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A Cycloalkane-based Thermomorphic System for Organocatalytic Cyclopropanation Using Ammonium Ylides

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Highly polar ammonium ylide intermediates derived from α-halocarbonyl compounds were successfully trapped by cycloalkane phase-tagged activated alkenes via a cycloalkane-based thermomorphic (CBT) process, which allows for facile product isolation using a single liquid–liquid extraction step to effectively generate cyclopropane libraries in the cyclohexane phase.

Solution-phase combinatorial chemistry has emerged as a useful alternative to solid-phase combinatorial chemistry in the advancement of drug discovery.[1,2] Currently, our laboratories are developing a CBT system that promotes reactions in monophasic solution, then allows product isolation upon cooling and phase separation (Figure 1). The CBT system can allow not only for selective separation of cycloalkane phase (CP)-tagged products from a reaction mixture, but also enables the practice of a wide range of existing reactions with higher reactivity than in solid phase, even in combination with CP-tagged substances and insoluble species: substrates, reagents catalysis.[3,4] Furthermore, the highly selective formation of separable CP-tagged products confers a significant advantage in monitoring reaction progress and identification of the products. In particular, the remarkable phase-miscibility of cycloalkanes in polar solvents enables efficient interactions between the highly polar intermediates and the CP-tagged substrate. Despite such attractive features, however, this methodology has been limited to peptide synthesis and palladium-catalyzed reactions.

Recently, organocatalytic reactions have gained much attention due to: i) the absence of toxic transition metals, ii) readily available starting materials, and iii) ease of handling.[5] In particular, ammonium ylide species have been successfully applied in various synthetic methodologies in the construction of unique building blocks.[6,7] To apply a CBT system toward organocatalytic cyclopropanation, a suitable CP-tag must be introduced onto one of the two starting substrates to assemble product libraries in the cycloalkane phase (Figure 2). In fact, inadequate construction of the CBT media and CP tags can often preclude the generation and stabilization of the highly polar ylide species, thus impeding subsequent intermolecular carbon–carbon bond-forming reactions. As a consequence, this challenge provided the impetus for us to develop a CBT method that would efficiently generate and stabilize such unstable ammonium ylides. In this paper, we report the application of a CBT system to organocatalytic cyclopropanation via ammonium ylides, with modifications of a CP tag, to generate cyclopropane libraries in a cycloalkane phase. Accordingly, the development of this CBT system provides a significant opportunity to extend the applicability to a wider variety of organocatalytic reaction processes.

As shown in Scheme 1, the organocatalytic cyclopropanation via a CBT process was initially investigated using hydrophobic α-bromo ester 1, DABCO (1,4-diazobicyclo[2.2.2]octane, as a

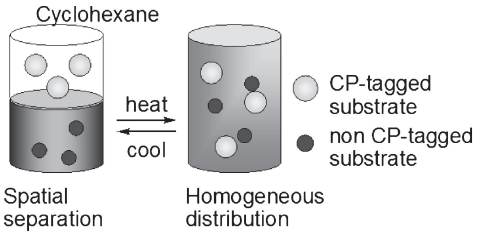


Figure 1. Schematic view of a CBT system.

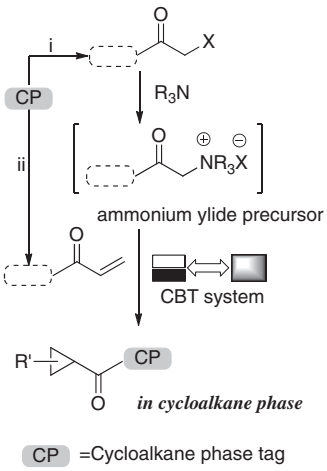
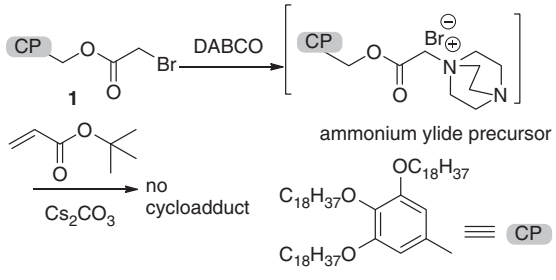
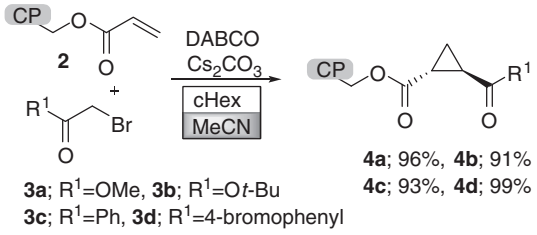


Figure 2. Two possible routes for a CBT synthesis of a CP-tagged product in cycloalkane phase. i) Modification of the CP-tag onto an α-halocarbonyl compound. ii) Modification of the CP-tag onto an α,β-unsaturated carbonyl compound.



Scheme 1.

nucleophilic tertiary amine), and *t*-butyl acrylate. After stirring under reflux conditions for 24 h, the CBT solution was allowed to cool to room temperature to afford a distinct cyclohexane phase under biphasic conditions. Under these reaction conditions, however, the expected cycloadduct was not obtained; the failure can attributed to the hydrophobic modification of an inappropriate



Scheme 2.

substrate site that cannot generate the ylide moiety, and to the amphipathic properties of the hydrophobic ammonium ylide that form undesirable aggregation structures interfering with CBT cyclopropanation.

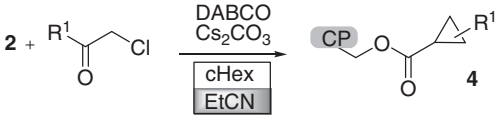
Subsequently, as shown in Scheme 2, a CP tag was introduced onto activated olefins to carry out the cyclopropanation reaction of **2** with methyl bromoacetate (**3a**) in a similar manner.[8] In this case, the expected cycloaddition reaction proceeded efficiently to afford cyclopropane **4a** (96% yield), which was almost exclusively distributed in the cyclohexane phase. As a note, the syn product was not detected (^{1}H NMR and HPLC analysis). The results demonstrate that the CBT system enables effective interactions between polar and apolar substrates in a monophasic solution, followed by product isolation upon cooling and phase separation. Additionally, for such organocatalytic CBT reactions, hydrophobic modifications of activated olefins, rather than those of ylide precursors, was found to be more effective. Subsequently, as shown in Scheme 2, organocatalytic cyclopropanation reactions of *t*-butyl bromoacetate (**3b**), 2-bromoacetophenone (**3c**), and 2,4′-dibromoacetophenone were shown to successfully afford the CP-tagged cyclopropanes in high yields.

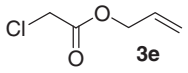
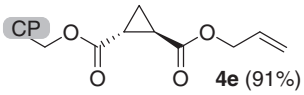
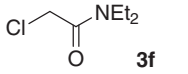
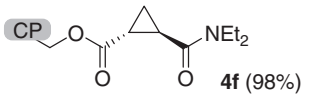
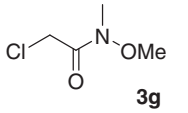
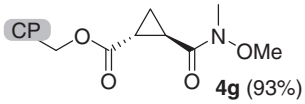
These results prompted us to apply the CBT technique in the reactions of several commercially available α-chlorocarbonyl compounds. Using allyl chloroacetate (**3e**), however, the reaction proceeded with merely 17% conversion, which is attributable to the lower reactivity and nucleophilicity of the ammonium ylide intermediates generated by α-chlorocarbonyl moieties to α,β-unsaturated carbonyl compounds, and to the use of a cHex/MeCN mixture, which cannot completely form a monophasic solution.

In order to increase the interactions between α-chlorocarbonyls and the CP-tagged substrate, a more appropriate CBT solution system was required. Accordingly, CBT cyclopropanation was studied using a combination of cHex and EtCN, which forms a complete monophase, resulting in an increased yield of the targeted products to 91%. Using the optimized procedures, treatment of 2-chloro-*N*,*N*-diethylacetamide (**3f**) and 2-chloro-*N*-methoxy-*N*-methylacetamide (**3g**) furnished the cycloadduct products in high yields (Table 1). In these cases, the alternative method for the CBT process involved addition of *n*-hexane (and/or MeCN) to form a biphasic mixture at room temperature allowing separation of the upper phase without cooling.

Our results show that a cHex/EtCN mixture was extremely efficient in forming the monophasic solution during organocatalytic cyclopropanation reactions. In contrast, complete reactions were not observed in conventional biphasic solutions, even under a partially miscible CBT system such as a cHex/MeCN mixture (Figure 2). Obviously, the effective mutual miscibility of the cosolvents plays a significant role in the reactions between the hydrophobic phase-tagged substrate and the highly polar quaternary ammonium salt.

Table 1. A CBT system for organocatalytic cyclopropanations using α-chlorocarbonyl compounds **3d**–**3f**



Entry	Substrate	Product[a,b]
1	 **3e**	 **4e** (91%)
2	 **3f**	 **4f** (98%)
3	 **3g**	 **4g** (93%)

[a]Syn stereoisomer was not observed by ^{1}H NMR experiments. [b]Isolated yied.

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