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Cycloadditions of Aromatic Azomethine Imines with 1,1-Cyclopropane Diesters

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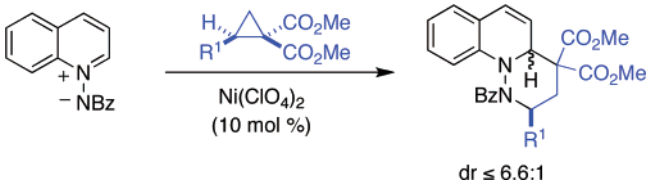
ABSTRACT



The cycloaddition of aromatic azomethine imines to 1,1-cyclopropane diesters was achieved using $Ni(ClO_4)_2$ as catalyst. The methodology gives access to unique tricyclic dihydroquinoline derivatives with dr up to 6.6:1. A nonconcerted mechanism is proposed on the basis of stereochemical analysis of the reaction.

Di- and tetrahydroquinoline derivatives are useful synthetic intermediates, and their subunits are also found in alkaloids and other biologically active compounds.[1] Consequently, there has been a lot of interest in the development of synthetic methodologies to access new chiral derivatives and ways to functionalize these scaffolds. The main methods to access enantioenriched di- and tetrahydroquinolines are based on asymmetric nucleophilic additions to activated quinolines. However, few methods proved to be effective, both in terms of yields and enantioselectivities.[2]

Our group has been interested in the synthesis and reactions of *N*-iminopyridinium, *N*-iminoquinolinium (NAQBz), and *N*-iminoisoquinolinium ylides.[3] We have demonstrated that *N*-benzoyliminopyridinium ylides can undergo enantioselective hydrogenation[4] or diastereoselective additions of Grignards[5] to give enantiopure piperidine derivatives. We envisioned exploring a new reactivity of these ylides by reacting them with electrophilic cyclopropane derivatives in a cycloaddition reaction. This would enable the preparation of novel 6,6,6-tricyclic dihydroquinoline derivatives. Moreover, if enantioenriched cyclopropanes are used, chiral nonracemic products could be generated. These new molecules could become important scaffolds for drug discovery and molecular diversity.[1f]

Recently, cycloaddition reactions of activated cyclopropanes[6] with aldehydes,[7] imines,[8] nitrones,[9] allenes, acety-

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(2) Selected examples: (a) Yamaoka, Y.; Miyabe, H.; Takemoto, Y. *J. Am. Chem. Soc.* **2007**, *129*, 6686. (b) Takamura, M.; Funabashi, K.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2000**, *122*, 6327. (c) Takamura, M.; Funabashi, K.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2001**, *123*, 6801.

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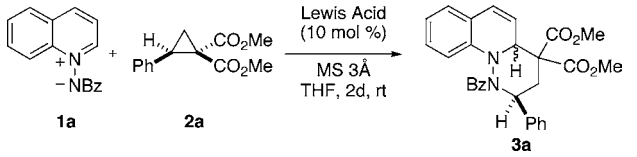
lenes,[10] nitriles,[11] isocyanates,[12] isothiocyanates,[13] isocyanides,[14] α,β-unsaturated ketones,[15] and diazenes[16] have attracted considerable attention, since they allow access to highly functionalized 5- and 6-membered rings. Notably, Kerr and co-workers reported a cycloaddition of 1,1-cyclopropane diesters with nitrones catalyzed by $Yb(OTf)_3$[9e,f] or MgI_2.[9d] Asymmetric versions of this reaction have also been reported using $Ni(ClO_4)_2$ in combination with dbfox[9c] or tox[9a] ligands.

Herein, we describe the cycloaddition reaction of aromatic azomethine imines with cyclopropanediesters. Studies into the mechanism of this reaction will also be presented.

We initially examined the reaction of NAQBz (**1a**) and cyclopropane **2a** in the presence of various Lewis acids that are commonly used to activate 1,3-dicarbonyl species (Table 1, entries 2−8). A control experiment established that a Lewis acid is needed to activate the cyclopropane, since no conversion was observed without it (Table 1, entry 1). While $Sc(OTf)_3$ and $Mg(ClO_4)_2$ proved to be good catalysts (Table 1, entries 5 and 7), MgI_2, $Yb(OTf)_3$, $Cu(OTf)_2$, and $Cu(ClO_4)_2$ gave little or no conversion (Table 1, entries 2−4, 6). The best result was obtained with $Ni(ClO_4)_2$ which gave 96% conversion and 3.3:1 dr (Table 1, entry 8). Furthermore, $Ni(ClO_4)_2$ has the added advantage of being relatively inexpensive and easy to handle.

In an attempt to increase the diastereoselectivity, the reaction was performed at lower temperatures. At −10 °C, there was no change in dr and little change in conversion. At −40 °C, dr remained the same, but the conversion significantly dropped. Likewise, reducing the catalyst loading to 5 mol % resulted in lower conversion and unchanged dr. Finally, the presence of water had a detrimental effect on the yield.[17]

Table 1. Optimization of the Reaction between Ylide **1a** and Cyclopropane **2a**[a]



entry	Lewis acid	conversion[b] (%)	dr (cis/trans)[b]
1		0	
2	MgI_2	0	
3	$Yb(OTf)_3$	3	1:1
4	$Cu(OTf)_2$	4	1:1
5	$Sc(OTf)_3$	79	3.2:1
6	$Cu(ClO_4)_2$	0	
7	$Mg(ClO_4)_2$	71	2.4:1
8[c]	$Ni(ClO_4)_2$	96	3.3:1
9[c,d]	$Ni(ClO_4)_2$	94	3.3:1
10[c,e]	$Ni(ClO_4)_2$	20	3.3:1
11[c,f]	$Ni(ClO_4)_2$	57	3.3:1

[a] All reactions were performed using an ylide/cyclopropane ratio of 1:1. [b] Determined by ^1H NMR using trimethoxybenzene as an internal standard. [c] Reaction time = 18 h. [d] Performed at −10 °C. [e] Performed at −40 °C. [f] 5 mol % of Lewis acid.

We next examined the effect of the quinolinium ylide protecting group. Low conversions were observed with pivaloyl and triflyl groups. Quinolinium *N*-oxide also gaved poor results. In the end, the original benzoyl protecting group proved to be the most effective. Its electronic nature makes the nitrogen nucleophilic enough to add to the cyclopropane, and, at the same time, activates the quinolinium to promote the cyclization. We, therefore, examined the electronic effect of this protecting group. An electron-withdrawing substituent on the benzoyl group resulted in both higher conversion and dr (Table 2, entry 3), whereas an electron-donating substituent gave a slightly higher dr but lower conversion (Table 2, entry 2).

We next evaluated the scope of the reaction by submitting various 1,1-cyclopropanediesters to the optimized conditions. In general, good results were obtained with electron-rich aryl substituted cyclopropanes. The best case was with 4-MeO-Ph (**2c**) which gave a 92% yield and 6.6:1 dr. In contrast, an electron-poor nitro-substituted aryl group afforded the product in a substantially lower yield, but with good dr. The reaction also proceeds well with vinyl cyclopropanes, albeit in modest yield and dr (Table 2, entry 8). This was also the case for unsubstituted 1,1-cyclopropanediesters (**2g**) which gave 32% yield (Table 2, entry 9).[18]

The relative configuration of both diastereoisomers of **3a** was unambiguously established by X-ray crystallographic analysis.

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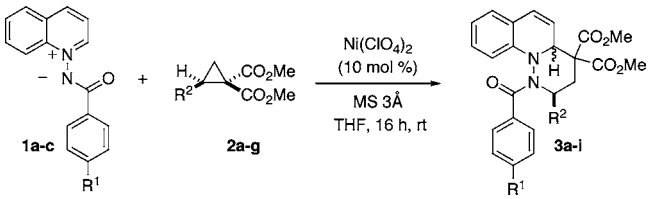
(17) Reaction was carried out in the absence of 3 Å molecular sieves to give 45% conversion. Addition of water (30 equiv) in the reaction also inhibited the formation of the desired product, giving 7% yield.

(18) 58% yield was obtained using 10 equiv of the commercially available cyclopropane.

Table 2. Reaction of Azomethine Imines (**1a**−**c**) with Different 1,1-Cyclopropane Diesters (**2a**−**g**)



entry	R^1	R^2	product	yield (%)	dr (cis/trans)[a]
1	H (**1a**)	Ph (**2a**)	**3a**	79	3.3:1
2	OMe (**1b**)	Ph (**2a**)	**3b**	54	3.8:1
3	CF_3 (**1c**)	Ph (**2a**)	**3c**	84	4.3:1
4	H (**1a**)	4-^{t}Bu-Ph (**2b**)	**3d**	76	3.3:1
5	H (**1a**)	4-MeO-Ph (**2c**)	**3e**	87	6.6:1
6	H (**1a**)	4-F-Ph (**2d**)	**3f**	81	4.4:1
7	H (**1a**)	4-NO_2-Ph (**2e**)	**3g**	11	5.9:1
8	H (**1a**)	vinyl (**2f**)	**3h**	31	2.6:1
9	H (**1a**)	H (**2g**)	**3i**	32	n/a

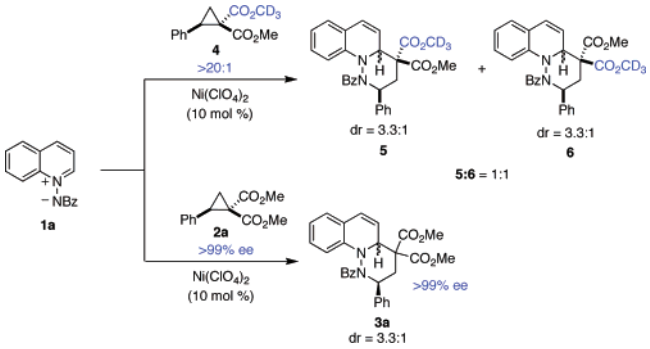
[a] Determined by ^{1}H NMR.

Several mechanisms have been suggested for the cycloaddition reaction of 1,1-cyclopropane diesters.[19,20] Possible pathways for the cycloaddition reaction with azomethine imines include the following: (1) a stepwise process involving a Lewis acid mediated cyclopropane ring-opening, followed by either the nucleophilic attack of the stabilized anion onto the imine or the attack of the nitrogen nucleophile onto the benzylic cation, and subsequent ring-closing;[16] (2) a stepwise S_N2 process where the nitrogen of the ylide acts as the nucleophile followed by a ring-closing reaction to form the six-membered ring; and (3) a concerted process.

In an effort to gain insights into the mechanism, we conducted a labeling experiment and a reaction with an enantiopure cyclopropane.

Reacting ylide **1a** with deuterated cyclopropane **4** led to a complete loss of the stereogenic information at the carbon bearing the two esters moieties (Scheme 1). In contrast,

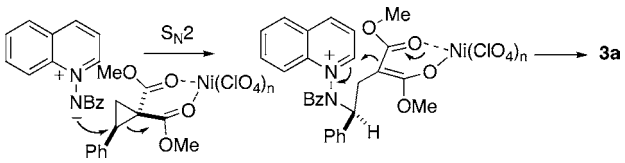
Scheme 1. Insights into the Mechanism



performing the reaction with enantiopure cyclopropane **2a** produced enantiopure products with total conservation of the stereogenic information. These experiments eliminate the possibility of mechanism (1), since a racemic mixture of products would have been observed. In addition, the product derived from the labeling experiment does not support a concerted mechanism (3). However, it may be possible that the reaction proceeds by a concerted pathway and that the corresponding product undergoes ring-opening/ring-closing through a retro-Mannich-type reaction to form the two diastereomers. To test this possibility, we subjected the major diastereomer of **3a** to the reaction conditions, but we did not observe any of the minor diastereomer. Thus, we eliminated the possibility of a concerted mechanism followed by a reversible ring opening process.

From these experimental observations, one reasonable mechanism remains. The first step would be an nucleophilic opening of the cyclopropane, whereby the nitrogen of the ylide acts as a nucleophile and inverts the stereogenic center of the cyclopropane (Scheme 2). This relatively long-lived

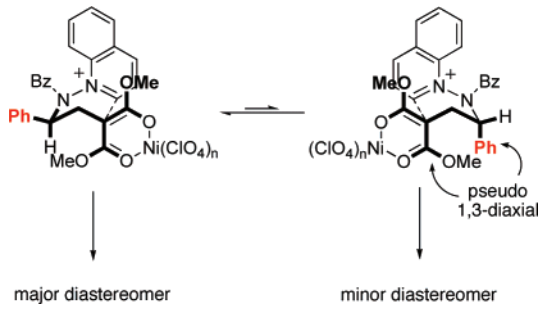
Scheme 2. Proposed Mechanism



intermediate could then attack either face of the quinolinium moiety, resulting in both diastereomers. Degradation studies on **3a** indicated that the first step of the reaction proceeded with complete inversion of the configuration.[21] This reaction is consistent with what Johnson proposed for the cycloaddition of 1,1-cyclopropane diesters with aldehydes.[7a] It also supports the highly diastereselective two-step process proposed by Kerr for the cycloaddition of 1,1-cyclopropane diesters with nitrones.[19]

In our system, the diastereoselectivity can be partly explained by a pseudo-1,3-diaxial interaction between the substituent on the cyclopropane and one of the ester groups in a boat-like transition state (Scheme 3). Strong evidence for this was obtained from single-crystal X-ray diffraction,

Scheme 3. Model of Two Possible Approaches for the Cyclization Step



which showed the favored boat conformation in both diastereomers (Figure 1). However, it is not clear at this stage

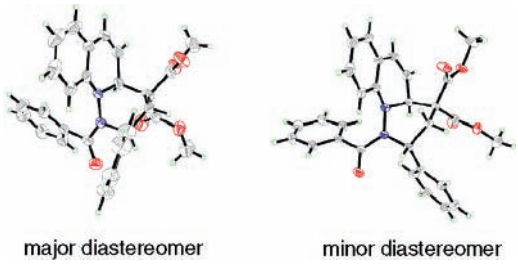


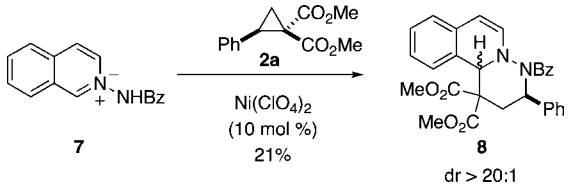
Figure 1. ORTEP representation of the two diastereoisomers of product **3a**.

how the electronics of the aromatic group would affect the diastereoselectivity.

N-Benzoyliminoisoquinolinium ylide was also submitted to standard reaction conditions in the presence of cyclopropane **2a** (Scheme 4). The cycloaddition adduct was obtained in modest yield but as a single diastereomer and only one regioisomer.

In summary, a cycloaddition of aromatic azomethine imines with 1,1-cyclopropane diesters was achieved using $Ni(ClO_4)_2$ as a catalyst. The methodology gives access to unique tricyclic dihydroquinoline derivatives with dr up to 6.6:1. Complete retention of stereogenic information of the cyclopropane was observed. Finally, we proposed a stepwise

Scheme 4. Reaction between Ylide **7** and Cyclopropane **2a**



mechanism which consists of a nucleophilic opening of the cyclopropane followed by a diastereoselective ring closure reaction.

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Supporting Information Available: Experimental procedure for the preparation of compounds and spectroscopic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(21) See the Supporting Information for details.