Organocatalytic Cyclopropanation

Organic-Catalyst-Mediated Cyclopropanation Reaction**

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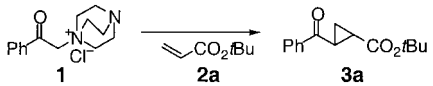
Cyclopropane units are a fundamental class of functional group that are the focus of many organic synthesis programs and perform a key structural role in a range of bioactive natural and nonnatural molecules.[1] The importance of cyclopropanes is reflected in the enormous effort that has been invested in their diastereo- and enantioselective synthesis.[1,2]

Recently, a strong emphasis has been placed on the development of catalytic methods to generate cyclopropanes. While there have been significant advances in the development of catalytic versions of the Simmons–Smith and carbene transfer reactions, there are few reports of catalytic methods based on the reaction of ylides with electron-deficient alkenes.[2] The use of ylides as cyclopropanation reagents dates back to work by Corey et al.[3] Of the many developments that have since been reported, the contributions from the groups of Hanessian,[4] Dai and Tang,[5] and Aggarwal[6] deserve special mention. In these processes, however, the ylide precursor is usually generated in a separate step and there is only one reported process that is catalytic in the ylide species.[6,7]

We were interested in utilizing a nitrogen ylide to effect a cyclopropanation reaction. Surprisingly, there are relatively few examples that employ nitrogen-derived ylides.[8,9] An ammonium ylide based reaction becomes an attractive target for a general diastereo- and enantioselective cyclopropanation process owing to the vast range of tertiary amines that are commercially available. In this communication we describe the development of a stoichiometric "one-pot" ammonium ylide based cyclopropanation process and our initial studies towards an enantioselective reaction. We also report the development of the first catalytic cyclopropanation reaction involving ammonium ylides where the catalyst is a tertiary amine.

We began our study by investigating the reactivity of preformed quaternary ammonium salts such as **1** as nitrogen ylide precursors. Treatment of salt **1** with base followed by *tert*-butyl acrylate (**2a**) formed cyclopropane **3a** in varying yields depending on the conditions employed; the best results are highlighted in Table 1. Of crucial importance was the temperature, with little or no reaction observed at room temperature. However, at 80 °C the reaction produced the highest yield of *trans*-disubstituted cyclopropane. It is important to note that the corresponding reaction between phenacyl chloride (instead of salt **1**) and acrylate **2a** does not form the cyclopropane.[10]

Table 1: Optimization of reaction conditions.[a]

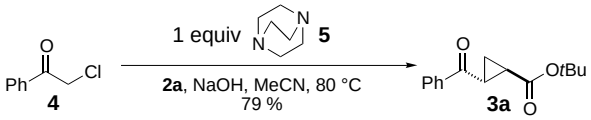


1 **2a** **3a**

Solvent	Base	*t* [h]	Yield[b]	d.r. (*trans*:*cis*)[c]
MeCN	**NaOH**	**6**	**96%**	**>95:5**
THF	NaOH	3.5	66%	15:1
DCE	NaOH	19	73%	>95:5
DMSO	NaOH	1.5	54%	>95:5
CH_2Cl_2[d]	NaOH	4.5	65%	>95:5
MeCN	KOH	4.5	68%	15:1
MeCN	**Na_2CO_3**	**25**	**79%**	**>95:5**
MeCN	**DBU**	**16**	**87%**	**>95:5**
MeCN	DABCO[e]	24	5%	>95:5
MeCN	Et_3N	24	10%	>95:5

[a] Salt **1**, acrylate **2a** (1 equiv), base (2 equiv), solvent (0.25 M), 80 °C (oil bath temperature). [b] Yield of isolated product after chromatography. [c] Determined by ^{1}H NMR spectroscopy. [d] Reaction stirred at 45 °C. [e] 2.5 equiv of DABCO was used. DABCO = 1,4-diazobicyclo[2.2.2]octane, DCE = 1,2-dichloroethane, DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene.

To increase the efficiency of this process we investigated the development of a stoichiometric "one-pot" cyclopropanation reaction, in which the ammonium salt and hence the ylide could be generated in situ from readily available starting materials. Accordingly, DABCO (**5**) was added to phenacyl chloride (**4**) in acetonitrile followed by the base and alkene **2a**, and the reaction mixture was stirred at 80 °C. After 18 h, cyclopropane **3a** was isolated in 79% yield after chromatography as a single diastereoisomer (Scheme 1).[11] It is noteworthy that the reaction proceeds without the formation of byproducts, and simple aqueous workup affords pure cyclopropane (^{1}H NMR spectroscopy, LCMS) that does not necessarily require further purification.



Scheme 1. One-pot cyclopropanation.

A stoichiometric "one-pot" cyclopropanation reaction offers significant advantages over other similar methods as it precludes the necessity to generate and isolate the ylide precursor (**1**) in a separate step. The general utility of this

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[**] We gratefully acknowledge financial support from the EPSRC and Pfizer Global Research and Development (Sandwich, UK) for Industrial Case Award (to C.D.P.), the Novartis Research Fellowship (to S.V.L.), and the British Ramsay Memorial Trust and Magdalene College for Research Fellowship (to M.J.G.). We also thank Dr. A. J. Morrison for helpful advice and discussion.

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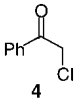
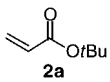
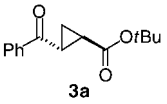
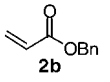
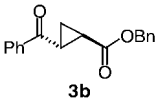
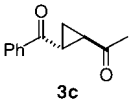
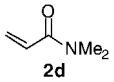
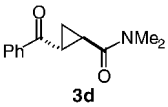
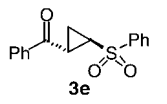
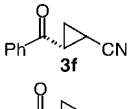
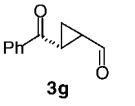
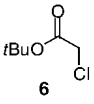
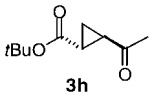
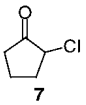
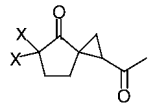
Table 2: Scope of reaction.

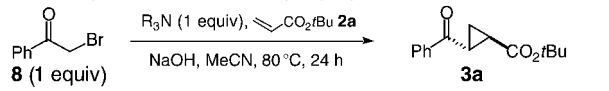
Entry	α-Chloro-carbonyl	Acceptor	Conditions[a]	Yield[b]	Product	d.r. (*trans*:*cis*)[c]
1	 **4**	 **2a**	NaOH, MeCN	79%	 **3a**	>95:5
2	**4**	 **2b**	Na_2CO_3, MeCN	77%	 **3b**	>95:5
3	**4**	 **2c**	Na_2CO_3, MeCN	96%	 **3c**	>95:5
4	**4**	 **2d**	NaOH, THF	73%	 **3d**	>95:5
5	**4**	 **2e**	NaOH, MeCN	81%	 **3e**	>95:5
6	**4**	 **2f**	Na_2CO_3, THF/DMSO	78%	 **3f**	2.3:1
7	**4**	 **2g**	Na_2CO_3, MeCN	40%	 **3g**	4.3:1
8	 **6**	**2c**	Na_2CO_3, MeCN	70%	 **3h**	>95:5
9[d]	 **7**	**2c**	Na_2CO_3, MeCN	70%	 X = CH_2CH_2COMe **3i**	>95:5

[a] α-Chlorocarbonyl, DABCO (1.0 equiv), MeCN (0.25 M), room temperature, 30 min, then alkene (1 equiv), base (1.5 equiv), 80 °C. [b] Yield of isolated product after chromatography. [c] Determined by ^{1}H NMR spectroscopy. [d] Preformed salt **1** was used in this reaction.

process was demonstrated across a range of substrates which established the efficacy of this new and versatile cyclopropane methodology (Table 2). The reaction worked well for a range of alkenes, with acrylates **2a** and **2b**, enone **2c**, acrylamide **2d**, and vinyl sulfone **2e** all forming only the *trans*-substituted 1,2-cyclopropanes **3a**–**3e** in good to excellent yield.[12] Acrylonitrile (**2f**) gave a mixture of cyclopropanes (**3f**; 2.3:1, *trans*:*cis*) in good yield, although some polymerization was observed. Acrolein (**2g**) also gave a separable mixture of cyclopropanes (**3g**; 4.3:1, *trans*:*cis*) in 40% yield when the preformed salt **1** was used. Ammonium ylide species bearing other functional groups were also investigated and produced cyclopropanes in good yield (entries 8 and 9, Table 2). Ketone **7** formed spiro[2.4]heptane derivative **3i** as a single diastereomer when reacted with 3 equivalents of **2c**.

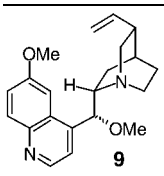
The simplicity of the one-pot ammonium ylide approach to cyclopropanation should allow the use of any tertiary amine.[13] DABCO (**5**) was chosen as a model tertiary amine to mimic the core structure of the cinchona alkaloids because they are a potential source of chirality for an enantioselective cyclopropanation reaction. The chiral quaternary ammonium salt **11** was readily formed in situ from the addition of phenacyl bromide (**8**) to amine **9**.[14] Subsequent addition of acrylate **2a** and sodium hydroxide (2 equiv), and stirring the reaction at 80 °C for 24 h generated cyclopropane (+)-**3a** in 61% yield (Table 3). The enantiomeric ratio (e.r.) from this initial reaction was 91.5:8.5 (83% *ee*), as determined by chiral HPLC.[15] While this result displayed excellent enantioselectivity we were concerned for the enantiomeric integrity of the cyclopropane in the reaction mixture. By monitoring the e.r. over the course of the reaction, we observed an erosion in the enantiomeric purity of the cyclopropane (Table 3, entry 1). However, reducing the amount of base in the reaction to 1.3 equivalents generated (+)-**3a** in 57% yield with an e.r. of 97:3 (94% *ee*). Furthermore, using dihydrocinchonine derivative **10** under our modified reaction conditions formed the opposite enantiomer, (−)-**3a**, in 58% yield and an e.r. of 97:3 (94% *ee*). To the best of our knowledge these are the first examples of an enantioselective cyclopropanation reaction based on a chiral ammonium ylide. We are currently screening the range of alkenes and other chiral tertiary

Table 3: One-pot enantioselective cyclopropanation.



8 (1 equiv) → **3a**

Entry[a]	Chiral amine	equiv NaOH	*t* [h]	Yield[b]	e.r. (*ee*)[c]
1	**9**	2	8	10%	97:3 (94) (+)
			16	46%	92:8 (84) (+)
			24	61%	91.5:8.5 (83) (+)
2	**9**	1.3	24	57%	97:3 (94) (+)
3	**10**	1.3	24	58%	97:3 (94) (−)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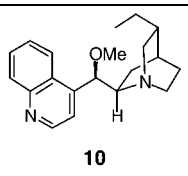
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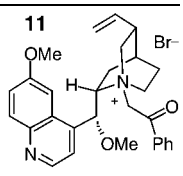
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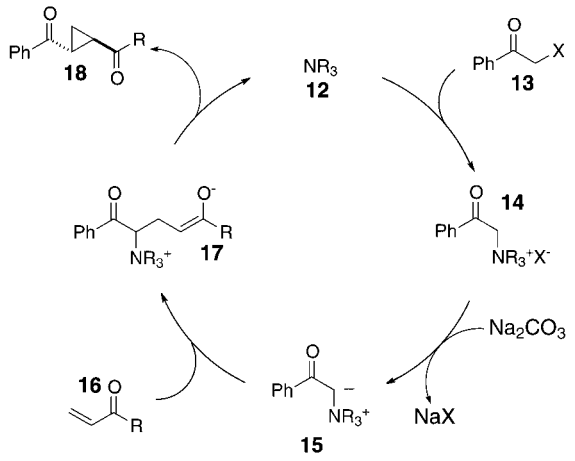


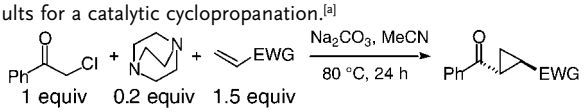
Scheme 2. Proposed catalytic cycle for cyclopropanation.

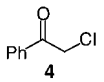
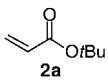
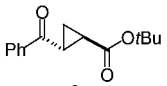
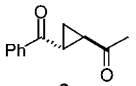
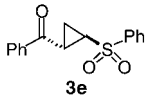
amines to investigate the scope of this new enantioselective process.

With an efficient stoichiometric one-pot cyclopropanation reaction in hand, we next investigated a catalytic process. Examination of a possible reaction mechanism suggests that the amine **12** should be released at the end of the reaction when the cyclopropane ring forms (Scheme 2).[16] Thus, in principle it should be possible to use the tertiary amine in catalytic quantities without fear of a competing background reaction. Accordingly, stirring a mixture of phenacyl chloride (**4**), **2c** (3 equiv),[17] sodium carbonate (1.2 equiv) and DABCO (0.2 equiv) in acetonitrile at 80 °C for 24 h produced cyclopropane **3c** in 82 % yield. *tert*-Butyl acrylate (**2a**) and vinyl sulfone **2e** also produce cyclopropanes **3a** and **3e**, respectively, under catalytic conditions (Table 4). In the absence of DABCO little or no reaction takes place which proves that the tertiary amine is required as a catalyst. We are currently exploring the scope of the reaction to develop a general catalytic cyclopropanation reaction based on ammonium ylides.

In summary, we have developed a practical and general "one-pot" cyclopropanation process, mediated by a tertiary amine via an ammonium ylide intermediate, by using readily available starting materials. We have demonstrated that this reaction is both diastereo- and enantioselective and that the reaction can be made catalytic.[18] We are currently exploring the scope of an asymmetric process with the goal of developing a catalytic enantioselective cyclopropanation reaction. Furthermore, application of this methodology to an intramolecular cyclopropanation system and to the synthesis of small-ring heterocycles is also being explored.

Table 4: Initial results for a catalytic cyclopropanation.[a]



α-Chlorocarbonyl	Acceptor	Yield[b]	Product	d.r. (*trans*:*cis*)[c]
 **4**	 **2a**	69	 **3a**	>95:5
4	 **2c**	82[d]	 **2c**	>95:5
4	 **2e**	63	 **3e**	>95:5

[a] Phenacyl chloride, DABCO (0.2 equiv), alkene (1.5 equiv), Na_2CO_3 (1.2 equiv), MeCN (0.25 M), 80 °C, 24 h. [b] Yield of isolated product after chromatography. [c] Determined by ^{1}H NMR spectroscopy. [d] 3 equiv Of **2c** was used.

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[2] For recent developments, see: W. A. Donaldson, *Tetrahedron* **2001**, *57*, 8589, and references therein. For other examples see ref. [1].

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[9] a) S. S. Bhattacarjee, H. Ila, H. Junjappa, *Synthesis* **1982**, 301; b) A. Jonczyk, A. Konarska, *Synlett* **1999**, 1085; for other examples, see c) N. H. Vo, C. J. Eyermann, C. N. Hodge, *Tetrahedron Lett.* **1997**, *38*, 7951; d) A. M. Shestopalov, V. P. Litvinov, L. A. Rodinovskaya, Y. A. Sharanin, *Zh. Org. Khim.* **1991**, *27*, 146.

[10] When Na_2CO_3 is used as the base, no reaction is observed. When NaOH is used, decomposition is observed.

[11] All compounds were characterized by ^{1}H and ^{13}C NMR spectroscopy, high-resolution mass spectrometry and infrared spectroscopy.

[12] *trans*-Stereochemistry was confirmed in **3a** by hydrolysis of the *tert*-butyl ester and comparison with an authentic sample, and in **3e** by X-ray crystal-structure analysis.

[13] We also found that using quinuclidine in place of DABCO produced **3a** in similar yield.

[14] Phenacyl chloride did not react with the more hindered chiral amine.

[15] See supporting information for details chiral HPLC analysis.

[16] No cyclopropane formation was observed when the reaction was

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carried out with styrene instead of the electron-deficient alkenes which suggests that the reaction does not proceed through a carbene mechanism.

[17] In the case of methyl vinyl ketone, 3.0 equiv was used because of its volatility. In the other cases only 1.5 equiv of the alkene was used.

[18] For an overview of organocatalysis, see: P. I. Dalko, L. Moisan, *Angew. Chem.* **2001**, *113*, 3840; *Angew. Chem. Int. Ed.* **2001**, *40*, 3726.

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