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VIP Very Important Paper

Ultra-Fast Continuous-Flow Photo-Thiol-Ene Functionalization of Conformation-Controlled Cinchona Alkaloids

Kouakou Eric Konan,^[a, b] Abollé Abollé,^[b] and François-Xavier Felpin^{*[a]}

In this work, we describe ultra-fast continuous flow photo-thiol-ene reactions on cinchona alkaloids derivatives through a control of the reactive conformation in solution. Flow thiol-ene reactions proceed at 32 °C under light irradiation at 365 nm and require only 2.5 minutes of residence time to reach completion. The short path length of the tubular flow photochemical

reactor, which maximizes and homogenizes the photon flux, associated to the fine tuning of the reactive conformation of cinchona alkaloids in solution are the main reasons for the high rates observed. The predominant conformation in solution of cinchona alkaloids was adjusted through the substitution of the hydroxyl group at C9 by a phenyl carbamate function.

Introduction

Quinine (1), cinchonidine (2), quinidine (3) and cinchonine (4) are iconic natural products isolated from the trees of cinchona plants (Figure 1). These alkaloids have a rich and unusual history in both medical and chemical sciences. Quinine (1) has been the first drug to fight against malaria and is still in the arsenal of treatments especially when synthetic drugs are not effective anymore due to resistance phenomena. On the other hand, cinchona alkaloids and their synthetic derivatives have a prominent place in asymmetric catalysis, serving as chiral organocatalyst and ligand for metal-catalyzed reactions,^[1–3] the asymmetric Sharpless dihydroxylation of olefins being the most notable example.^[4,5]

In a more unusual application, we recently exploited the ability of quinine (1) to bind metallic species through the development of quinine grafted cellulose depolluting membranes with the aim of establishing affordable and equipment-free water purification technologies directly deliverable to end-users in developing countries.^[6] While we developed several generations of membranes,^[7,8] our last quinine-based prototype exploits the coordination properties of quinine (1) with respect to heavy metals at pH compatible with the pH of drinking water.^[6] This quinine-based membrane was fabricated by copper-catalyzed 1,3-dipolar cycloaddition of quinine–alkyne

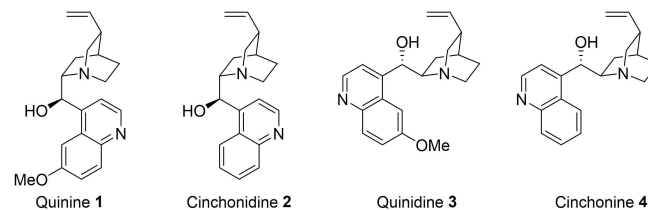


Figure 1. Alkaloids isolated from cinchona plants.

with cellulose–azide paper. With the objective of developing a technology that could be scaled-up and then industrialized, we searched for metal-free alternative functionalization strategies of cinchona alkaloids that could be conducted under continuous process. In this frame, we recently described a general strategy for the functionalization of cinchona alkaloids through photochemical thiol-ene reactions conducted in a flow photochemical reactor.^[9] Under typical experimental conditions quinine reacted with thiol partners and 2,2-dimethoxy-2-phenylacetophenone (DMPA) as photo-initiator in chloroform for 10–30 minutes of residence time. While these conditions usually provided thiol-ene product in high yields ($\geq 75\%$), the moderate reaction throughput prevented any scaling-up for industrial transfer.

In this contribution, we describe our efforts toward the development of ultra-fast continuous flow photo-thiol-ene reactions of cinchona alkaloids derivatives through a fine tuning of conformation predominating in solution. The validity of this strategy is demonstrated on a variety of examples.

Results and Discussion

During preliminary studies, we observed that the continuous flow photo-thiol-ene reaction of 1-hexene with 2-mercaptoethanol proceeded in less than 1 minute while the same transformation applied to quinine instead of 1-hexene required 10 minutes of residence time. While the ultra-fast functionaliza-

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tion of 1-hexene was outside the scope of our study, it turned out that reaction kinetics depend, at least in part, on the reactivity of the double bond. We reasoned that double bond reactivity might be increased by tuning the reactive conformation of cinchona alkaloids in solution. Wynberg and co-workers calculated by molecular mechanics that quinine (1) has in principle three low-energy conformations termed “open” and “closed” conformations reflecting the relative arrangement of the quinoline ring to the quinuclidine nitrogen around the C8–C9 bond (Figure 2).^[10,11] In the “open” conformation **A**, the quinuclidine nitrogen points away from the quinoline ring while in “closed” conformations **B** and **C** the quinuclidine nitrogen points toward the quinoline ring.

Molecular mechanics combined with NMR analyses revealed that the conformational behavior of cinchona alkaloids is mainly governed by solute-alkaloids interactions and intramolecular interactions. For instance, quinine 1 and cinchonine 2 are known to both adopt open conformation **A** in most organic solvents.^[12] Switching the hydroxyl group of cinchona alkaloids at C9 by an acetyl or benzoyl substituent led to a conformational evolution and open conformer **A** co-exists with closed form **B**.

In this frame, we anticipated that chemical modification/alteration of the hydroxyl function of cinchona alkaloids might modify the reactive conformation and eventually increase the reactivity of the proximal double bond. Following this assumption, we masked the hydroxyl function of quinine with various protecting groups (Figure 3A) and evaluated the flow photo-thiol-ene reaction kinetics with 2-mercaptoethanol as benchmark thiol in the presence of 2,2-dimethoxy-2-phenylacetone (DMPA) as photo-initiator (Figure 3C). The reaction occurred in a custom built photochemical reactor equipped with a compact fluorescent lamp emitting at 365 nm (Figure 3B). The temperature of the flow reactor was stabilized at 32 °C ± 1 °C using an air cooling system.

Reaction conversions were recorded at 0, 1, 2.5, 5 and 10 minutes of residence time and the results are depicted in Figure 4. The thiol-ene reaction carried out on unmodified quinine 1 reached completion after 10 minutes of residence time to produce compounds 10. The induction period observed below 1 minute of residence time suggested a conformational change in solution to a more reactive species. This assumption was confirmed by the kinetic profile observed with quinine methyl ether derivative 5, which followed a similar behavior but without induction period to give product 11. The small steric hindrance of the methyl ether function is likely not sufficient to

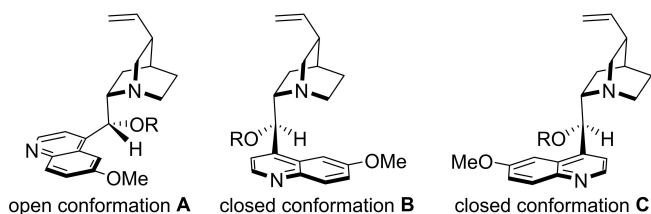
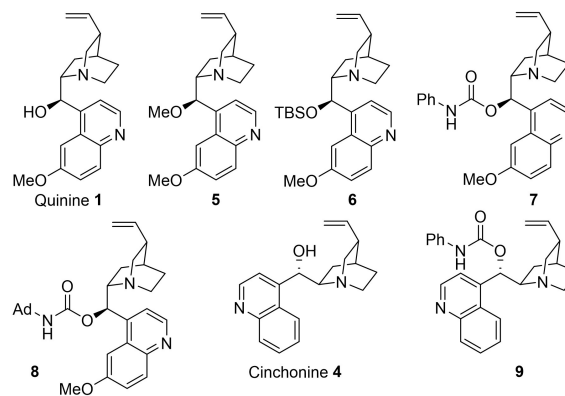
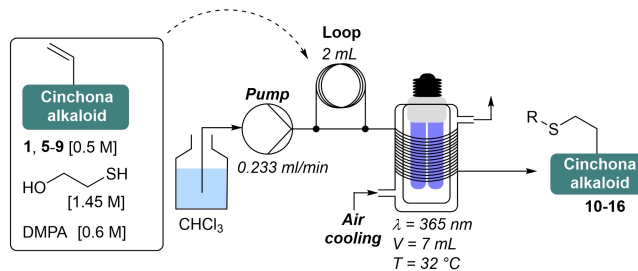


Figure 2. Low-energy conformations of quinine derivatives.

A/ Cinchona alkaloid derivatives evaluated for the photo-thiol-ene reaction



B/ Experimental setup used for the kinetic studies



C/ Cinchona alkaloid derivatives obtained through photo-thiol-ene reactions

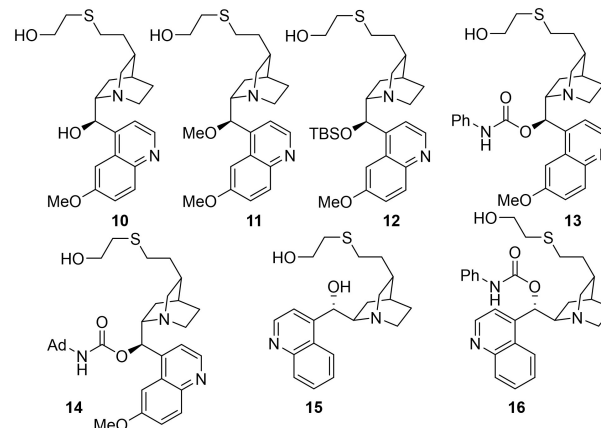


Figure 3. Kinetic studies carried out on cinchona alkaloids derivatives.

favor a high proportion of closed conformer **B**. An increase of the steric hindrance through the use of a silyl ether protecting group (compound 6) should favor closed conformation **B** to the detriment of open form **A** due to unfavorable steric repulsions between the silyl group and the quinuclidine ring. Gratifyingly, the reaction rate significantly increased and 95% conversion was reached after 5 minutes of residence time to yield 12. These results validated our initial intuition that the thiol-ene reaction is sensitive to the conformation(s) of quinine derivatives in solution. However, in the frame our work on depolluting membranes, it is unlikely that quinine derivative 6 retains metal species coordination properties which are essential for metal adsorption. Therefore, we evaluated the influence of carbamate groups on thiol-ene reaction rates. The carbamate function

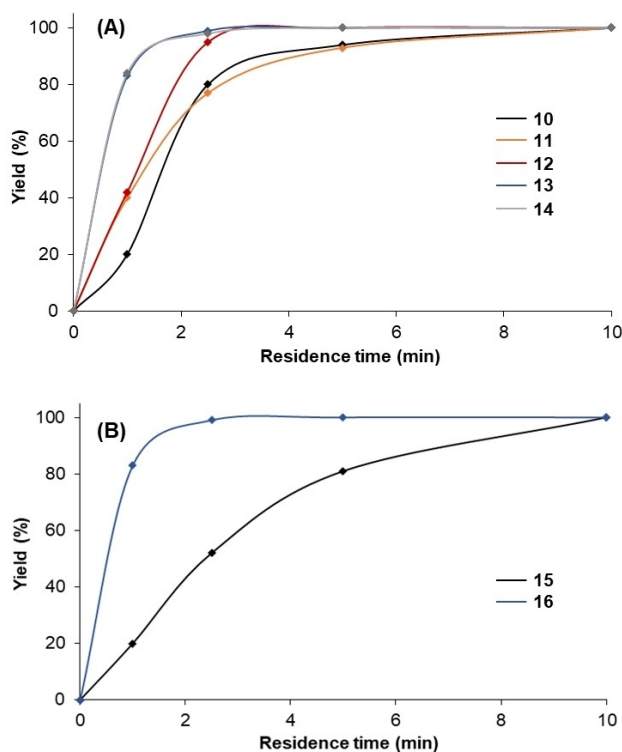


Figure 4. (A) Kinetic profiles for the formation of quinine derivatives 10–14. (B) Kinetic profiles for the formation of cinchonine derivatives 15–16. Yields were determined by NMR using 2-bromomesitylene as internal standard.

belong to a large family of metal ligands^[13] and the affinity of quinine-based carbamate derivatives with metals has been exploited in asymmetric catalysis^[14,15] and medicinal chemistry.^[16] Quinine modified as the phenyl carbamate derivative **7** spectacularly increased the reaction rate and complete conversion was reached after only 2.5 minutes of residence time to give adduct **13** (Figure 4A). Switching the phenyl carbamate function for the highly sterically hindered adamantyl carbamate derivative **8** produced compound **14** with no modification of the reaction rate, suggesting that the transformation is mostly insensitive to steric hindrance.

In our previous study, we observed that cinchonine **4** was less reactive than quinine **1** in thiol-ene transformations and this reduced reactivity was intuitively attributed to a peculiar less-reactive conformation in solution.^[9] We can now prove this hypothesis since a spectacularly increase of reactivity was observed when the hydroxyl group of cinchonine **4** was masked with a phenyl carbamate function to give derivative **9** (Figure 4B). From these kinetics studies on quinine and cinchonine derivatives we concluded that the phenyl carbamate function gave the fastest reaction rates for thiol-ene reactions since completion of the reactions was reached at least 4 times faster compared to unmodified cinchona alkaloids.

With these results in hand, we moved on to expand this chemistry to a variety of thiol partners using quinine phenyl carbamate **7** and cinchonine phenyl carbamate **9** partners (Figure 5, see also Table S1 in SI). Pleasingly, all combinations

studied reached completion in 2.5 minutes of residence time as evidenced by NMR analysis and thiol-ene adducts were isolated in high isolated yields. The transformation was so fast that we were not able to observe any significant differences regardless of the cinchona alkaloid (**7** or **9**) used and the electronic nature of the organic thiol derivative. The rate enhancement reached with this conformation-guided strategy is remarkable for cinchonine derivatives. Cinchonine **4** was poorly reactive for thiol-ene reactions and isolated yields were typically < 50% even after 30 minutes of residence time.^[9] Moving from cinchonine **4** to its phenyl carbamate **9** derivative spectacularly improved both conversion and reactions yields since compounds **16** and **22–26** reached > 98% conversion after only 2.5 minutes of residence time and isolated yields ranged from 86 to 95%. We attribute the exceptional reactivity of cinchona alkaloid derivatives **7** and **9** for thiol-ene reactions – much higher than those usually observed in batch processes – to the conjunction of beneficial factors: i/the high photon flux allowed in the flow photochemical reactor,^[17–19] ii/the high reproducibility of photochemical reactions in flow^[20–27] and iii/the control of a highly reactive conformation in solution.

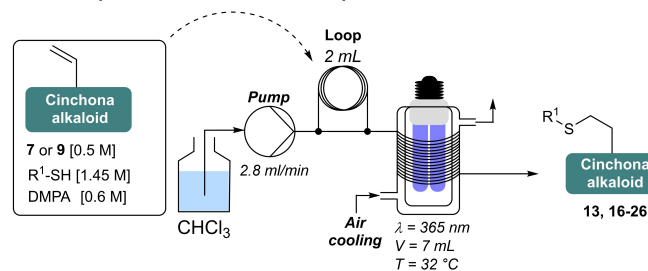
Conclusion

In this work we demonstrated the importance of the C9-substituent of cinchona alkaloids on the thiol-ene reactions conducted under continuous flow. Masking the alcohol function with various protecting groups significantly increased thiol-ene reaction rates. Reactions conducted with carbamate derivatives reached maximum conversion 4 to 10 times faster than those conducted with unmodified alkaloids. The ultra-fast photo-thiol-ene functionalization of cinchona alkaloids results from the combination of the high absorption of photons emitted by the light source thanks to the short path length in the tubular flow photochemical reactor and the control of the reactive conformation in solution. The results described in this manuscript provide important insights that go far beyond the scope of this study, particularly for the development of more reactive chiral catalysts from cinchona alkaloids. We are now adapting this chemistry to graft quinine derivatives on a thio-cellulose platform^[28–31] with the aim of developing a photochemical process in flow compatible with the requirements of industrial setting.^[32–35]

Experimental Section

General procedure for the flow photo-thiol-ene functionalization of cinchona alkaloids derivatives. The experimental setup consisted of a single stream equipped with a PEEK injection loop (2 mL, 0.76 mm id) as depicted in Figure 5A. The loop was loaded with a solution of cinchona alkaloids **1**, **5–9** (0.50 M in CHCl₃), thiol compounds (1.45 M in CHCl₃) and 2,2-dimethoxy-2-phenylacetophenone (DMPA) as photo-initiator (0.60 M in CHCl₃). The mixture was flowed at 2.8 mL/min corresponding to 2.5 minutes of residence time. The thiol-ene reaction occurred in the flow photochemical reactor consisting of FEP tubing (7 mL, i.d. 0.75 mm) wrapped around a double wall glassware. A compact fluorescent

A/ Experimental setup used for the reaction scope



B/ Photochemical thiol-ene reactions in flow on cinchona alkaloids ($R^2 = \text{CONHPh}$)

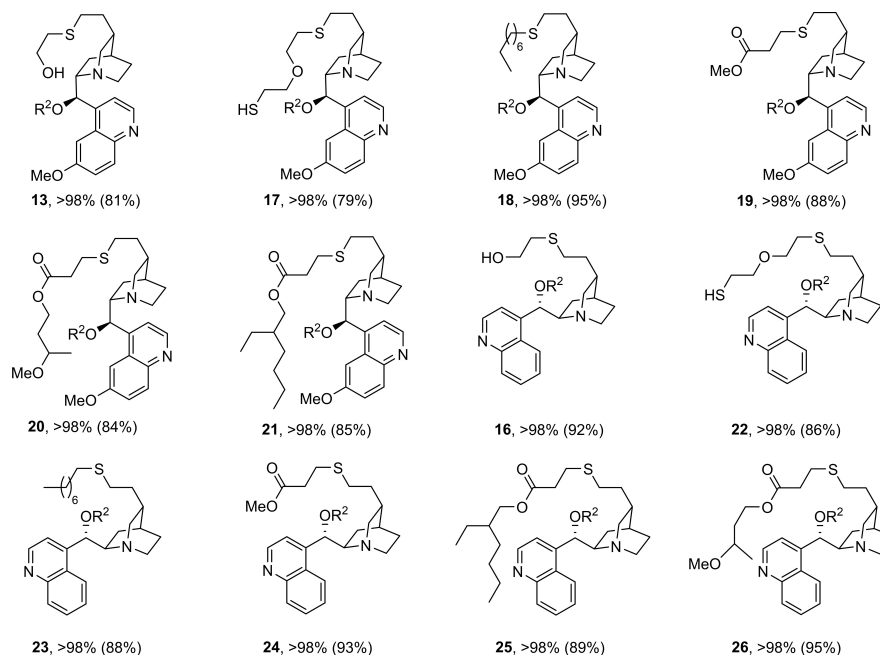


Figure 5. A/Experimental setup used for the reaction scope study. B/Cinchona alkaloids prepared through photo thiol-ene reactions. NMR conversion are reported and values in bracket refer to isolated yields.

lamp emitting at 365 nm was inserted in the photochemical reactor and an air cooling system stabilized at $32\text{ }^\circ\text{C} \pm 1\text{ }^\circ\text{C}$. The resulting functionalized cinchona alkaloids were collected in vials. Volatiles were removed under reduced pressure and the crude residues were purified by flash chromatography. Conversions were assessed by ^1H NMR using 2-bromomesitylene as internal standard.

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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