## Construction of stereodefined 1,1,2,2-tetrasubstituted cyclopropanes by acid catalyzed reaction of aryldiazoacetates and $\alpha$ -substituted acroleins<sup>†</sup>

Takuya Hashimoto, Yuki Naganawa, Taichi Kano and Keiji Maruoka\*

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Michael-initiated ring closure of aryldiazoacetates and  $\alpha$ -substituted acroleins under acid catalysis offers a unique opportunity for the stereoselective formation of various tetrasubstituted cyclopropanes.

Cyclopropane rings are ubiquitous in nature and many biologically active compounds contain complex cyclopropane moieties.<sup>1</sup> In addition to this intrinsic utility of cyclopropanes, they can be the key intermediates for further transformations.<sup>2</sup> The development of efficient methods to access these molecules is thus considered to be of great importance and many types of cyclopropanation reactions have emerged to date, Simmons-Smith type reactions and transition metal catalyzed reactions utilizing metal carbenoid intermediates being two of them.<sup>3,4</sup> Cyclopropanation reactions via Michael-initiated ring closure between  $\alpha$ ,  $\beta$ -unsaturated carbonyl compounds and various ylides have also been studied extensively.<sup>2</sup> Despite the possibility that certain acid catalysts might accelerate Michael-initiated processes by the electrophilic activation of  $\alpha,\beta$ unsaturated carbonyl compounds, such a strategy has rarely been realized due to the general incompatibility of basic ylides and acids.6



During our research on Lewis acid catalyzed 1,3-dipolar cycloaddition reaction of diazoacetates and  $\alpha$ , $\beta$ -unsaturated aldehydes,<sup>7</sup> we became interested in the use of diazoacetates as ylides compatible with acid catalysts.<sup>8</sup> Thus, depending on the choice of the acid and the condition, cyclopropanation reaction proceeded predominantly *via* Michael addition of diazo compounds followed by denitrogenation.<sup>9,10</sup> Although two precedents exist in the literature,<sup>11</sup> this type of reaction has never been utilized in the stereocontrolled synthesis of a diverse array of complex cyclopropane rings.

Reported herein is our preliminary result on the acid catalyzed reaction of  $\alpha$ -substituted acroleins with aryldiazoacetates as a

Department of Chemistry, Graduate School of Science, Kyoto University, Sakyo, Kyoto, 606-8502, Japan.

E-mail: maruoka@kuchem.kyoto-u.ac.jp; Fax: +81 75-753-4041;

powerful tool for the diastereoselective synthesis of cyclopropanes containing contiguous quaternary centers.<sup>12</sup> An additional unique feature of our strategy is the complementary relationship with rhodium catalyzed reaction of  $\alpha$ , $\beta$ -unsaturated aldehydes and aryldiazoacetates, which is known to give the corresponding epoxides.<sup>13</sup>

Several Lewis acids were first screened in the reaction of methacrolein and *tert*-butyl phenyldiazoacetate (Table 1). When the reaction was performed with  $BF_3 \cdot Et_2O$  at 0 °C, immediate evolution of nitrogen gas was observed and the cyclopropane **1a** was formed in moderate yield with an unexpectedly high level of *trans* selectivity (entry 1).<sup>14</sup> At the same time, a considerable amount of the aldehyde **2a** was isolated. Use of TiCl<sub>4</sub> attenuated the formation of **2a**, and the cyclopropane **1a** was obtained in 54% yield maintaining high diastereoselectivity (entry 2). Since other Lewis acids showed low reactivity or selectivity (entries 5 and 6), the utilization of Brønsted acids was then examined. The reaction at 0 °C under the influence of TfOH did not provide any cyclopropanes, although most of the diazo compound was consumed immediately (entry 7). By lowering the temperature to

**Table 1** Acid catalyzed cyclopropanation reaction of phenyldiazo-<br/>acetate and methacrolein $^a$ 

N <sub>2</sub>	Ph + CHO	catalyst (20 mol %) solvent [°C, h] <i>t</i> -f	Phu. BuO <sub>2</sub> C Me 1a	Me CHO + Ph 2a CO;	CHO 2 <i>t</i> -Bu
Entry	Catalyst	Solvent	<i>T</i> /°C, <i>t</i> /h	%Yield $\mathbf{1a}^b$ ( <i>trans</i> : <i>cis</i> ) <sup>c</sup>	%Yield $2a^b$
1	BF <sub>3</sub> ·Et <sub>2</sub> O	CH <sub>2</sub> Cl <sub>2</sub>	0, 0.5	46 (>20 : 1)	24
2	TiCl₄	CH <sub>2</sub> Cl <sub>2</sub>	0, 0.5	54 (17 : 1)	4
3	TiCl <sub>4</sub>	toluene	0, 0.5	20(11:1)	2
$4^d$	TiCl <sub>4</sub>	$CH_2Cl_2$	0, 0.5	50 (5.3 : 1)	5
5	SnCl <sub>4</sub>	$CH_2Cl_2$	0, 0.5	36 (5.7 : 1)	30
6	$Sc(OTf)_3$	$CH_2Cl_2$	0, 0.5	trace	
7	TfOH	$CH_2Cl_2$	0, 0.5		
8	TfOH	$CH_2Cl_2$	-78, 0.5	56 (>20 : 1)	6
9	Tf <sub>2</sub> NH	$CH_2Cl_2$	-78, 0.5	13(>20:1)	1
10	$Tf_2NH$	toluene	-78, 0.5	25 (9.1 : 1)	5
11	Tf <sub>2</sub> NH	C <sub>2</sub> H <sub>5</sub> CN	-78, 0.5	64 (>20 : 1)	6
$12^{d}$	$Tf_2NH$	C <sub>2</sub> H <sub>5</sub> CN	-78, 0.5	73 (6.3 : 1)	6
<sup>a</sup> Perfo	rmed with 1	methacrolein	(0.30 mmo	l) and <i>tert</i> -but	vl phenvl-

<sup>*a*</sup> Performed with methacrolein (0.30 mmol) and *tert*-butyl phenyldiazoacetate (0.25 mmol) in the presence of the catalysts (20 mol %). <sup>*b*</sup> Isolated yields after chromatography. <sup>*c*</sup> Determined by <sup>1</sup>H NMR of the crude reaction mixture. <sup>*d*</sup> Performed with methyl phenyldiazoacetate (0.25 mmol).

Tel: +81 75-753-4041

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Downloaded by University of Missouri at Columbia on 14 March 2013 Published on 15 November 2007 on http://pubs.rsc.org | doi:10.1039/B715803C -78 °C, cyclopropane **1a** was obtained in 56% yield stereoselectively, concomitant with a small amount of **2a** (entry 8).<sup>15</sup> After various attempts to improve the efficiency of this Brønsted acid catalyzed process, we finally settled on the condition employing 20 mol% of Tf<sub>2</sub>NH in propionitrile at -78 °C, which provided the *trans*-cyclopropane **1a** in 64% yield (entry 11). Changing the ester moiety of phenyldiazoacetate from *tert*-butyl to methyl resulted in a deterioration in the diastereoselectivity (entries 4 and 12), implying the importance of the steric factor to attain high diastereoselectivity.

With these preliminary results in hand, the scope of this cyclopropanation reaction was surveyed using  $TiCl_4$  and  $Tf_2NH$ 

Table 2 Acid catalyzed cyclopropanation reaction of aryldiazo-acetates and  $\alpha\text{-substituted acroleins}^{\alpha}$ 



Method A: TiCl<sub>4</sub>, CH<sub>2</sub>Cl<sub>2</sub>, 0 °C, 30 min. Method B: Tf<sub>2</sub>NH, C<sub>2</sub>H<sub>5</sub>CN, -78 °C, 30 min.

Entry	Method	R	Ar	%Yield $1^b$	%Yield $2^{b}$
$1^c$	В	Et	Ph	64	4
2	В	<i>i</i> -Pr	Ph	56	2
3	А	Су	Ph	44	1
$4^c$	В			50	3
$5^c$	В	BnO(CH <sub>2</sub> ) <sub>2</sub>	Ph	63	4
6	Α	Me	2-Np	54	3
7	В			66	4
8	Α	Me	4-tolyl	57	3
9	В			72	2
10	Α	Me	3-tolyl	58	5
11	В			57	6
12	Α	Me	$4-FC_6H_4$	53	3
13	В			66	4
$14^{c}$	В	Me	$2-FC_6H_4$	69	6
$15^{c}$	В	Me	$4-ClC_6H_4$	69	5
16	Α	Me	3,4-Cl <sub>2</sub> C <sub>6</sub> H <sub>3</sub>	21	4
$17^{c}$	В			28	6
18 <sup>c</sup>	В	Me	$4-BrC_6H_4$	67	5
19	В	Me	4-vinylC <sub>6</sub> H <sub>4</sub>	44	trace
20	В	Me	4-MeOC <sub>6</sub> H <sub>4</sub>	$38 (1.4:1)^d$	trace
21 <sup>c</sup>	В	Me	3-MeOC <sub>6</sub> H <sub>4</sub>	55	9
22	В	Me	$3,5-(MeO)_2-C_6H_3$	31	6
23	В	Me	2-Br-5-MeO-C <sub>6</sub> H <sub>3</sub>	51	8
24	В	Me	Ph Ph	17 (51) <sup>e</sup>	trace
25	А	BzO	Ph	$45 (3.0:1)^{f,g}$	trace
26	А	BzO	2-Np	48 $(2.6:1)^{f,g}$	trace
27	А	BzO	4-tolyl	42 $(2.0:1)^{f,g}$	trace
28	А	BzO	$4-ClC_6H_4$	$25 (4.3:1)^{f,g}$	trace
29	А	BzO	3-MeOC <sub>6</sub> H <sub>4</sub>	$38 (2.3:1)^{f,g}$	trace
a					

<sup>*a*</sup> Method A: performed with  $\alpha$ -substituted acrolein (0.30 mmol) and aryldiazoacetate (0.25 mmol) in the presence of 20 mol% TiCl<sub>4</sub> at 0 °C for 30 min. Method B: performed with  $\alpha$ -substituted acrolein (0.30 mmol) and aryldiazoacetate (0.25 mmol) in the presence of 20 mol% Tf<sub>2</sub>NH at -78 °C for 30 min. <sup>*b*</sup> Isolated yields after chromatography. <sup>*c*</sup> 30 mol% Tf<sub>2</sub>NH. <sup>*d*</sup> Trans : cis ratio determined by <sup>1</sup>H NMR of the crude reaction mixture. <sup>*e*</sup> Performed with 20 mol% TfOH in CH<sub>2</sub>Cl<sub>2</sub> at -78 °C for 30 min. <sup>*f*</sup> Dr determined by <sup>1</sup>H NMR of the crude reaction mixture. <sup>*g*</sup> The relative stereochemistry was not assigned.

as suitable catalysts (Table 2). Irrespective of the α-substituent on acrolein, both TiCl<sub>4</sub> and Tf<sub>2</sub>NH catalyzed processes provided the corresponding cyclopropanes in moderate yields with uniformly high diastereoselectivity, though use of 30 mol% Tf2NH was found to be optimal (entries 1-5). The reactions of methacrolein with diazoacetates bearing electronically neutral aryl groups furnished the cyclopropanes in yields ranging from 54 to 72% with nearly complete trans selectivity (entries 6-11). Aromatics bearing halide groups were also successfully incorporated into the cyclopropanes in 21 to 69% yields (entries 12-18). The electron rich alkene moiety remained intact under the reaction conditions (entry 19). Diastereoselectivity was lowered significantly when electrondonating *p*-methoxyphenyldiazoacetate was employed (entry 20). However, introduction of the methoxy group at the meta-position of the phenyl ring was tolerated, furnishing the cyclopropanes containing 3-methoxyphenyl and 3,5-dimethoxyphenyl moieties in moderate vields with high diastereoselectivities respectively (entries 21 and 22). As an additional example, the reaction of tert-butyl aryldiazoacetate bearing bromo and methoxy groups at the 2- and 5-positions of the phenyl ring was conducted to give the corresponding cyclopropane in 51% yield without any difficulty (entry 23).16

The reaction of  $\alpha$ -(2,2-diphenylvinyl)diazoacetate and methacrolein was examined, aiming at the applicability of this method to substrates other than aryldiazoacetate. Although the corresponding cyclopropane was obtained only in 17% yield by using method B (entry 24), the use of TfOH as acid catalyst in CH<sub>2</sub>Cl<sub>2</sub> (see, Table 1, entry 8) overcame this deficiency leading to the formation of the cyclopropane in 51% yield with >20 : 1 diastereoselectivity (entry 24 in parentheses). Use of styryldiazoacetate resulted in lower yield and selectivity (data not shown). In the reactions of  $\alpha$ -alkyldiazoacetates, such as *tert*-butyl 2-diazopropanoate, the formation of **2** as well as  $\beta$ -keto ester **3**, which derived from the Roskamp-type reaction,<sup>17</sup> dominated over the cyclopropanation.



To further expand the scope of this cyclopropanation, use of  $\alpha$ -benzoyloxyacrolein<sup>18</sup> was then surveyed considering the importance of donor–acceptor cyclopropanes in organic synthesis.<sup>2b</sup> Although the use of Tf<sub>2</sub>NH furnished none of the desired products, TiCl<sub>4</sub> promoted the reaction smoothly and provided the corresponding cyclopropanes in moderate yields and diastereoselectivities (entries 25–29).

The relative stereochemistry was determined unambiguously by X-ray crystallographic analysis after the derivatization of the cyclopropanecarboxaldehyde **1b** to the corresponding *p*-nitrobenzoyl ester (Scheme 1 and Fig. 1).<sup>19</sup> The stereochemistry of the other products was tentatively assigned by comparing the <sup>1</sup>H NMR spectra of those cyclopropanes with **1b**.



Scheme 1 Reagents and conditions: (i) NaBH<sub>4</sub>, MeOH; (ii) *p*-NO<sub>2</sub>-BzCl, TEA, DMAP, CH<sub>2</sub>Cl<sub>2</sub>, 83% yield (2 steps).

Fig. 1 ORTEP representation of 4 with ellipsoids shown at 50% probability level. Hydrogen atoms are omitted for clarity.



Scheme 2 Titanium-BINOLate catalyzed asymmetric cyclopropanation reaction.

To test the viability of the asymmetric variant, (*S*)-BINOL– Ti(O*i*-Pr)<sub>4</sub> (2 : 1 molar ratio) catalyzed cyclopropanation reaction of *tert*-butyl phenyldiazoacetate and  $\alpha$ -benzoyloxyacrolein was examined (Scheme 2). Although the reaction was sluggish even at 0 °C, providing the cyclopropane in only moderate enantioselectivity, our preliminary study clearly indicated the possibility of further refining the Lewis acid catalyzed asymmetric cyclopropanation.

In summary, we demonstrated the effectiveness of acid catalyzed Michael-initiated cyclopropanation reactions for the preparation of sterically congested cyclopropanes in a highly diastereoselective manner. Our research also shed light on the use of aryldiazoacetates in acid catalysis, which is a truly unexplored area in organic synthesis. Research is currently underway to develop catalytic asymmetric methods and chiral auxiliary based approaches.

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