Asymmetric Synthesis

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Enantioselective Catalytic Intramolecular Cyclopropanation using Modified Cinchona Alkaloid Organocatalysts**

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New asymmetric methods to generate the cyclopropane motif have attracted widespread attention from the synthetic community owing to their ubiquitous presence in a diverse range of natural products and their crucial role in the mode of action of many therapeutic agents.[1] Furthermore, the rigid structure and strain-driven reactivity make them attractive intermediates in complex molecule synthesis.[2] Because of these important properties and the need for efficient methods for their stereoselective formation, the synthesis of cyclopropane-containing molecules has become a platform for the development of new asymmetric catalytic processes.[3] Notably, in the last few years numerous metal-catalyzed and organocatalytic intermolecular cyclopropanation reactions have been reported that enable the generation of discrete three-membered ring systems with high diastereo- and enantioselectivity.[4] In contrast, there are few corresponding catalytic asymmetric intramolecular reactions. Although recently a number of catalytic diastereoselective intramolecular cyclopropanation processes have been reported,[5] only methods that exploit the metal-catalyzed decomposition of α-diazo-carbonyl compounds lead to a general enantioselective assembly of [*n*.1.0]-bicycloalkane frameworks.[6] The development of a new catalytic enantioselective intramolecular cyclopropanation method would be a valuable tool for the synthetic chemist and would further aid the quest for novel

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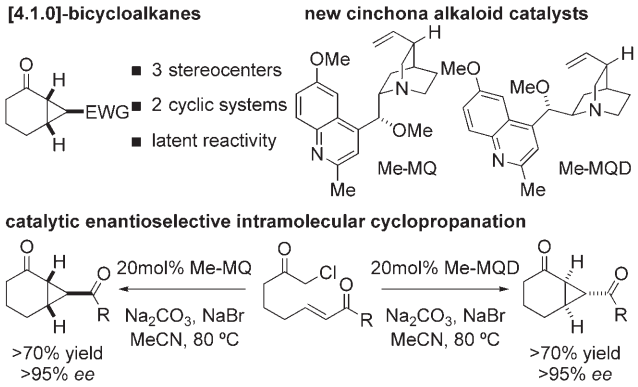
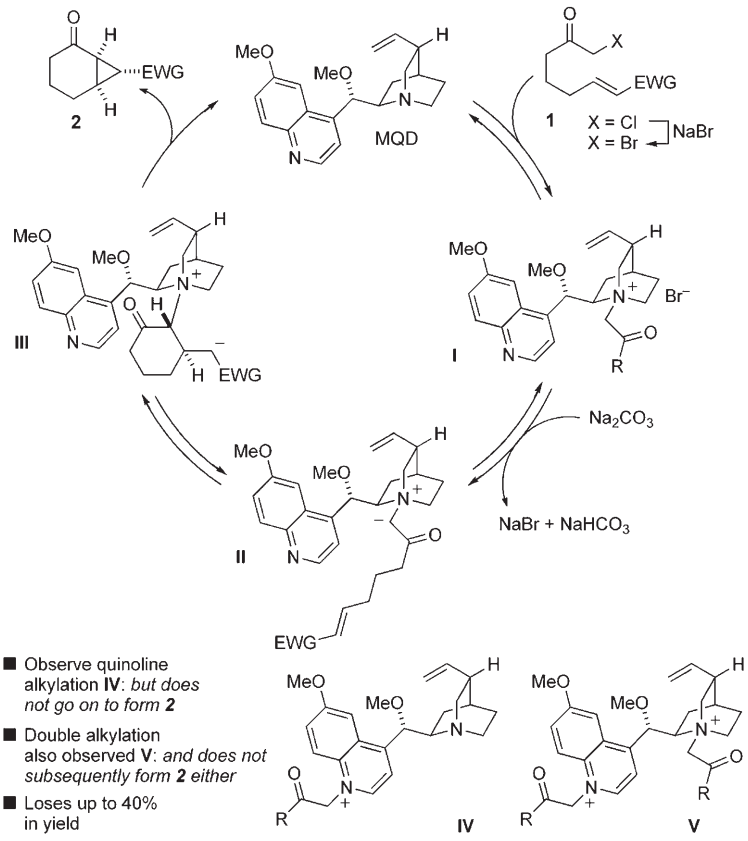
ways to efficiently assemble architecturally complex molecules.[7]

Herein, we describe the development of an organocatalytic enantioselective intramolecular cyclopropanation reaction via ammonium ylides that forms [4.1.0]-bicycloalkanes with high stereoselectivity. The process is catalyzed by novel cinchona alkaloids that were developed through a mechanism-guided design strategy and produce the products in excellent yields and as single diastereomers and with *ee* values usually over 95% (Scheme 1).



Scheme 1. Enantioselective organocatalytic cyclopropanation. EWG = electron-withdrawing group.



Scheme 2. Catalytic cycle for intramolecular cyclopropanation.

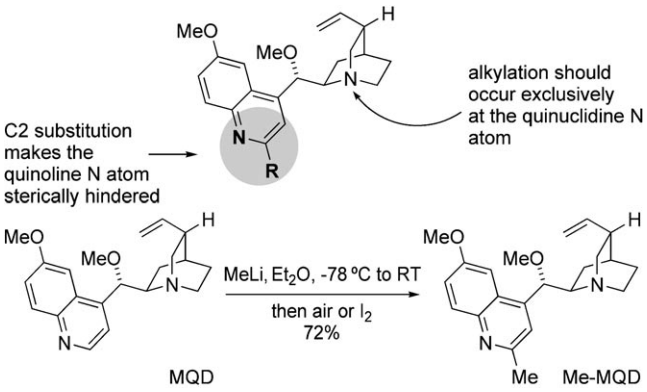
We recently reported that an intramolecular cyclopropanation reaction could be catalyzed by the nucleophilic amine 1,4-diazabicyclo[2.2.2]octane (DABCO). When we replaced DABCO with a catalytic quantity of the chiral quinidine derivative 9-*O*-methylquinidine (MQD; MQ = 9-*O*-methylquinine), the cyclopropane was formed with an excellent *ee* value of 94%, although in poor yield.[8] The corresponding quinine catalyst gave similar results when producing the opposite enantiomer, and frustratingly all attempts to improve the yield and maintain the *ee* value through variation of the conditions were met with failure. It was notable during these optimization studies that in the reaction of **1a** with 20 mol% of the MQD catalyst it was not possible to quantitatively reisolate the catalyst at the end of the process.

We speculated the catalyst was being derailed from its desired mechanistic pathway, thus resulting in a deleterious effect on the yield of the cyclopropane (−)-**2a**. The catalytic cycle for the enantioselective intramolecular cyclopropanation initially involves Finkelstein substitution at the chloroketone unit with sodium bromide (Scheme 2). Displacement of the bromide with the alkaloid catalyst forms the quaternary ammonium salt **I**, which undergoes deprotonation with sodium carbonate to the ylide-type species **II**. Intramolecular conjugate addition forms a new intermediate **III** and subsequently the cyclopropane **2**, thus expelling the catalyst MQD to restart the cycle. Therefore, to investigate the poor yield in this process we analyzed a reaction that was carried out until 60% conversion of the starting material was achieved. From this we could identify the expected salt **I**; however, a complex combination of salts was also obtained. Although we were not able to purify them, we speculate these intermediates result from alkylation at the quinoline nitrogen atom of **IV** and both nitrogen atoms of the alkaloid catalyst **V**.[9a] Importantly, no further cyclopropanation was observed when these salts were resubjected to the reactions conditions. This behavior suggested that the proposed side reaction at the quinoline nitrogen atom consumed both the catalyst and starting material and was responsible for the poor yield in the reaction.[9b]

We therefore speculated that a modified catalyst with substitution at the C2′ position on the quinoline ring would render the nitrogen atom inert and should inhibit this problematic reaction.[10] Towards the synthesis of these catalysts, we found that treatment of the cinchona alkaloid catalysts MQD and MQ with methyl lithium in diethyl ether at room temperature followed by exposure to air or iodine afforded 2′-methyl-9-*O*-methylquinine (Me-MQ) and 2′-methyl-9-*O*-methylquinidine (Me-MQD) in good yield (Scheme 3).

The modified cinchona catalysts were tested in the intramolecular cyclopropanation, and to our delight use of the Me-MQD catalyst resulted in the formation of (−)-**2a** in a high yield (88%) with 97% *ee* (Scheme 4). The Me-MQ catalyst also improved the yield of the reaction to 84%, again with 97% *ee* of the opposite isomer (+)-**2a**.[11] We found that the reaction was most effective when 20 mol% of the cinchona alkaloid catalyst was used.

We next investigated the scope and limitations of this new catalytic asymmetric process. The reaction worked on a range



Scheme 3. Synthesis of modified cinchona alkaloid organocatalysts.

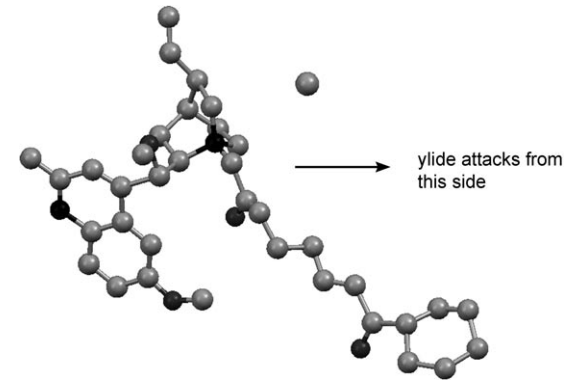
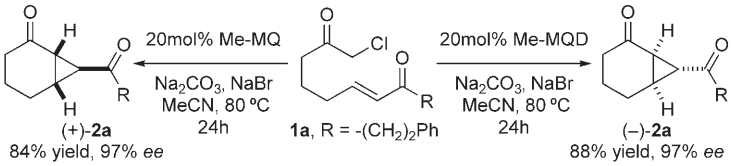


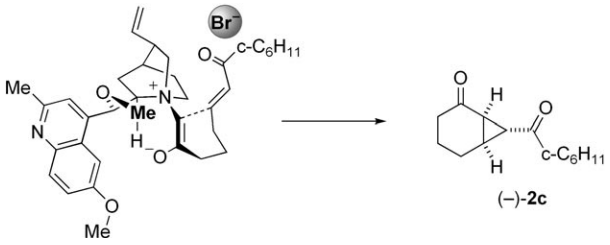
Figure 1. X-ray crystal structure of a Me-MQD salt, **1c**.



Scheme 4. Cyclopropanation with modified cinchona catalysts.

of systems as shown in Table 1.[12] Enones were the best substrates for this reaction, and a range of substituents could be tolerated, including alkyl (branched and unbranched; entries 1–3 and 10–12), aryl (electron-rich and electron-deficient substituents; entries 4–6 and 13–15) and heteroaryl motifs (entries 7 and 16). In all cases, a single diastereomer was observed. Yields were generally greater than 70%, the enantiomeric excess was >95% in almost all cases, and the bicycloalkanes could be accessed as either enantiomer depending on whether the Me-MQ or Me-MQD catalyst was used. Although the catalytic process works well for the formation of [4.1.0]-bicycloalkanes, the process is unsuccessful under these conditions for the corresponding [3.1.0] system. Formation of a heterocyclic amide product could be achieved with excellent enantiomeric excess, although the turnover in the reaction was surprisingly poor (entry 8). The reaction also works well when the enone is replaced with an α,β-unsaturated diimide (entries 9 and 18), thus providing convenient access to substrates with higher oxidation states. This new enantioselective organocatalytic process represents a facile and efficient method for the synthesis of these useful functionalized molecules in a high-yielding and stereocontrolled manner.

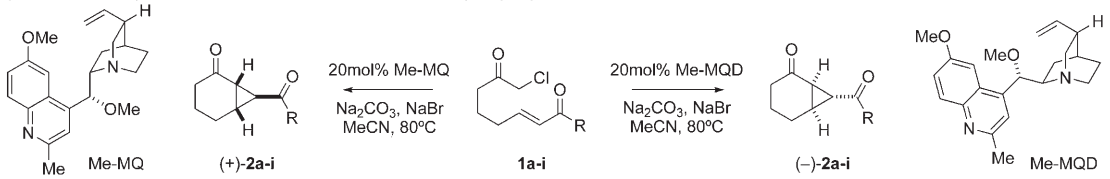
With an efficient new process in hand we investigated the origin of the enantioselectivity. A crystal structure of (+)-**2e** provided the absolute configuration of the cyclopropanes from the quinine series, and the opposite rotation of (−)-**2e** confirmed that the quinidine-based catalysts gave the other enantiomer.[12] Stirring bromoketone **1c** with one equivalent of Me-MQD in acetonitrile afforded the corresponding salt intermediate **1c**, which was crystallized from the same solvent, thus enabling analysis of the structure by X-ray diffraction (Figure 1). This study showed that the ammonium salt adopts a conformation that would give a *Z* enolate on deprotonation with the sodium carbonate. Although we are assuming that the structure suggested by the X-ray diffraction is indeed related to the active conformation in solution, it does allow us to propose a model that is consistent with the formation of the observed enantiomer (Scheme 5). Interestingly, from this model the required enantiomer will form from intramolecular conjugate addition through a boat-type transition state.

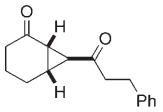
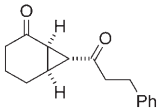
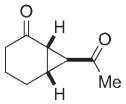
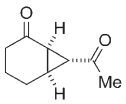
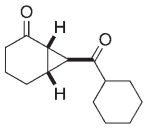
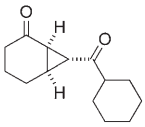
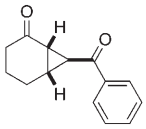
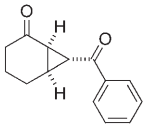
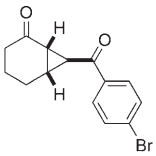
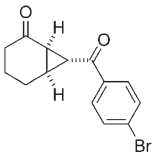
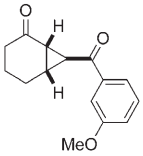
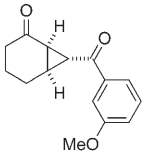
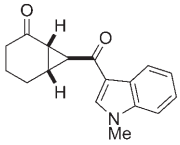
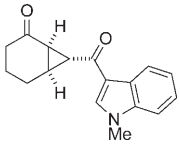
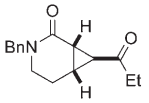
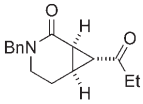
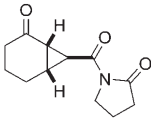
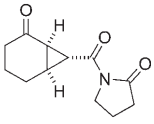


Scheme 5. Proposed origin of enantioselectivity.

Having demonstrated the effectiveness of our new enantioselective organocatalytic cyclopropanation process we turned our attention towards its application in complex molecule synthesis. We were intrigued by the possibility of using these readily accessible cyclopropanes as immediate precursors to polycyclic natural products. Of particular interest were structures such as guanacastapene A[13] and rameswaralide,[14] targets of significant biological interest. Furthermore, these natural products have a common 5–7–6 tricyclic framework, and we envisioned that these structures could be rapidly accessed through our organocatalytic cyclopropanation tactic and an intramolecular metal-catalyzed [5+2] cycloaddition reaction similar to that reported by Trost et al.[15] Accordingly, alkynyl vinyl cyclopropane **5** was synthesized from the corresponding aldehyde through a Wittig olefination. We were able to isolate both the *Z* and *E* isomers from this olefination, which was important as we speculated that the olefin isomers would lead to different diastereomers in the [5+2] cycloadditon. Accordingly, the treatment of (*Z*)-**5** with the ruthenium catalyst **6**[15a,b,16] surprisingly afforded none of the [5+2] cycloaddition prod-

Table 1: Scope of the catalytic enantioselective intramolecular cyclopropanation reaction.

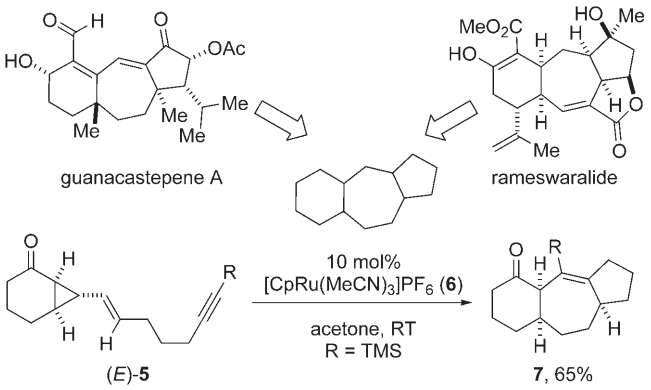


Entry[a]		Product	Yield[b] [%]	*ee* [%]	Entry[a]		Product	Yield[b] [%]	*ee* [%]
1	(+)-**2a**		84	97	10	(−)-**2a**		75	93
2	(+)-**2b**		68	98	11	(−)-**2b**		65	99
3	(+)-**2c**		79	95	12	(−)-**2c**		71	99
4	(+)-**2d**		78	98	13	(−)-**2d**		85	98
5	(+)-**2e**		83	96	14	(−)-**2e**		88	99
6	(+)-**2f**		77	99	15	(−)-**2f**		83	99
7	(+)-**2g**		95	98	16	(−)-**2g**		85	99
8[c]	(+)-**2h**		27	97	17[d]	(−)-**2h**		n.d.	n.d.
9	(+)-**2i**		77	99	18	(−)-**2i**		87	99

[a] Reactions run for 36 h. [b] Yield of the isolated product after chromatography. [c] One equivalent of catalyst was used. [d] Reaction not carried out.

uct, thus returning only the starting material. However, treatment of (*E*)-**5** with the same catalyst **6** led to the 5–7–6 ring system as the all *syn*-diastereomer **7**, which resembles the core of rameswaralide.[15a,b] We are further investigating the [5+2] cycloaddition of (*Z*)-**5**, as this process would form the *anti* relationship present in guanacastapene A. However, it is noteworthy that we can assemble the polycyclic framework present in many natural products from readily available starting materials in only four steps[17] by using three catalytic operations that control the installation of five C–C bonds and three stereocenters (Scheme 6).

In summary, we have developed a highly enantioselective catalytic intramolecular cyclopropanation process that uses modified cinchona alkaloids to generate the desired functionalized [4.1.0]-bicycloheptanes in excellent yields and enantioselectivities. The new catalysts contain an alkyl substituent at the C2′ position, thus preventing the quinoline nitrogen atom from interfering in the reaction. We are currently investigat-



Scheme 6. Catalytic elaboration of [4.1.0]-bicycloalkenes in complex molecule synthesis. Cp = cyclopentadienyl, TMS = trimethylsilyl.

ing the application of this new catalytic reaction in the synthesis of architecturally complex natural products.

Experimental Section

The cinchona alkaloid catalyst (20 mol %) was added to a mixture of the chloroketone **1** (1.0 equiv), sodium bromide (0.25 equiv), and sodium carbonate (1.3 equiv) in anhydrous acetonitrile (0.1M), and the reaction mixture was stirred at 80 °C for 24–36 h until complete, as shown by TLC and LC–mass-spectrometric analysis. The reaction was concentrated and diluted with diethyl ether before filtering through a pad of silica. After concentration of the filtrate the residue was purified by flash column chromatography on silica gel to afford the [4.1.0]-bicycloalkane.

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Keywords: asymmetric synthesis · cinchona alkaloids · cyclopropanation · intramolecular reactions · organocatalysis

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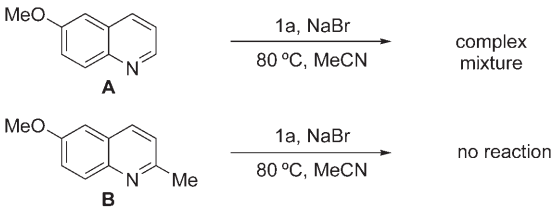
[8] a) N. Bremeyer, S. C. Smith, S. V. Ley, M. J. Gaunt, *Angew. Chem.* **2004**, *116*, 2735; *Angew. Chem. Int. Ed.* **2004**, *43*, 2681.
[9] a) Based on LC–mass-spectrometric analysis of the mixture; b) quinoline **A**, when treated with **1a** and NaBr in MeCN at 80 °C, leads to an intractable mixture of products and consumes all the starting material; quinoline **B** does not react with **1a** under the same conditions, thus both materials are returned untouched; no cyclopropanantion was observed in these reactions.



[10] 1′-deazo cinchona alkaloids have been synthesized previously through a nontrivial route: a) C. Exner, A. Pfaltz, M. Studer, H.-U. Blaser, *Adv. Synth. Catal.* **2003**, *345*, 1253; b) E. V. Dehmlow, S. Düttmann, B. Neumann, H.-G. Stammler, *Eur. J. Org. Chem.* **2002**, 2087.
[11] We also tested catalysts containing C2′-Ph (83 % yield, 96 % *ee*), *i*Pr (59 % yield, 98 % *ee*), and *t*Bu (46 % yield, 93 % *ee*), but the Me-MQ/ Me-MQD catalysts gave the best results.
[12] See the Supporting Information for details.
[13] For isolation, see: a) S. F. Brady, M. P. Singh, J. E. Janso, J. Clardy, *J. Am. Chem. Soc.* **2000**, *122*, 2116; for the first synthesis, see: b) S. Lin, G. S. Dudley, D. S. Tan, S. J. Danishevsky, *Angew. Chem.* **2002**, *114*, 2292; *Angew. Chem. Int. Ed.* **2002**, *41*, 2188.
[14] P. Ramesh, N. Srinivasa, Y. Venkateswarlu, M. V. R. Reddy, D. J. Faulkner, *Tetrahedron Lett.* **1998**, *39*, 8217.
[15] For a related example of intramolecular [5+2] cycloadditions, see: a) B. M. Trost, H. C. Shen, *Angew. Chem.* **2001**, *113*, 2375–2378; *Angew. Chem. Int. Ed.* **2001**, *40*, 2313–2316; b) B. M. Trost, H. C. Shen, D. B. Horne, F. D. Toste, B. G. Steinmetz, C. Koradin, *Chem. Eur. J.* **2005**, *11*, 2577; see also: c) P. A. Wender, F. C. Bi, M. A. Brodney, F. Gosselin, *Org. Lett.* **2001**, *3*, 2105, and references therein.
[16] T. P. Gill, K. R. Mann, *Organometallics* **1982**, *1*, 485.
[17] The chloroketone precursors are made through an alkene cross metathesis reaction using the Grubbs second generation catalyst.

