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In Situ Generation of Zinc Carbenoids from Diazo Compounds and Zinc Salts: Asymmetric Synthesis of 1,2,3-Substituted Cyclopropanes

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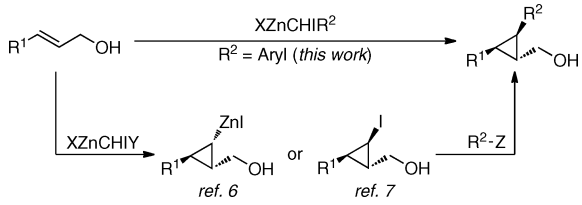
The Simmons−Smith reaction has proven to be a very powerful tool for the synthesis of cyclopropanes.[1] Since the seminal report,[2] many methods have been reported to generate zinc carbenoids. Among them, the reaction of *gem*-dihaloalkanes with diethyl zinc has proven to be the most efficient.[3] However, to the best of our knowledge, no Simmons−Smith reaction using a catalytic amount of zinc has proven to be efficient in the synthesis of enantioenriched cyclopropanes.[1]

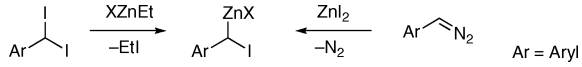
1,2,3-Substituted cyclopropanes are naturally occurring subunits that not only have potential biological activity but also are powerful intermediates in the synthesis of complex molecules.[1,4] Many approaches have been used to prepare these compounds, notably by the cyclopropanation of alkenes[1] or by carbometalation of cyclopropenes.[5] Although zinc carbenoids have been successfully used to synthesize these cyclopropanes in highly enantioenriched form,[6−8] the preactivation of the cyclopropane ring is generally required to introduce the desired functionality (Scheme 1).

Scheme 1. Synthesis of 1,2,3-Substituted Cyclopropanes Using Zinc Carbenoids



An alternative approach would employ substituted zinc carbenoids, introducing the substituent and the three-membered ring in the same step. However, to date, there is no enantioselective method using aryl-substituted zinc carbenoids to directly produce aryl-substituted cyclopropanes.[9] According to literature precedents,[10e,11] and to our preliminary investigations, the unstable aryl-substituted carbenoids have to be formed *in situ* to obtain the desired cyclopropane. However the independent preformation of carbenoids is crucial in enantioselective Simmons−Smith cyclopropanation reactions,[12,13] and this is generally achieved by treating an organozinc reagent with a *gem*-diiodoalkane in a separate reaction vessel (Scheme 2).[1]

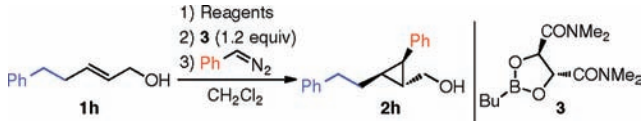
Scheme 2. Synthesis of Aryl-Substituted Carbenoids



In addition to the low stability of aryl-carbenoids, their *gem*-diiodide precursors are unstable compounds and not easily accessible. Facing these challenging problems, we sought the development of suitable conditions to generate zinc carbenoids *in situ* from different precursors. We envisioned that zinc iodide and diazo reagents could be used as carbenoid precursors and should be compatible with enantioselective procedures (Scheme 2). Although diazo compounds occupy a vast area of research in cyclopropanation, there are only a few reports on their use in Simmons−Smith cyclopropanation reactions.[10]

Herein we report the first enantioselective cyclopropanation of alkenes using zinc carbenoids generated *in situ* from diazo compounds and a zinc salt (Scheme 2). This new method allows the highly enantio- and diastereoselective synthesis of 1,2,3-substituted cyclopropanes via aryl-substituted carbenoids. We also report the first Simmons−Smith reaction using a catalytic amount of zinc salt to generate an enantioenriched cyclopropane.

Table 1. Reaction Conditions Optimization[a]



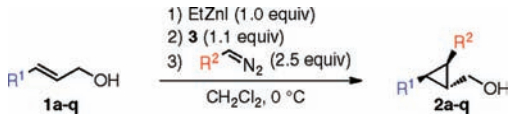
entry	reagent 1 (1.0 equiv)	reagent 2 (1.0 equiv)	*T* (°C)	conv[b] (%)	dr[b]	ee[c] (%)
1[d]	NaH	ZnI_2	−20	>95	88:12	0
2	NaH	ZnI_2	−20	5	nd	nd
3	KH	ZnI_2	−20	34	>95:5	94
4	EtZnI	−	−20	52	>95:5	95
5[e]	**EtZnI**	−	**0**	**72**	**>95:5**	**94**
6	EtZnI	−	20	78	>95:5	93

[a] Reactions were performed using 2.5 equiv of phenyldiazomethane. [b] Determined by ^{1}H NMR. [c] Determined by SFC analysis on chiral stationary phase. [d] Performed without the ligand **3**. [e] 1.1 equiv of **3** was used

We began our investigation using the allylic alcohol **1h** as a test substrate for the nonasymmetric process. Our preliminary optimization showed that when the alcohol **1h** is treated at −20 °C in CH_2Cl_2 with 1.0 equiv of NaH, 1.0 equiv of ZnI_2, and 2.5 equiv of phenyldiazomethane, >95% conversion is obtained (Table 1, entry 1). These conditions proved to be general for a variety of allylic alcohols and diazo reagents (Table 2). However, when 1.2 equiv of the chiral ligand **3**[6b,7c,8,14] were used under the same conditions, the conversion decreased drastically to 5% (entry 2). To our delight, using KH to deprotonate the alcohol afforded 34% conversion with >95:5 dr and 94% ee (entry 3), proving the compatibility of this method with ligand **3**. It is noteworthy that preforming the carbenoid led to no product because of its rapid degradation. After screening multiple bases and zinc sources, we determined that using EtZnI afforded 52% conversion with >95:5 dr and 95% ee (entry 4). Increasing the

reaction temperature to 0 °C and lowering the amount of ligand **3** to 1.1 equiv provided the best compromise between the conversions, the dr's, and ee's (entry 5).

Table 2. Scope Study

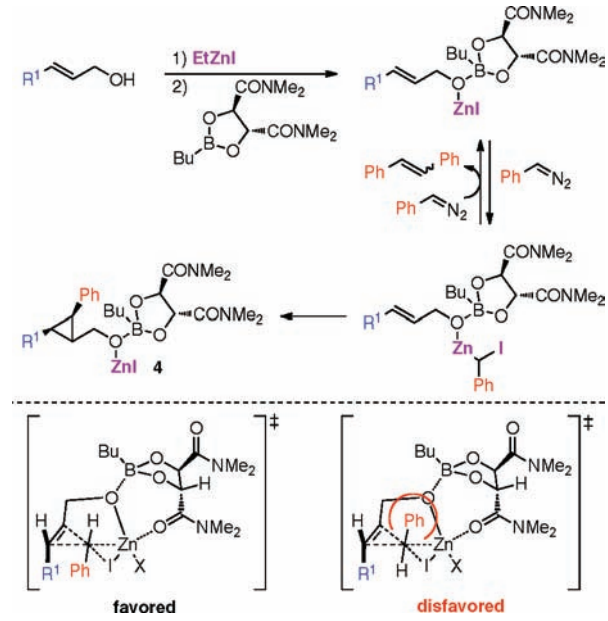


		racemic			enantioselective		
entry	R^1		yield (%)[a]	dr[b]	yield (%)[a]	dr[b]	ee (%)[c]
1	4-Cl-Ph	**2a**	77	>95:5	93	>95:5	**96**
2	2-Cl-Ph	**2b**	87	>95:5	94	>95:5	**97**
3	4-Br-Ph	**2c**	84	>95:5	93	>95:5	**96**
4	4-F-Ph	**2d**	80	>95:5	93	>95:5	**96**
5	4-CF_3-Ph	**2e**	86	>95:5	98	>95:5	**99**
6	4-Me-Ph	**2f**	84[d]	>95:5	86	>95:5	**92**
7	2,6-Me_2-Ph	**2g**	99	>95:5	98	>95:5	**97**
8	Ph	**2h**	99	88:12	67	>95:5	**94**
9	Cy	**2i**	90	78:22	49	94:6	**96**
10	*n*-Pr	**2j**	87	82:18	84	89:11	**91**
11	TIPSO	**2k**	73	82:18	59	88:12	**86**
12	H	**2l**	50	85:15	42	93:7	**90**
13	Ph, 4-F-Ph	**2d**	98	>95:5	75	>95:5	**96**
14	Ph, 4-Cl-Ph	**2a**	87	>95:5	82	>95:5	**98**
15	Ph, 4-CF_3-Ph	**2e**	72	>95:5	82	>95:5	**99**

[a] Isolated yield. [b] Determined by ^{1}H NMR of the crude mixture. [c] Determined by SFC analysis on chiral stationary phase. [d] 1.25 equiv of phenyldiazomethane was used.

With these conditions in hand, we next investigated the scope of the enantioselective reaction (Table 2). Performing the reaction on cinnamyl alcohol derivatives with phenyldiazomethane led to complete conversion and excellent ee's, and only one diastereomer was detected in all cases (Table 2, entries 1−7). The reaction conditions were compatible with *para* or *ortho* aromatic halogens resulting in excellent yields and enantioselectivities (entries 1−4). Using the electron-poor 4-CF_3−Ph allylic alcohol (**1e**) led to 98% yield, >95:5 dr, and 99% ee. Excellent results were also obtained with 4-Me-Ph allylic alcohol (**1f**) (entry 6) and with the hindered 2,6-Me_2-Ph allylic alcohol (**1g**) (entry 7). Less reactive alkyl-substituted allylic alcohols reacted with good yields, good dr's, and excellent enantioselectivities (entries 8−12). The reaction tolerated primary alkyls (entries 8,10), secondary alkyls (entry 9), and functionalized alkyl groups (entry 11). Other aryl diazo reagents also proved to be efficient in these conditions (entries 13−15). Good yields, excellent enantioselectivities, and only one diastereomer were obtained. Remarkably, in this transformation two new C−C bonds and three contiguous strereocenters are formed.

Scheme 3. Proposed Mechanism

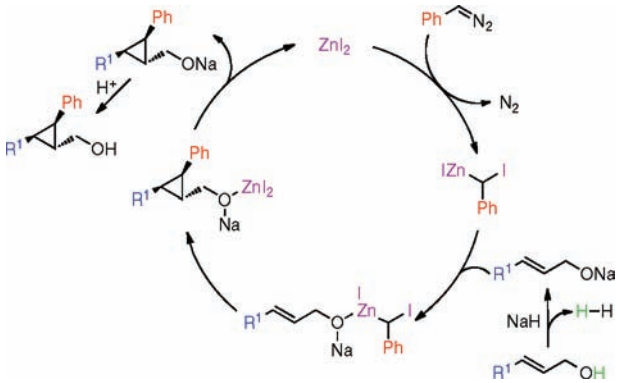


The proposed mechanism for this reaction begins by the deprotonation of the alcohol by EtZnI followed by the complexation of the dioxaborolane ligand to the zinc alkoxide after its addition (Scheme 3). Phenyldiazomethane reacts with the zinc iodide salt to generate the phenyl-substituted carbenoid. This carbenoid is then delivered selectively to one of the two faces of the alkene by the dioxaborolane. The diastereoselectivity observed is explained by favorable π-stacking when R^1 is an aryl and by the steric repulsion of the directing group. The latter is consistent with the higher dr's obtained when ligand **3** was used (entries 8−12) as observed in our previous reports.[7c,8]

Interestingly, the carbenoid can react with either the alkene or the diazo reagent, and in both cases the zinc iodide salt is regenerated. Indeed, the entire diazo reagent (2.5 equiv) is degraded by the zinc iodide salt (1.0 equiv), which demonstrated its catalytic activity. Based on these observations, we investigated the possible catalytic use of zinc salts.[15] We envisaged that ZnI_2 could react with phenyldiazomethane to form the carbenoid, which would react with an allylic alkoxide to form the cyclopropane and ZnI_2. The latter could then be released to achieve another catalytic cycle (Scheme 4). We were pleased to note that using only 5 mol % of zinc iodide in CH_2Cl_2 and NaH (1.0 equiv) allowed the cyclopropanation of cinnamyl alcohol in good yield.[16,17]

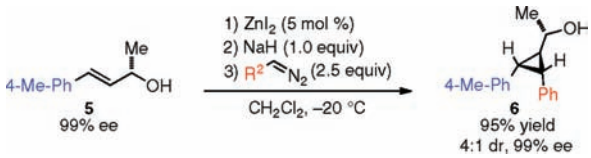
We then envisioned that these conditions could be applied in a diastereoselective Simmons−Smith reaction. We previously reported that the diastereoselective cyclopropanation of (3*E*)-4-phenylbut-3-en-2-ol using $Zn(CH_2I)_2$ gives the corresponding 1,2-disustituted cyclopropane with 3.2:1 dr, which represents one of the less selective substrates.[18] To test the limits of our

Scheme 4. Catalytic Cycle of the ZnI_2-Catalyzed Simmons–Smith Cyclopropanation



system, we performed the cyclopropanation on a similar alkene. We were pleased to find that treating allylic alcohol **5** with 5 mol % of ZnI_2 and only 1.25 equiv of phenyldiazomethane furnished the cyclopropane **6** in 95% yield, 4:1 dr (Scheme 5). This similar level of diastereoselectivity demonstrated the potential of the reaction for diastereoselective cyclopropanation reactions.

Scheme 5. ZnI_2-Catalyzed Simmons–Smith Cyclopropanation



In summary, we developed the first enantioselective cyclopropanation of alkenes using zinc carbenoids generated *in situ* from diazo compounds and zinc salts. This new method allows the highly enantio- and diastereoselective synthesis of 1,2,3-substituted cyclopropanes via aryl-substituted carbenoids. The first Simmons–Smith reaction using a catalytic amount of zinc to generate enantioenriched cyclopropane was also reported. The development of the catalytic enantioselective cyclopropanation reaction will be reported in due course.

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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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