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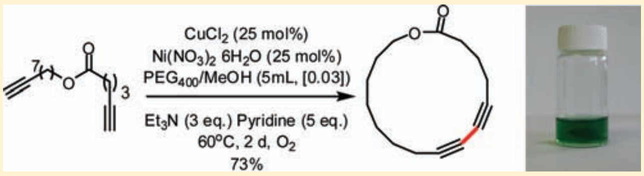
Phase Separation As a Strategy Toward Controlling Dilution Effects in Macrocyclic Glaser-Hay Couplings

Anne-Catherine Bédard and Shawn K. Collins*

Département de Chimie, Centre for Green Chemistry and Catalysis, Université de Montréal, CP 6128 Station Downtown, Montréal, Québec H3C 3J7 Canada

Ⓢ *Supporting Information*



ABSTRACT: Macrocycles are abundant in numerous chemical applications, however the traditional strategy for the preparation of these compounds remains cumbersome and environmentally damaging; involving tedious reaction set-ups and extremely dilute reaction media. The development of a macrocyclization strategy conducted at high concentrations is described which exploits phase separation of the catalyst and substrate, as a strategy to control dilution effects. Sequestering a copper catalyst in a highly polar and/or hydrophilic phase can be achieved using a hydrophilic ligand, T-PEG$_{1900}$, a PEGylated TMEDA derivative. Similarly, phase separation is possible when suitable copper complexes are soluble in PEG$_{400}$, a green and efficient solvent which can be utilized in biphasic mixtures for promoting macrocyclization at high concentrations. The latter phase separation technique can be exploited for the synthesis of a wide range of industrially relevant macrocycles with varying ring sizes and functional groups.

INTRODUCTION

Macrocycles are one of the most common cyclic motifs found in Nature.[1] Their unique chemical structures and properties have important applications in numerous scientific fields. Perhaps the greatest impact of macrocycles has been felt in the pharmaceutical and cosmetic industries.[2] In terms of drug discovery, synthetic macrocycles with structures inspired from natural products have been used successfully against many biological targets, often as rigidified peptide ligand mimics.[3] The cosmetic industry has been exploiting naturally occurring macrocyclic musks for use as perfumes,[4−6] however these compounds are not obtained from their respective plant sources and are prepared by synthesis on a multiton scale annually. Strangely, as the application of macrocycles continues to grow, the general strategy for the preparation of these compounds remains a challenge.

The efficiency of a macrocyclization is often controlled by the nature of the three-dimensional conformation of the macrocyclization precursor. Although some exceptions are known where a precursor adopts a conformation that allows for selective and efficient macrocyclization,[7,8] in most instances the preparation of large rings is plagued by slow rates of intramolecular cyclization (Figure 1a). Consequently, the rates of the intermolecular reactions between precursors become competitive and oligomerization or extensive polymerization becomes problematic. Accordingly, synthetic chemists have devised two techniques to improve macrocyclization processes. The first involves conformational control, whereby through some chemical method, the macrocyclization precursor is made to adopt a conformation highly conducive to ring closure, thereby increasing the rate of intramolecular cyclization.

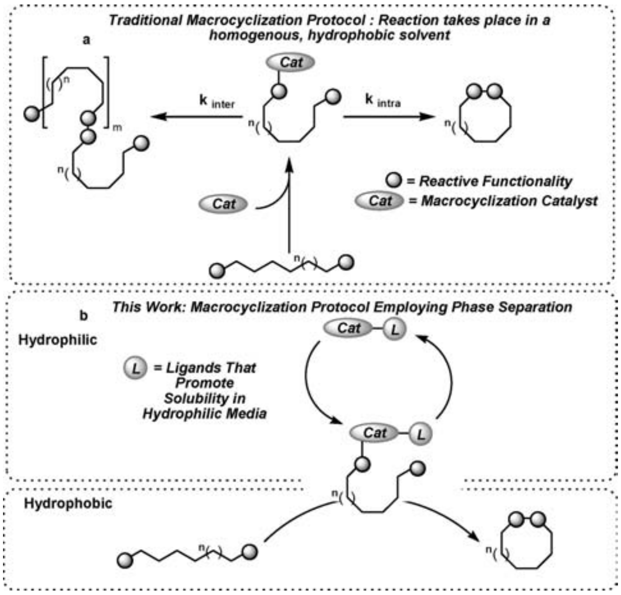


Figure 1. (a) Traditional macrocyclization in homogeneous hydrophobic media. (b) Macrocyclization employing phase separation.

In contrast, the second and most popular strategy to improve macrocyclization reactions involves slowing the rate of intermolecular reactions. Most often, macrocyclization reactions are run at very low concentration and it is common that the

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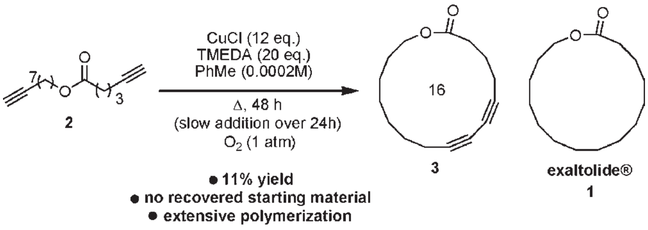
precursor will be added to the reaction mixture via slow addition over an extended period of time. The extremely dilute reaction media requires that large volumes of solvent are used. In an era where most chemical processes are scrutinized for their environmental impact, the traditional macrocycle synthesis is perhaps one of the greatest offenders of the principles of green chemistry.[9] Indeed, in both academic and industrial laboratories, macrocycle synthesis involving common methods such as standard peptide coupling techniques, the Yamaguchi lactonization[10] and ring closing olefin metathesis[11,12] are all normally conducted under high dilution conditions. In addition to the obvious environmental concerns, both the issues of cost and scale-up to industrially relevant quantities of material combine to make macrocyclization reactions prohibitive in many industrial applications. In some rare instances, a significant effort can result in a substantial increase in yields and concentrations for a macrocyclization process,[13−15] but the scarcity of examples underscores the need for new synthetic strategies. Considering both the importance of synthetic macrocycles and the widespread appeal of green chemical processes, the development of a general and green macrocyclization protocol that could be conducted via catalysis at high concentration, eliminating the need for high dilution, is an important synthetic goal that has yet to be achieved.[16] Herein, we describe a phase separation strategy that can be applied to catalytic macrocyclic Glaser-Hay couplings and demonstrate its application in the synthesis of macrocyclic musks.

In traditional methods, the macrocyclization precursor is normally placed in a dilute homogeneous solution with a reagent or catalyst which mediates the cyclization at low concentrations (Figure 1a). In order to achieve macrocyclization at high concentrations, we chose to investigate techniques whereby the macrocyclization event between the catalyst and precursor would take place in an environment where the relative concentration of the precursor is low. It was believed that replacing traditional homogeneous reaction media with biphasic media could achieve this goal. While chemistry at the solid/liquid interface has become common in organic synthesis, organic synthesis at a liquid/liquid interface is surprisingly rare[17] and often instead exploited in separation techniques.[18]

In order to force a macrocyclization event to occur at the interface of the two phases, the catalyst or reagent that catalyzes or mediates the macrocyclization would be sequestered in a single phase while the substrate would preferentially solubilize in a different phase (Figure 1b).[19] In doing so, the effective concentration of the substrate at the interface would be small and mirror the low concentration typically employed in traditional macrocyclization reactions. Through phase separation of the catalyst and precursors, the need for high dilution becomes unnecessary and intramolecular cyclization should become the favored reaction pathway. One method to achieve such a process would be to use two solvents that are sparingly miscible in conjunction with a catalyst whose ligands allow for it to be soluble and active in only one of the phases. Given that most organic substrates are soluble in hydrophobic media, the catalysts developed for such a process must maintain their activity in highly polar and/or hydrophilic media.[20]

In order to evaluate whether such a process is feasible, we turned our attention toward developing a macrocyclization reaction that would not only demonstrate the proof-of-principle for phase separation as technique for achieving macrocyclization at high concentration, but also highlight its applicability toward macrocyclization in industrially relevant processes. We were attracted by the chemical challenges associated with the synthesis of macrocyclic musks, particularly the macrolactone exaltolide **1**, which is currently the most industrially produced macrocyclic musk (Scheme 1).[21] In examining a retrosynthesis of **1**, we choose to develop a route to **3** based upon a Glaser-Hay oxidative coupling of terminal alkynes. The Glaser-Hay coupling[22−24] of **2** provides an appropriate starting point for the investigations for a number of reasons, including: (1) the copper catalysts for these reactions are inexpensive, nontoxic and can easily be modified with ligands that permit solubility in hydrophilic media, (2) the reaction results in the formation of a carbon−carbon bond, classically referred to as one of the most difficult bonds to prepare in organic synthesis, and (3) the diyne precursor **2** exists as a linear aliphatic chain devoid of any conformational bias, hence efficient macrocyclization would only be achieved through control of the reaction concentration.

Scheme 1. Synthesis of 3 Based upon Traditional Conditions



The investigations began by conducting a traditional Glaser-Hay coupling on diyne **2** using standard conditions from the chemical literature.[25] The cyclization of alkyl alkynes is notoriously slower than aryl alkynes and superstoichiometric amounts of copper reagent are normally necessary to achieve acceptable rates of cyclization. As such, **2** was added by syringe pump to a solution of CuCl, tetramethylethylene diamine (TMEDA) in refluxing PhMe under an oxygen atmosphere over 24 h and the solution was allowed to stir for an additional 24 h (Scheme 1). Following purification by chromatography, a complete conversion of **2** was observed but only an 11% yield of the desired macrocycle **3** was obtained. In addition, when the macrocyclization of **2** is carried out using the same reaction conditions but at 150X the concentration shown in Figure 2, only extensive polymerization of **2** is observed. With the result of the traditional macrocylization at various concentrations in hand, we sought to explore the phase separation strategy to improve the synthesis of **3**.

■ RESULTS AND DISCUSSION

Developing Hydrophilic Ligands for Transition Metal Complexes for Use in "Green" Macrocyclizations. In order to develop a catalyst for macrocyclization via a Glaser-Hay coupling that could impart a preference for the catalyst complex to solubilize in hydrophilic media, it was necessary to modify the traditional TMEDA ligand to increase its water solubility. Our approach involved replacing one of the methyl groups of the ligand with a polyethylene glycol (PEG) polymer (Scheme 2). The PEG alcohol monomethyl ether **4** can be easily transformed into its corresponding mesylate and used to alkylate trimethyldiamine **6**, affording the ligand **7** (T-PEG$_{1900}$). After both the mesylation of alcohol **4** and the alkylation of amine **6**, the products are easily recovered via precipitation from the reaction

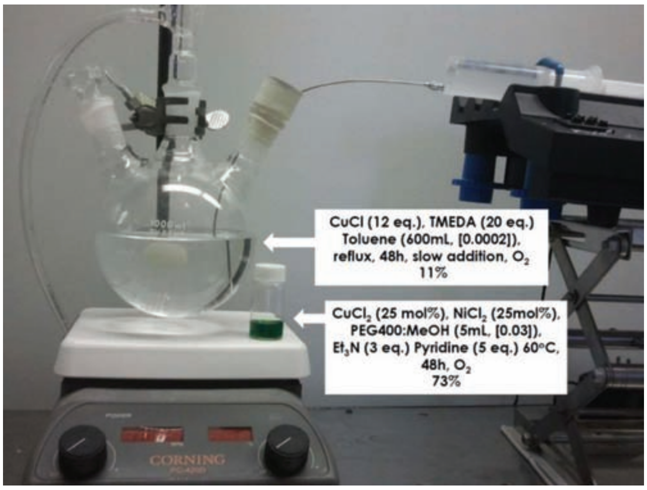
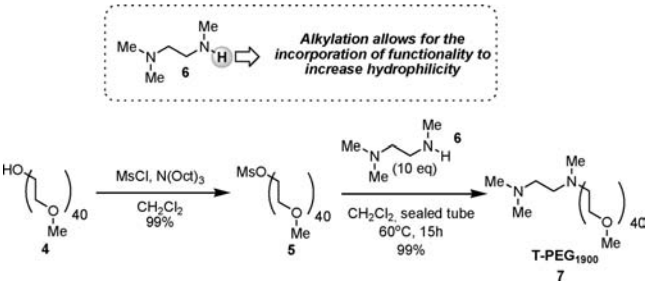


Figure 2. Simplified experimental setup for the "green" macrocyclization using phase separation.

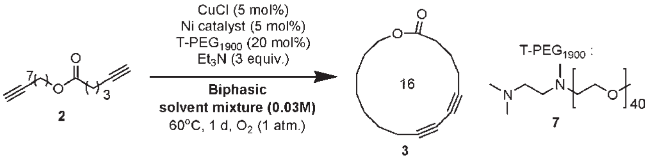
Scheme 2. Synthesis of PEGylated TMEDA Derivative, T-PEG$_{1900}$



mixture with Et_2O. T-PEG$_{1900}$ **7** can also be further purified by filtration on a short column of neutral alumina.

As only extensive polymerization of **2** is observed under classical catalysis (CuCl, TMEDA) at 150X greater concentrations than the traditional synthesis depicted in Scheme 1, we next moved to investigate the macrocyclization of **2** in solvent mixtures. Initially, it was sought to study complexes of copper with the T-PEG$_{1900}$ ligand in a mixture of nonmiscible solvents such as H_2O/PhMe (1:1), again at 150X the traditional concentration (Table 1). Under the aqueous solvent conditions, however, the T-PEG$_{1900}$ Cu complexes were not active in the Glaser-Hay coupling, however gratifyingly the starting material **2** was quantitatively recovered. As such, we chose to further improve the reactivity of the Glaser-Hay coupling through the inclusion of a Ni-based cocatalyst. Lei and co-workers[26] have previously shown that a Ni cocatalyst can improve the reaction rates of Glaser-Hay couplings. Despite the addition of $NiCl_2$ to the reaction mixture, no macrocyclization was observed. Substitution of H_2O with MeOH in the solvent mixture produced a reaction that was initially biphasic but slowly became homogeneous at elevated temperatures. Gratifyingly, an isolated yield of 15% for **3** was obtained, although the remaining starting material was oligomerized. Even though we had achieved identical yields to the traditional macrocycle synthesis (Figure 2), we sought to further improve the reaction through optimization of both the nature of the solvent and the ratio of hydrophilic to hydrophobic media. It was found that Et_2O/MeOH (1:1) was an optimal solvent combination which resulted in a 34−42% isolated yield of the 1,3-diyne product **3**. Under these conditions, the $NiCl_2$ cocatalyst was finely suspended in the reaction mixture and it was believed that the heterogeneity was responsible for the varying yields. A variety of Ni salts were investigated as alternatives to $NiCl_2$ and $Ni(NO_3)_2 \cdot 6H_2O$ was found to be highly soluble and provided similar yields of **3** (35%). Finally, when the catalyst loading was increased to 25 mol %, the isolated yield of macrocycle **3** was also increased to 65%

Table 1. Model studies on the macrocyclization of 3 using a copper/T-PEG$_{1900}$ system and phase separation as a strategy to control reactivity



entry	Ni catalyst	solvent (ratio)	yield (%)
1	none	PhMe/H_2O (1:1)	0
2	$NiCl_2$	PhMe/H_2O (1:1)	0
3	$NiCl_2$	PhMe/MeOH (1:1)	15
4	$NiCl_2$	Et_2O/MeOH (1:1)	34−42[a]
5[b]	$Ni(NO_3)_2 \cdot 6H_2O$	Et_2O/MeOH (1:1)	35
6[c]	$Ni(NO_3)_2 \cdot 6H_2O$	Et_2O/MeOH (1:1)	65

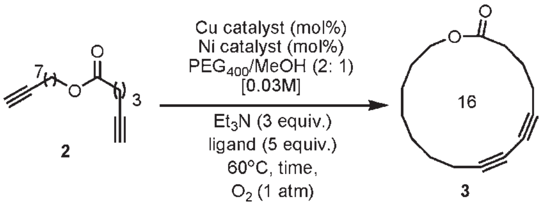
[a] In some cases, complete consumption of the starting material was observed while in other instances 10−20% could be recovered and up to 38% of a linear dimer could be isolated. [b] A 5 day reaction time. [c] 25 mol % of CuCl and $Ni(NO_3)_2 \cdot 6H_2O$ were used. 50 mol % of **7** was used.

The above results demonstrate that phase separation can be an effective technique to promote efficient macrocyclization at high concentrations. A novel Cu- and Ni-based catalyst system was developed using a PEGylated diamine ligand T-PEG$_{1900}$ which allowed the diyne macrocycle **3** to be prepared at significantly higher concentration (0.0002 M (600 mL) → 0.03 M (5 mL)) and yields (11% →65%) than that utilized in traditional methods.

Polyethylene Glycol (PEG) As a Solvent for "Green" Macrocyclization. The success of the T-PEG$_{1900}$ ligand in the previous macrocyclization reactions encouraged us to investigate the use of PEG itself as a solvent in the phase separation strategy. Polyethylene glycol (PEG) has already been extensively studied as a reaction media for transition metal catalyzed reactions, particularly cross coupling transformations.[27,28] PEG (low molecular weight) is well suited as a "green" solvent as it is a water-soluble hydrophilic polymer that is relatively nontoxic, nonvolatile, inexpensive and thermally stable.[29−31]

The aforementioned properties of PEG are normally highly sought after when searching for alternatives to traditional organic solvents and consequently, PEG$_{400}$ was chosen as an ideal solvent for the development of a "green" macrocyclization protocol. In order to investigate the macrocyclization of **2** at high concentrations using PEG$_{400}$ as a hydrophilic solvent, we initially performed a control experiment to demonstrate that complexes of Cu salts with TMEDA or pyridine were soluble and homogeneous in PEG$_{400}$ solution under rapid stirring. Control experiments also demonstrated that in either homogeneous MeOH or PEG$_{400}$ solution, only polymerization of **2** is observed

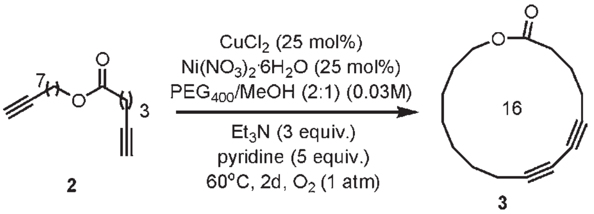
Table 2. Model Studies on the Macrocyclization of **2** Using a Copper/Nickel Catalyst System and Phase Separation As a Strategy to Control Reactivity



entry	Cu/Ni (mol %); ligand	time (d)	yield (%)
1[a]	CuCl (100); TMEDA	1	22
2[a]	CuCl/NiCl$_2$ (100); TMEDA	3	24
3	CuCl/NiCl$_2$ (100); TMEDA	1	57
4	CuCl/NiCl$_2$ (100); bipy	2	48
5	CuCl/NiCl$_2$ (100); phen	4	26
6	CuCl/NiCl$_2$ (100); pyridine	1	80
7	CuCl$_2$ /NiCl$_2$ (100); pyridine	1	78
8	CuCl$_2$/NiCl$_2$ (50); pyridine	4	79
9	CuCl$_2$/NiCl$_2$ (25); pyridine	4	68
10	CuCl$_2$/Ni(acac)$_2$ (50); pyridine	5	22
11	CuCl$_2$/NiBr$_2$ (100); pyridine	1	67
12	CuCl$_2$/NiF$_2$·4H$_2$O (100); pyridine	1	68
13	CuCl$_2$/Ni (100); pyridine	2	76
14	CuCl$_2$/Ni(NO$_3$)$_2$·6H$_2$O (100); pyridine	1	83
15	CuCl$_2$/Ni(NO$_3$)$_2$·6H$_2$O (50); pyridine	1	68
16	CuCl$_2$/Ni(NO$_3$)$_2$·6H$_2$O (25); pyridine	2	73

[a] Solvent ratio PEG$_{400}$/MeOH (1:1).

Table 3. Model Studies on the Macrocyclization of **3** Using a Copper/T-PEG$_{1900}$ System and Phase Separation As a Strategy to Control Reactivity



entry	scale (mmol **2**)	yield (%)	solvent volume,[a] biphasic (mL)	solvent volume,[b] monophasic (mL)
1	0.12	73	5	600
2	0.36	65	15	1800
3	1.00	60	45	5400

[a] Total volume of solvent required for the reaction using PEG$_{400}$/MeOH solvent mixture. [b] Total solvent required if an analogous reaction were performed using the traditional conditions reported in Scheme 1.

under classical catalysis (CuCl, TMEDA) at 150X the concentration used in the traditional conditions (Scheme 1).

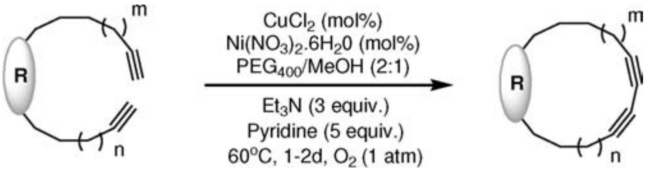
As with the macrocyclization reactions employing the T-PEG$_{1900}$ ligand, we sought to improve the macrocyclization reaction using PEG$_{400}$ as a solvent through the use of Ni-based cocatalysts. Upon repeating the macrocyclization reaction of **2** in the presence of a stoichiometric amount of NiCl$_2$ a similar yield of 24% yield was observed (Table 2).[32] The reaction yields and rates could be increased (24 → 57%, 3 → 1 day) by adjusting the ratio of PEG$_{400}$/MeOH from 1:1 to 2:1. We investigated other ligands for the Cu catalyzed process and pyridine was shown to be superior (66% yield of **3**) to TMEDA, phenanthroline or 2,6-bipyridine (Table 2, entries 3−6). Gratifyingly, the catalyst loading could be decreased to 25 mol % for both CuCl$_2$ and NiCl$_2$ without significant decreases in yield, although the reaction time was longer (Table 2, entries 6−9). The macrocyclization of **2** under these reaction conditions was slightly irreproducible, perhaps due to the fact that the NiCl$_2$ cocatalyst was not completely soluble in the reaction media. Analogous to previous studies, a series of more soluble Ni cocatalysts was surveyed (Table 2, entries 10−14) and Ni(NO$_3$)$_2$·6H$_2$O was again found to be highly soluble in PEG$_{400}$, and afforded good yields of the product **3** (73%) at 25 mol % catalyst loading (Table 2, entries 16).

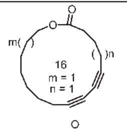
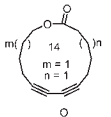
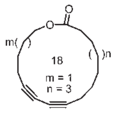
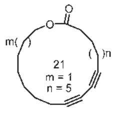
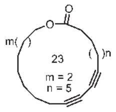
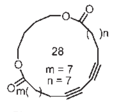
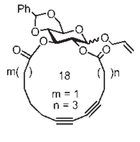
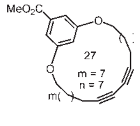
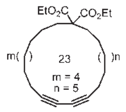
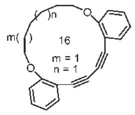
Upon optimization of the catalytic system and the reaction conditions, we performed some preliminary investigations on the feasibility of scale-up using the phase separation strategy for macrocyclization (Table 3). When the macrocyclization of diyne **2** was performed on three times the previous scale (0.36 mmol), we were pleased to observe very little change in the overall isolated yield of the reaction (Table 3, entry 2). When the reaction was scaled up to 1 mmol scale, an isolated yield of 60% was obtained for the desired macrocycle **3**. Importantly, the macrocyclization on 1 mmol scale needed only 45 mL of a mixture of PEG$_{400}$/MeOH while the analogous macrocyclization would have required 5400 mL of PhMe or CH$_2$Cl$_2$ to perform (Table 3).

While further optimization of the catalyst and/or ligand structure may afford higher yields, the increase in concentration, reduction of solvent and high yields demonstrate a significant step toward achieving a general and green macrocyclization protocol. In addition, it should be noted that the phase separation strategy allows for a simpler experimental setup when conducting the macrocyclization (Figure 2), whereby the use of cumbersome syringe pumps and expensive glassware is avoided and replaced by a simple screw-cap vial.

To demonstrate some generality of the optimized catalytic system and reaction conditions, we explored the substrate scope of the macrocyclization. We first explored the scope of the ring size for the synthesis of macrolactones using the phase separation strategy (Table 4, entries 1−6). Each macrocyclization was performed using both stoichiometric and catalytic amounts of Cu and Ni complexes. In general, yields are good to excellent using catalytic amounts of Cu and Ni and only small increases were observed when using stoichiometric quantities. First, a smaller rigidified 14-membered macrolactone **8** was isolated in 62% yield (Table 4, entry 1). Second, the macrocyclization of larger macrolactones was investigated and it was found that lactones having ring sizes of 18, 21, and 23 atoms at high concentrations were all possible using the phase separation strategy. The 18-membered macrolactone **9** was isolated in 74% yield using 25 mol % of catalysts (stoichiometric Cu/Ni = 87%). The synthesis of 21- and 23-membered macrolactones was equally efficient. The diyne macrocycles **10** and **11** were isolated in 81% and 78% yield, respectively, under catalytic conditions. Finally, a 28-membered macrolactone **12** was prepared in 91% isolated yield using stoichiometric reagents and in 98% when

Table 4. **Macrocyclization via Glaser-Hay Coupling of Various Diynes Using a Copper/Nickel Co-Catalyst System and Phase Separation**



entry	product		catalyst (mol %)	yield (%)
1		**3**	100 25	83 73
2		**8**	100 25	68 62
3		**9**	100 25	87 74
4		**10**	100 25	93 81
5		**11**	100 25	85 78
6		**12**	100 25	91 98
7		**13**	100 25	67 65
8		**14**	100 25	69 70
9		**15**	100 25	65 63
10		**16**	100 25	77 98

using the catalytic Cu/Ni combination. A variety of functional groups were also tolerant of the reactions conditions (Table 4, entries 7−10). An 18-membered diyne macrocycle embedded within a suitably protected glucose core **13** was isolated in 65% yield under catalytic conditions. Similarly, esters and phenolic ethers all afforded high yields of the corresponding macrocyclization products. Under catalytic conditions, the ester-containing macrocycle **14** was isolated in 70% yield under the catalytic conditions. In addition, the malonate derived macrocycle **15** was isolated in 63% yield under catalytic conditions. Macrocyclization of aryl substituted alkynes was similarly efficient, as the 16-membered diether **16** was isolated in nearly quantitative yields (98%) under the optimized catalytic conditions.[33]

Importantly, in all of the above examples, control reactions whereby the substrates were placed in homogeneous MeOH solution at the identical high concentrations only resulted in complete consumption of the diyne precursors and the formation of polymer products demonstrating that phase separation using transitional metal complexes solubilized in PEG_{400} can be exploited to promote efficient macrocyclization of a wide range of diyne macrocycles (**8**−**16**) in good to excellent yields (65−98%) at high concentrations.

■ CONCLUSIONS

Macrocyclic Glaser-Hay coupling at high concentrations can be achieved using phase separation as a strategy to control dilution effects. Two different strategies for performing macrocyclizations in biphasic media have been developed using the diyne macrocycle **3** as a target to demonstrate that the developed macrocyclizations could be performed on industrially relevant compounds. First, we demonstrated that when necessary, phase separation between catalyst and substrates can be achieved by developing hydrophilic ligands for transition metal complexes that allow for the catalysts to be sequestered in a highly polar and/or hydrophilic phase. To demonstrate this strategy, a PEGylated TMEDA derivative T-PEG_{1900} was prepared and promoted the cyclization of **2** at a significantly higher concentration [0.0002 M (600 mL) → 0.03 M (5 mL)] and better yields (11% → 65%) than that utilized in traditional methods. Second, solubilization of Cu/pyridine complexes in PEG_{400} demonstrates its applicability as a green and efficient solvent for use in biphasic mixtures for macrocyclization at high concentrations. Copper/nickel cocatalyst systems can be used to promote the macrocyclization of a wide range of macrocycles with varying ring sizes and functional groups. The concept that phase separation can be used to control dilution effects in macrocyclization reactions should allow for the practical synthesis of this class of compounds to provide highly valuable chemical products using practices that are significantly more environmentally benign. In addition, the phase separation strategies discussed herein are currently being applied to develop other macrocyclization protocols for macrocyclic olefin metathesis and macrolactonization, using environmentally benign solvents and concentrations.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information. Experimental procedures and spectroscopic data for all new compounds and complete ref 3. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

shawn.collins@umontreal.ca

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