Intramolecular Cyclization

An Intramolecular Organocatalytic Cyclopropanation Reaction**

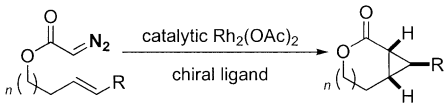
*Nadine Bremeyer, Stephen C. Smith, Steven V. Ley, and Matthew J. Gaunt**

Catalytic processes that form functionalized cyclic molecules represent a key transformation for synthetic organic chemistry.[1,2] Recently, a number of organocatalytic processes have emerged that often provide excellent levels of both enantio- and diastereocontrol for the synthesis of cyclic molecules.[3,4]

Our recent studies have identified the utility of ammonium ylides for carbon–carbon bond formation. Herein we describe the development of a new organocatalytic intramolecular cyclopropanation reaction that forms synthetically versatile [*n*.1.0]bicycloalkanes by using a nucleophilic tertiary amine catalyst.

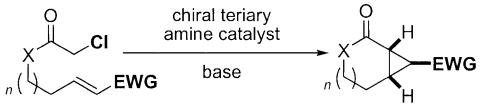
The synthesis of these bicycloalkanes is most commonly carried out by inter- or intramolecular metal-catalyzed carbene transfer of diazo compounds to electron-rich alkenes [Eq. (1)].[5] Other than these methods there are few general

Metal Catalysis: metallocarbenoid-mediated cyclopropanation



(1)

Organocatalysis: ammonium-ylide-mediated cyclopropanation

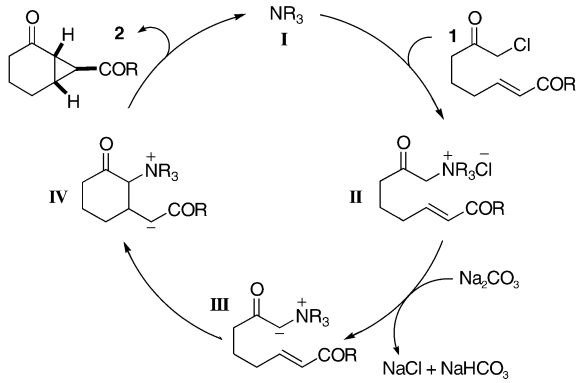


(2)

alternatives to form [*n*.1.0]bicycloalkanes.[5c,6] [*n*.1.0]Bicycloalkanes offer many exciting applications in complex molecule synthesis due to the high levels of stereochemistry and latent reactivity inherent within their structure.[7] Therefore, new complementary methods for their catalytic enantioselective synthesis are very important. We have identified an interesting organocatalytic intramolecular cyclopropanation process that is stereoselective and produces highly functionalized bicycloalkanes that contain three stereocentres, two rings, and three levels of orthogonal functionality in a single step from linear building blocks [Eq. (2)].

In this approach an α-chloroketone with a tethered electron deficient alkene reacts through a catalytically generated ammonium ylide to form the bicyclic structure [Eq. (2)]. This organocatalytic strategy precludes the use of highly sensitive diazo compounds. It should also offer a wider scope of substrates owing to compatibility with the metal-free catalyst, and produce bicylcoalkanes with higher levels of functionality. Furthermore, there are many readily available chiral tertiary amines from which an enantioselective process can be developed.

A proposed catalytic cycle is shown in Scheme 1. The amine catalyst **I** displaces the chloride in **1** to give the



Scheme 1. Proposed catalytic cycle.

[*] N. Bremeyer, Prof. Dr. S. V. Ley, Dr. M. J. Gaunt
Department of Chemistry, University of Cambridge, Lensfield Road, Cambridge, CB2 1EW (UK)
Fax: (+44) 122-333-6442
E-mail: mjg32@cam.ac.uk
Dr. S. C. Smith
Syngenta, Jealott's Hill International Research Centre, Bracknell, Berkshire, RG42 6EY (UK)

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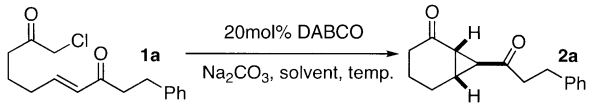
quaternary ammonium salt **II**. Deprotonation forms the ammonium ylide **III** and intramolecular conjugate addition forms **IV** and finally the bicycloalkane **2** is generated through displacement of the ammonium group, concurrently regenerating catalyst **I**.

To assess the viability of this intramolecular process, a range of reaction conditions were investigated by using alkenyl chloroketone **1a**, the results of which are summarized in Table 1. At room temperature little or no reaction was observed in dichloromethane when 20 mol% of 1,4-diazabicyclo[2.2.2]octane (DABCO) as catalyst and 1.3 equivalents of sodium carbonate as base were used (entry 1). At elevated temperature (45°C) the yield rose to 45%, but the reaction was slow (entry 2). With 1,2-dichloroethane (DCE) as solvent and reaction at 60°C a 91% yield of **2a** was isolated after 18 h (entry 3). A similar yield was obtained for reaction in acetonitrile (MeCN) at 80°C with a reduced reaction time of 5 h. Catalytic quantities of quinuclidine could also be used, thus producing similar results to DABCO, although few other tertiary amines gave acceptable reaction. The choice of base was important due to a potential background reaction. After screening a range of organic and inorganic bases, sodium carbonate was found to be the optimal choice. Importantly, a single diastereoisomer was formed and no background reaction was observed in the absence of the catalyst. Therefore, in a single transformation this catalytic process effects the stereocontrolled formation of three stereocenters, two carbon–carbon bonds, and two rings from an acyclic molecule.

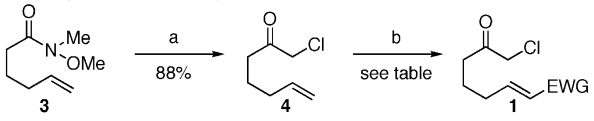
Table 1: Effect of reaction conditions for the conversion of **1a** into **2a**.



Entry	Solvent	*T* [°C]	*t* [h]	Yield	d.r.
1	CH_2Cl_2	22	48	<10	>95:5
2	CH_2Cl_2	45	48	45	>95:5
3	DCE	60	18	91	>95:5
4	MeCN	80	5	84	>95:5

Once an intramolecular cyclopropanation process had been identified, a reliable and operationally simple two-step synthesis of the precursors **1** was developed. Alkenyl α-chloroketone **4** was formed by using a modification of the procedure reported by Barluenga et al.,[9] in which lithiochloromethane (generated in situ through the addition of methyllithium to a solution of chloroiodomethane) reacts with a Weinreb amide **3** to form the desired chloroketone **4** in excellent yield. Alkene cross-metathesis between the alkenyl α-chloroketone **4** and an electron-deficient alkene by using 2.5 mol% of the Grubbs second-generation catalyst, formed the desired substrate **1** in good yield.[10] Furthermore, the functional-group sensitivity of alkenyl α-chloroketones clearly demonstrates the mild nature of the alkene cross-metathesis process (Table 2).

Table 2: Synthesis of alkenyl chloroketones **1**.



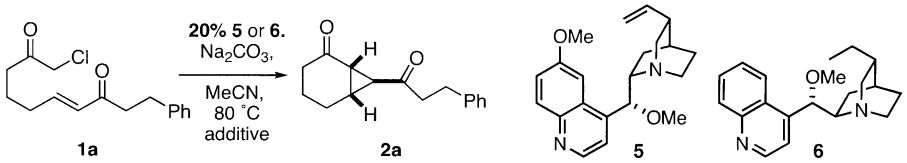
Entry	Alkene-cross metathesis Alkene	*t* [h]	Yield
1	COMe	12	82
2	$CO(CH_2)_2Ph$	12	83
3	CHO	9	80
4	$CO_2{}^tBu$	18	85

[a] 2 equiv $ClCH_2I$, 1.5 equiv MeLi, Et_2O, −78°C, 0.5 h; [b] the Grubbs second-generation catalyst (2.5 mol%), 1.5 equiv Alkene, CH_2Cl_2, 45°C. EWG = electron withdrawing group.

The scope of the intramolecular cyclopropanation reaction was subsequently investigated under the optimized conditions.[11] The results in Table 4 (next page) demonstrate that the reaction is applicable with many types of functionality and all examples produced a single diastereoisomer.

The most reactive substrates were enones **1a–c**, which form the cyclopropanes **2a–c** in excellent yields. The reaction with enoate **1e** also progressed well in MeCN at 80°C to afford **2e**. Unsaturated sulfone **1f** delivered the desired product **2f** in moderate yield, however, most pleasing was the formation of aldehyde **2d** isolated in 82% yield from **1d**. This demonstrates that even sensitive functional groups are compatible with this process. Moreover, aldehyde **2d** is a versatile scaffold for subsequent elaboration. The reaction also worked with diene **1g** to form the vinyl cyclopropane **2g** in 72% yield. [3.1.0]Bicyclohexanes that contained a five-membered ring system could also be formed as single diastereoisomers. Heteroatoms were compatible with the reaction and amide derivative **1i** gave the heterocycle **2i** in 81% yield. In all examples no background cyclopropanation was observed in the absence of catalyst.

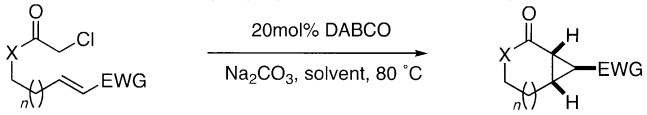
Table 3: Enantioselective organocatalytic cyclopropanation.[a]



Entry	Catalyst loading	*t* [h]	Additive	Yield [%]	*ee* [%]
1	20 mol% **5**	96	-	**67**	**64** (+)
2	20 mol% **5**	24	40 mol% NaBr	**61**	**94** (+)
3	20 mol% **5**	24	40 mol% NaI	**64**	**95** (+)
4	20 mol% **6**	24	40 mol% NaBr	**48**	**94** (−)

[a] Reagents and conditions: catalyst, 1.3 equiv Na_2CO_3, MeCN, 80°C, 24 h.[12]

Table 4: Scope of the intramolecular cyclopropanation reaction under optimal conditions.



Entry	Substrate	Time	Product	Yield %
1[a]	**1a**	18	**2a**	**91**
2[a]	**1b**	2	**2b**	**95**
3[b]	**1c**	7	**2c**	**90**
4[b]	**1d**	2	**2d**	**82**
5[b]	**1e**	9	**2e**	**65**
6[b]	**1f**	18	**2f**	**42**
7[b]	**1g**	11	**2g**	**72**
8[b]	**1h**	9	**2h**	**50**
9a[b]	**1i**	9	**2i**	**48**
9b[b]		9		**65**[c]
10[b]	**1j**	38	**2j**	**81**

[a] DCE at 60 °C. [b] MeCN at 80 °C. [c] 1 equiv of DABCO.

DABCO was selected as the catalyst because of structural similarity to the cinchona alkaloids, thus making it a racemic model for an enantioselective reaction. On replacement of DABCO with 20 mol % of **5**, cyclopropane **2a** was produced in 67 % yield with an enantiomeric excess (*ee*) of 64 %, after a 5 day reaction (Table 4).[11] However, we proposed that the addition of NaBr would accelerate the reaction by facilitating formation of the quaternary ammonium salt. Therefore, the addition of 0.4 equivalents of NaBr led to a 61 % yield of **2a** with an *ee* value of 94 %. To the best of our knowledge this excellent result represents the first enantioselective organocatalytic intramolecular cyclopropantion reaction. The use of NaI as an additive gave a similar yield and enantiomeric excess. Moreover, with amine **6** as catalyst, the opposite cyclopropane enantiomer was obtained with an excellent *ee* value (94 %), thus demonstrating the potential efficacy of this organocatalytic process (see Table 3).

In summary, we have developed an organocatalytic intramolecular cyclopropanation reaction for the formation of synthetically versatile [*n*.1.0]bicycloalkanes as single diastereoisomers. This powerful catalytic process effects the controlled formation of three stereocenters, two carbon–carbon bonds, and two rings in a single transformation. The reaction is enantioselective with a catalytic amount of chiral amine and can form either enantiomer. We are currently exploring the scope of the catalytic enantioselective process and applications towards the synthesis of complex molecules.

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[11] For full experimental data see the Supporting Information.

[12] The ee values were determined by using chiral HPLC.

