH was then evaporated and the crude was dissolved in 500 mL Me-THF. The mixture was inserted in the filtration unit and diverted over the Borsig *oNF-2* membrane and subjected to diafiltration with Me-THF at a flow of 45-52 Kg/h (0.3 m/s) in which 3 diafiltration volumes were washed over the membrane allowing the product to permeate through the membrane keeping only the solution of the catalyst in the retained phase. Regular sampling after each diafiltration volume was then taken from the retentate and permeate for both ICP and GC analysis.

Thereafter, the retained phase was evaporated to dryness to result in a crude mixture as a brown semi solid containing product, catalyst **Au-2** and some gold decomposed species. The crude was washed 4 times with diethyl ether to yield catalyst **Au-2** in 50% yield. The 50% yield loss is due to incomplete emptying of the filtration unit, some catalyst decomposition and sampling.

**RESULTS AND DISCUSSION**

In an attempt to investigate catalyst recyclability and to solve the problem of the ligand being a single use component, two Au(I)-NHC complexes were compared in the carboxylative cyclization of PPA; dinuclear gold(I) complex bearing alkyl-bridged bis-NHC ligands [Au2(L)Cl2] (**Au-1**) and the monomeric analogue [Au(Cl)(IPr)] (**Au-2**) (Scheme 1). In both cases, upon completion of the reaction, attempts were made to recover the catalyst, as a whole, via downstream processing.

In our recent study on the carboxylative cyclization of *N*-benzylbut-2-yn-1-amine (**PPA-1**), higher activity was obtained using catalyst **Au-1** with which the reaction reached completion to the desired 3-benzyl-5-vinyloxazolidin-2-one product (**2**) in 24 hours compared to catalyst **Au-2** which led to 75% yield after 24 hours.28 Therefore, we started our investigations using the more active dinuclear catalyst **Au-1** in which the batch reaction was conducted under our optimized reaction conditions (Scheme 1).28

***Membrane and screening conditions for Au-1 separation***

On completion of the reaction and using the final reaction mixture, we conducted screening filtration experiments aimed to identify the most suitable membrane to separate catalyst **Au-1** from the reaction product; the overall gold content was quantified by ICP-MS analysis (Table 1).

Based on our experience, removal of Au(I)-NHC catalysts from crude reaction mixtures is best achieved over non-porous Borsig-type polymeric membranes,8 therefore these were chosen as starting point in this study.

Screening filtrations of **Au-1** over Borsig *oNF-1* (MWCO = 600 Da), were conducted in different solvents (Table 1, entries 1-4). The procedure for conducting the screening filtrations is followed as described in the materials and methods section (Figure 1).

The highest rejections were obtained in THF and in Me-THF (Table 1, entries 1, 4) which gave almost identical gold rejections of 99.2% and 99.5% respectively. However, rejection of the product **2** obtained in THF (69%) was significantly higher than that obtained in Me-THF (31%) (Table 1, entry 1 *vs* 4). The consequence of which would be that a larger volume of THF is thus required to efficiently perform the separation and achieve high product recovery, when compared to Me-THF. In addition, the separation could also be achieved in MeOH and EtOH, leading to very good gold rejections (Table 1, entries 2, 3). This is particularly interesting since the carboxylation reaction is successfully performed in these solvents. However, with both alcoholic solvents, the permeability of the membrane is relatively low with a permeance of 0.12 and 0.92 L.m-2.h-1.bar-1, respectively (Table 1, entries 2 and 3). This is mainly due to the high polarity of these solvents which mismatched with the non-polar Borsig *oNF-1* membrane surface, thus leading to low solvent/membrane affinity which in turn reduces the rate of permeance. Upon switching to the tighter Borsig *oNF-2* membrane (MWCO = 350 Da), lower gold rejection to that obtained with

**Table 1.** Rejection and permeance data of catalyst **Au-1** used in this study over Borsig-type polymeric membrane.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| entry*a* | Membrane*b,c*(MWCO) | Solvent | Permeance | Rejection (%) |
|  | (L.m-2.h-1.bar-1) | Au | product |
| 1 | Borsig *oNF-1*(600 Da) | THF | 6.51 | 99.2 | 69 |
| 2 | Borsig *oNF-1* | MeOH | 0.12 | 96 | 2.8 |
| 3 | Borsig *oNF-1* | EtOH | 0.92 | 95 | 10.3 |
| 4 | Borsig *oNF-1* | Me-THF | 5.08 | 99.5 | 31 |
| 5 | Borsig *oNF-2*(350 Da) | Me-THF | 4.6 | 95.4 | 30 |
| 6 | Borsig *oNF-3*(900 Da) | Me-THF | 7.5 | 91.5 | 33 |
| *a*Batch Reaction conditions: Reactions were carried out with **PPA-1** (5 mmol) and catalyst **Au-1** (2 mol% with respect to gold) in MeOH (1.25M) at room temperature under 1 atm of CO2. *b*Reaction mixtures were diluted with solvent to a volume of 500 mL and then OSN were done at 25°C , P = 20 bar. *c*Membrane information can be found on the supplier’s website <https://www.borsig.de/en/inside/downloads/organic-solvent-nanofiltration-pdf/pageflip#1>  |

Borsig *oNF-1* was observed(Table 1, entry 5 *vs* 4). This result is similar to that obtained previously when separating [Au(IPr)(OTf)] from alkyne hydration reaction mixtures over both these membranes, indicating that the transport of the Au complexes across the membrane is influenced by membrane affinity aspects.25 Size exclusion also comes in play as evidenced by the use of the most open Borsig-type membrane, Borsig *oNF-3* (MWCO = 900 Da), which led to the lowest gold rejection of 91.5% (Table 1, entry 6).

***Catalyst Au-1 recovery***

A batch reaction was conducted on 58 mmol, with 9.2 g of **PPA-1** leading to 99% conversion to the product **2** in 24 h. Therefore, after identifying the best filtration conditions, the recovery of the catalyst from this reaction mixture was carried out next. Constant volume diafiltration was used to retain the gold complex while washing the product through the membrane; 4 diafiltration volumes 30 were needed to completely wash the product through the membrane, resulting in a solution of the catalyst in the final retentate phase (see Figure 1 for schematic representation of the diafiltration process). During the diafiltration process regular sampling after each diafiltration volume was taken for ICP and UPLC analysis (Table 2). The results in Table 2 indicated almost complete rejection of the gold catalyst at all the stages of the diafiltration. At the end of the diafiltration process the permeate was a pure solution of product contaminated with as little as 38 ppm of Au. Unfortunately, an attempt to recover the catalyst as a whole was unsuccessful due to the insufficient catalyst stability under either reaction or filtration conditions. The retentate solution in this case was a mixture of various gold-containing complexes and thus, only the metal could theoretically be recovered through a reprocessing methodology.

**Table 2.** Rejection and permeance data of catalyst **Au-1** over Borsig *oNF-1* polymeric membrane.

|  |  |  |  |
| --- | --- | --- | --- |
| Entry*a* | Diafiltration volume(Me-THF)*b* | Permeance (L.m-2.h-1.bar-1) | Rejection (%) |
| Au | Product |
| 1 | 1st diafiltration volume | 2.27 | 99.5 | 52 |
| 2 | 2nd diafiltration volume | 3.28 | 99.4 | 42 |
| 3 | 3rd diafiltration volume | 4.6 | 99.4 | 32 |
| 4 | 4th diafiltration volume | 4 | 99.4 | 15 |
| *a*Batch reaction conditions: Reaction was carried out with **PPA-1** (58 mmol) and catalyst **Au-1** (2 mol% with respect to gold) in MeOH (1.25M) at room temperature under 1 atm of CO2. *b*Diafiltration conducted with flow of 45-52 kg. h-1 (0.3 m.s-1) at 25°C , P = 20 bar.  |

***Membrane and conditions screening for Au-2 separation***

In our hands, catalyst **Au-2** have always shown good to excellent stability under various reaction conditions. Therefore, the reaction was attempted using **Au-2** as catalyst, in an effort to recover the metal-ligand catalyst as a whole.

**Table 3.** Rejection and permeance data of catalyst **Au-2** used in this study over polymeric membranes.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Entry*a* | Membrane*b*(MWCO) | Solvent | Permeance | Rejection (%) |
|  | (L.m-2.h-1.bar-1) | Au | product |
| 1 | Borsig *oNF-1*(600 Da) | THF | 5.4 | 83 | 69 |
| 2 | Borsig *oNF-2*(350 Da) | THF | 4.6 | 61 | 69 |
| 3 | Borsig *oNF-1* | Acetone | 2.32 | 84 | 32 |
| 4 | Borsig *oNF-2* | Me-THF | 4.6 | 90 | 33 |
| 5 | Borsig *oNF-1* | EtOH | 0.86 | 90 | 0.2 |
| 6 | PuraMem selective*c* | Acetone | 2 | 56 | 53 |
| 7 | PuraMem performance*c* | Acetone | 2.8 | 83 | 53 |
| 8 | Puramem 280(280 Da) | Acetone | 0.7 | 41.8 | 23 |
| *a*Batch Reaction conditions: Reactions were carried out with **PPA-1** (5 mmol) and catalyst **Au-2** (2 mol%) in MeOH (1.25 M) at room temperature under 1 atm of CO2. *b*Reaction mixtures were diluted with solvent to a volume of 500 mL and then OSN were done at 25°C , P = 20 bar. *c*PuraMem Selective and PuraMem performance are composite membranes, solubility (and not diffusion) dominates these membrane separation. Therefore, the cut-off of these membranes is strongly dependent on solvent/solute combination. MWCO obtained in one standard system is not characteristic for these type of membranes. Best suitable membrane for the application can be chosen by testing real solutions. More membrane information can be found on the supplier’s website <https://www.membrane-separation.com/en/organic-solvent-nanofiltration-with-puramem-duramem/product-overview>  |

After carrying out batch reactions using catalyst **Au-2**, several membrane screening filtrations over a variety of polymeric membranes of low surface polarity were conducted and are summarized in Table 3. In all cases, low rejections were obtained in comparison to the dinuclear catalyst **Au-1**. 90% being the highest rejection obtained when using Borsig *oNF-2* membrane in Me-THF and when using Borsig *oNF-1* in EtOH (Table 3, entries 4-5). Puramem-type membranes led to insufficient gold rejections (Table 3, entries 6-8) under the employed conditions.

**Catalyst Au-2 recovery**

A batch reaction was conducted on 48 mmol, with 7.7 g of **PPA-1** leading to 99% conversion to the product **2** in 38 h. Since the screening filtrations indicated that highest rejection was obtained over Borsig *oNF-2* in Me-THF, this reaction mixture was than filtered under these conditions. Gold rejection results during the diafiltration process were in the range of 90-93% (Table 4), resulting in higher Au contamination of the permeate stream than the one obtained when filtering the digold analogue **Au-1**.

Recovery of the catalyst from the retained phase was targeted next. After evaporation of the solvent and quick washing of the obtained solid with diethyl ether, 50% of **Au-2** was recovered as confirmed by NMR analysis.

**Table 4.** Rejection and permeance data of catalyst **Au-2** over Borsig *oNF-2* polymeric membrane.

|  |  |  |  |
| --- | --- | --- | --- |
| Entrya | Diafiltration volume(Me-THF)*b* | Permeance (L.m-2.h-1.bar-1) | Rejection (%) |
| Au | Product |
| 1 | 1st diafiltration volume | 3.5 | 93 | 40 |
| 2 | 2nd diafiltration volume | 3.9 | 91 | 28 |
| 3 | 3rd diafiltration volume | 4.2 | 90 | 14 |
| *a*Batch reaction conditions: Reaction was carried out with **PPA-1** (48 mmol) and catalyst **Au-2** (2 mol%) in MeOH (1.25 M) at room temperature under 1 atm of CO2. *b*Diafiltration conducted with flow of 45-52 kg. h-1 (0.3 m.s-1) at 25°C , P = 20 bar. |

Results obtained in this report highlight two possible ways in which a membrane integrated process can be used to recycle a catalyst. The first consists of internal recycling, in which the catalyst is maintained within the filtration unit either in an active form or in a resting state under the conditions of the reaction, thus increasing catalyst efficiency and turnover number, while isolating the pure product without any need for further purification. At some point however, the reaction will have to be stopped and the reactor emptied. In this case, the recovered organometallic species are typically recovered for metal reprocessing. This is the case for the majority of catalyst membrane separations reported in the literature to-date. Alternatively, upon completion of the reaction, the intact catalyst, -complete with its ancillary ligand- can be isolated from the retentate or permeate phase in which it is found, here termed external recycling.

Both situations are economically and environmentally an improvement on simple batch reaction methodologies, since the recovery of the most expensive part of this reaction, the gold metal center, was achieved in both cases. Results from this work show the larger catalyst **Au-1** to be more suited for internal catalyst recycling. Whereas, smaller and more stable catalyst **Au-2** is shown to be more suitable for external recycling. Whatever method is used will depend on catalyst design (different ligand-metal designs will lead to different rejection profiles), product purity specifications and whether there are further down-stream purifications required before the ultimate target molecule is obtained.

This work is still ongoing in our group in hopes of achieving better rejection profiles that will allow for membrane integration into a continuous catalytic process.

**CONCLUSION**

In summary, separation of the dinuclear gold catalyst **Au-1** and the mononuclear gold catalyst **Au-2** used in the carboxylative cyclization of **PPA-1** were achieved over Borsig-type polymeric membranes. The downstream separation led to the recovery of catalyst **Au-2** in 50% yield without any further treatment. This isolated species is widely used as a precursor for the synthesis of several other important gold catalysts.31

However, as incomplete rejection of catalyst **Au-2** was achieved, the product in the permeate phase will require an additional purification step. On the other hand, almost complete rejection of catalyst **Au-1** was achieved meaning that the permeated product will not require any additional purification. Attempts to recover catalyst **Au-1** were unsuccessful due to catalyst decomposition. This work further highlights the importance of catalyst design and the tedious reaction fine-tuning needed, on a case by case basis, to achieve an efficient and continuous membrane integrated catalytic process.

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**ABBREVIATIONS**

OSN, organic solvent nanofiltration; PPA, propargylamine; Au, gold; NHC, N-heterocyclic carbene.

**REFERENCES**

1. Dixneuf PH, Soulé J-F. Organometallics for Green Catalysis: *Springer* (2019).

2. Centi G, Perathoner S. Catalysis and sustainable (green) chemistry. *Catalysis Today* **77**: 287-297 (2003). <http://www.sciencedirect.com/science/article/pii/S0920586102003747>.

3. Dunn PJ, Hii K, Krische MJ, Williams MT. Sustainable Catalysis (2013).

4. Sheldon RA. The E factor 25 years on: the rise of green chemistry and sustainability. *Green Chem.* **19**: 18-43 (2017). <http://dx.doi.org/10.1039/C6GC02157C>.

5. Díez-González S, Marion N, Nolan SP. N-Heterocyclic Carbenes in Late Transition Metal Catalysis. *Chem. Rev.* **109**: 3612-3676 (2009). <https://doi.org/10.1021/cr900074m>.

6. Zhao Q, Meng G, Nolan SP, Szostak M. N-Heterocyclic Carbene Complexes in C–H Activation Reactions. *Chem Rev.* **120**: 1981-2048 (2020). <https://doi.org/10.1021/acs.chemrev.9b00634>.

7. A. C. A. Bayrakdar T, Scattolin T, Ma X, Nolan SP. Dinuclear gold(i) complexes: from bonding to applications. *Chem. Soc. Rev.* **49**: 7044-7100 (2020). <http://dx.doi.org/10.1039/D0CS00438C>.

8. Nahra F, Cazin CSJ. Sustainability in Ru- and Pd-based catalytic systems using N-heterocyclic carbenes as ligands. *Chem. Soc. Rev.* **50**: 3094-3142 (2021). <http://dx.doi.org/10.1039/C8CS00836A>.

9. Hayler JD, Leahy DK, Simmons EM. A Pharmaceutical Industry Perspective on Sustainable Metal Catalysis. *Organometallics* **38**: 36-46 (2018). <https://doi.org/10.1021/acs.organomet.8b00566>

10. Busacca CA, Fandrick DR, Song JJ, Senanayake CH. The Growing Impact of Catalysis in the Pharmaceutical Industry. *Adv. Synth. Catal.* **353**: 1825-1864 (2011). <https://doi.org/10.1002/adsc.201100488>.

11. Hunt AJ, Farmer TJ, Clark JH. Elemental Sustainability and the Importance of Scarce Element Recovery. In: Hunt AJ, editor. Cambridge: RSC publishing; 2013. p. 1-28.

12. McElroy CR, Constantinou A, Jones LC, Summerton L, Clark J. Towards a holistic approach to metrics for the 21st Century pharmaceutical industry. *Green Chem.* **17**: 3111-3121 (2015). http://pubs.rsc.org/en/content/articlepdf/2015/gc/c5gc00340g.

13. Collis AEC, Horváth IT. Heterogenization of homogeneous catalytic systems. *Catal. Sci. Technol.* **1**: 912-919 (2011).

14. Wang W, Cui L, Sun P, Shi L, Yue C, Li F. Reusable N-Heterocyclic Carbene Complex Catalysts and Beyond: A Perspective on Recycling Strategies. *Chem. Rev.* **118**: 9843-9929 (2018). <https://www.ncbi.nlm.nih.gov/pubmed/29847935>.

15. de Almeida MP, Carabineiro SAC. The Best of Two Worlds from the Gold Catalysis Universe: Making Homogeneous Heterogeneous. *ChemCatChem.* **4**: 18-29 (2012). <https://onlinelibrary.wiley.com/doi/abs/10.1002/cctc.201100288>.

16. de Almeida MP, Martins LMDRS, Carabineiro SAC, Lauterbach T, Rominger F, Hashmi ASK, et al. Homogeneous and heterogenised new gold C-scorpionate complexes as catalysts for cyclohexane oxidation. *Catal. Sci. Technol.* **3**: 3056-3069 (2013). <http://dx.doi.org/10.1039/C3CY00552F>.

17. Tšupova S, Cadu A, Carabineiro SAC, Rudolph M, Hashmi ASK. Solid-supported nitrogen acyclic carbene (SNAC) complexes of gold: Preparation and catalytic activity. *J. Catal.* **350**: 97-102 (2017). <http://www.sciencedirect.com/science/article/pii/S0021951717300908>.

18. Carabineiro SAC, Martins LMDRS, Pombeiro AJL, Figueiredo JL. Commercial Gold(I) and Gold(III) Compounds Supported on Carbon Materials as Greener Catalysts for the Oxidation of Alkanes and Alcohols. *ChemCatChem.* **10**: 1804-1813 (2018). <https://onlinelibrary.wiley.com/doi/abs/10.1002/cctc.201701886>.

19. Vural Gürsel I, Noël T, Wang Q, Hessel V. Separation/recycling methods for homogeneous transition metal catalysts in continuous flow. *Green Chem.* **17**: 2012-2026 (2015). <http://dx.doi.org/10.1039/C4GC02160F>.

20. Mandoli A. Catalyst recycling in continuous flow reactors. In: Benaglia M, Puglisi A, editors. Catalyst Immobilization: Methods and Applications: Wiley;. p. 257-306 (2020).

21. Nolan SP. The Development and Catalytic Uses of N-Heterocyclic Carbene Gold Complexes. *Acc. Chem. Res.* **44**: 91-100 (2011). <https://doi.org/10.1021/ar1000764>.

22. Marchione D, Belpassi L, Bistoni G, Macchioni A, Tarantelli F, Zuccaccia D. The Chemical Bond in Gold(I) Complexes with N-Heterocyclic Carbenes. *Organometallics* **33**: 4200-4208 (2014). <https://doi.org/10.1021/om5003667>

23. Nelson DJ, Nolan SP. Quantifying and understanding the electronic properties of N-heterocyclic carbenes. *Chem. Soc. Rev.* **42**: 6723-2753 (2013). <https://www.ncbi.nlm.nih.gov/pubmed/23788114>.

24. Kelly Iii RA, Clavier H, Giudice S, Scott NM, Stevens ED, Bordner J, et al. Determination of N-Heterocyclic Carbene (NHC) Steric and Electronic Parameters using the [(NHC)Ir(CO)2Cl] System. *Organometallics* **27**: 202-210 (2008). https://doi.org/10.1021/om701001g.

25. A. C. A. Bayrakdar T, Nahra F, Zugazua O, Eykens L, Ormerod D, Nolan SP. Improving process efficiency of gold-catalyzed hydration of alkynes: merging catalysis with membrane separation. *Green Chem.* **22**: 2598-2604 (2020). <https://doi.org/10.1039/D0GC00498G>.

26. Hase S, Kayaki Y, Ikariya T. Mechanistic Aspects of the Carboxylative Cyclization of Propargylamines and Carbon Dioxide Catalyzed by Gold(I) Complexes Bearing an N-Heterocyclic Carbene Ligand. *ACS Catal.* **5**: 5135-5140 (2015). h[ttps://doi.org/10.1021/acscatal.5b01335](https://doi.org/10.1021/acscatal.5b01335).

27. Hase S, Kayaki Y, Ikariya T. NHC–Gold(I) Complexes as Effective Catalysts for the Carboxylative Cyclization of Propargylamines with Carbon Dioxide. *Organometallics* **32**: 5285-5288 (2013). h[ttps://doi.org/10.1021/om400949m](https://doi.org/10.1021/om400949m).

28. A. C. A. Bayrakdar T, Nahra F, Davis JV, Gamage MM, Captain B, Temprado M, et al. Dinuclear Gold(I) Complexes Bearing Alkyl-Bridged Bis(N-heterocyclic carbene) Ligands as Catalysts for Carboxylative Cyclization of Propargylamine: Synthesis, Structure, and Kinetic and Mechanistic Comparison to the Mononuclear Complex [Au(IPr)Cl]. *Organometallics* **39**: 2907-2916 (2020). <https://doi.org/10.1021/acs.organomet.0c00404>.

29. Collado A, Gómez-Suárez A, Martin AR, Slawin AMZ, Nolan SP. Straightforward synthesis of [Au(NHC)X] (NHC = N-heterocyclic carbene, X = Cl, Br, I) complexes. *Chem. Commun.* **49**: 5541-5543 (2013). <http://dx.doi.org/10.1039/C3CC43076F>.

30. One diafiltration volume is the volume of solvent washed through the membrane via a diafiltration process that is equivalent to the volume of the original feed.

31. Nahra F, Tzouras NV, Collado A, Nolan SP. Synthesis of N-heterocyclic carbene gold(I) complexes. *Nat. Protoc.* **16**: 1476-1493 (2021). <https://doi.org/10.1038/s41596-020-00461-6>.