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### **Cyclopropanation Mediated by Lithium Iodide of Electron-Deficient Alkenes** with Activated Dibromomethylene Compounds

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**Abstract:** Reactions of electron-deficient alkenes with dibromomethylene compounds activated by cyanide and ester groups were promoted by LiI to afford the corresponding cyclopropanes in high yields.

**Key words:** cyclopropanes, dibromides, cyanides, esters, stereoselective synthesis

A cyclopropane unit can be found in a broad range of natural products and its properties as well as practical syntheses have been a great concern to organic chemists.<sup>1</sup>

Previously, we reported that the indium-mediated reaction of electron-deficient alkenes with active methylene dibromides in the presence of LiI afforded the corresponding cyclopropanes in high yields (Equation 1).<sup>2</sup> Without LiI the yield was little diminished (70%).



Equation 1 (from ref. 2)

During the course of re-screening the reaction conditions, we found that the presence of indium metal was not necessary for promoting the reaction, and only a stoichiometric amount of LiI was enough to facilitate the cyclopropanation (Equation 2).

#### **Equation 2**

To gain insight into the reaction, we examined the reactions of ethyl dibromocyanoacetate (1a) or dimethyl dibromomalonate (1b) with benzylidene malononitrile (2b)by changing added salts. The results are summarized in Table 1. Without LiI no reaction proceeded and a catalytic amount of LiI was not enough to complete the reactions (entries 1–3). Both the reactions of **1a** and **1b** proceeded smoothly in the presence of a stoichiometric amount of

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<sup>b</sup> Values in parentheses refer to the diastereomeric ratio.

LiI (entries 4 and 5). When LiBr or LiCl was employed, **1a** afforded **3ab** in moderate to good yields (entries 6 and 8), whereas **1b** gave very poor yields of **3bb** (entries 7 and 9). The use of NaI and KI resulted in similar results to the

Table 1 Cyclopropanations of 2b with 1<sup>a</sup>

Br Br	a <sup>2</sup> + Ph 3r 2b		salt DMF, r.t.	- Ph $R^2$	
1a R <sup>1</sup> = 1b R <sup>1</sup> =	CN, R <sup>2</sup> R <sup>2</sup> = C	<sup>2</sup> = CO <sub>2</sub> Et :O <sub>2</sub> Me	3ab i 3bb i	$R^1 = CN, R^2 = CO_2Et$ $R^1 = R^2 = CO_2Me$	
Entry	1	Salt (mol%)	Time (	h) Yield $(\%)^b$	
1	1a	LiI (10)	24	9 (60:40)	
2	1b	LiI (10)	24	6	
3	1b	LiI (50)	24	46	
4	1b	LiI (100)	1	94	
5	1a	LiI (100)	1	94 (51:49)	
6	1a	LiBr (100)	1	75 (69:31)	
7	1b	LiBr (100)	24	6	
8	1a	LiCl (100)	3	48 (73:27)	
9	1b	LiCl (100)	24	trace	
10	1a	NaI (100)	1	82 (55:45)	
11	1b	NaI (100)	1	70	
12	1a	KI (100)	1	95 (56:44)	
13	1b	KI (100)	1	70	
14	1a	KBr (100)	24	56 (67:33)	
15	1a	KF (100)	19	38 (64:36)	
16	<b>1</b> a	TBAB (100)	1	69 (56:44)	
17	<b>1</b> a	TBAC1 (100)	1	40 (92:8)	
18	<b>1</b> a	$Na_2S_2O_3$ (100	)) 2	50 (63:37)	
19	1a	KPF <sub>6</sub> (100)	23	13 (53:47)	
20	1a	NaBF <sub>4</sub> (100)	23	14 (58:42)	
21	1a	LiClO <sub>4</sub> (100)	21	6 (53:47)	

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<sup>&</sup>lt;sup>a</sup> Conditions: **1** (0.50 mmol), **2b** (0.60 mmol), DMF (1 mL), r.t.

case of LiI (entries 10–13). KBr and KF also promoted the reaction, although a longer reaction time was requested (entries 14 and 15). Ammonium salts were found to promote the reaction and a high stereoselection occurred when tetrabutylammonium chloride was used (entries 16 and 17). Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> gave a moderate yield (entry 18). KPF<sub>6</sub>, NaBF<sub>4</sub>, and LiClO<sub>4</sub> were not effective for this reaction (entries 19–21).

Next, solvent effects on the cyclopropanation were examined by applying the optimized conditions (Table 1, entries 4 and 5). The use of THF and acetone gave good results for both **1a** and **1b** (Table 2, entries 1–4). The reaction of **1a** in EtOH afforded **3ab** in good yield (entry 5), whereas the yield of **3bb** was lower (Table 2, entry 6). The reactions of the bromides in  $CH_2Cl_2$  gave moderate yields (entries 7 and 8). Diethyl ether affected the stereoselection giving **3ab** with strong bias for one diastereomer (entry 9).<sup>3</sup> The reaction in hexane gave a similar stereoselection to that in diethyl ether, albeit the yield was moderate (entry 10).

 Table 2
 Solvent Effects on the Cyclopropanation of 2b<sup>a</sup>

Entry	1	Solvent	Time (h)	Yield (%) <sup>b</sup>
1	1a	THF	1	77 (57:43)
2	1b	THF	1	94
3	<b>1</b> a	acetone	1	82 (55:45)
4	1b	acetone	1	92
5	<b>1</b> a	EtOH	5	81 (58:42)
6	1b	EtOH	5	38
7	<b>1</b> a	$CH_2Cl_2$	23	44 (91:9)
8	1b	$CH_2Cl_2$	23	27
9	<b>1</b> a	Et <sub>2</sub> O	3	78 (92:8)
10	<b>1</b> a	hexane	20	45 (86:14)

<sup>a</sup> Conditions: **1** (0.50 mmol), **2b** (0.60 mmol), LiI (0.50 mmol), solvent (1 mL), r.t.

<sup>b</sup> Values in parentheses refer to the diastereomeric ratio.

Various dibromides **1c**–**g** were submitted to the cyclopropanation of **2b**. The results are summarized in Table 3. Diethyl dibromomalonate (**1c**) and dibromodibenzoylmethane (**1d**) gave cyclopropanes **3cb** and **3db**, respectively, in good yields (entries 1 and 2). When cyclic dibromides **1e** and **1f** were used, the corresponding spiro compounds were obtained (entries 3 and 4). Dichloride **1g** was proved to be less effective for this reaction (entry 5). Dibromodifluoromethane did not afford a coupling product.

The scope and limitation of alkenes that can be used in this cyclopropanation were examined by using **1a** (Table 4). Ethyl 2-cyano-3-phenylacrylate (**2c**) afforded **3ac** in high yield (Table 4, entry 1). However, **2d–g** were completely





Conditions: <b>1</b> (0.50 mmol) <b>2b</b> (0.60 mmol) DMF (1 mL)	
The structure of <b>3bb</b> is shown in Table 1.	

b

converted into a *cis/trans* mixture of dimer **4** (entries 2– 5). When a larger amount of **2g** was used, the corresponding cyclopropane **3ag** was obtained in low yield together with still a considerable amount of dimer **4** (entry 6). Propylidenemalononitrile (**2h**) provided **3ah** in moderate yield (entry 7). These results suggest that the presence of at least one cyano functionality in alkenes is a key for success of the cyclopropanation. In the indium-mediated reactions,<sup>2</sup> ethyl acrylate and acrylonitrile gave the corresponding cyclopropanes upon the reactions of **1a**; however, the reaction without indium metal resulted in a dimerization of **1a**. These facts indicate that the nature of the reactive intermediate in the present cyclopropanation distinctly differs from that of the indium-mediated version.

Although we are unable to discuss the precise mechanism of the present cyclopropanation at this stage, the following observations are informative: (1) Cyclopropanation of electron-deficient alkenes with bromomalononitrile<sup>4</sup> and malononitrile has been reported,<sup>5</sup> where bromomalononitrile is postulated as a common intermediate (Equation 3 and Equation 4). (2) Diethyl dibromomalonate (**1c**) and diethyl bromomalonate were reported to be good electro-

 Table 4
 Reactions of 1a with Various Electron-Deficient Alkenes<sup>a</sup>

1a +	<sup>२1</sup> \( 2c−h	R <sup>2</sup> 	Lil ₩F, r.t.		O <sub>2</sub> Et	EtO <sub>2</sub> C	O <sub>2</sub> Et
Entry	2	$\mathbb{R}^1$	R <sup>2</sup>	R <sup>3</sup>	Time (h)	Yield (%)	
						<b>3</b> <sup>b</sup>	4
1	2c	Ph	CN	CO <sub>2</sub> Et	1	<b>3ac</b> 90 (47:53)	0
2	2d	Ph	Ac	Ac	1	0	79
3	2e	Ph	Ac	CO <sub>2</sub> Et	3	trace	41
4	2f	Ph	CO <sub>2</sub> Et	Ac	3	trace	49
5	2g	Ph	CO <sub>2</sub> Et	CO <sub>2</sub> Et	1	trace	83
6 <sup>c</sup>	2g	Ph	CO <sub>2</sub> Et	CO <sub>2</sub> Et	1	<b>3ag</b> 24 (45:55)	63
7	2h	Et	CN	CN	3	<b>3ah</b> 48 (50:50)	0

<sup>a</sup> Conditions: **1a** (0.50 mmol), **2** (0.60 mmol), DMF (1 mL), r.t.

<sup>b</sup> Values in parentheses refer to the diastereomeric ratio.

<sup>c</sup> Alkene (3 equiv) and LiI (2 equiv) were used.

philic brominating agents (Equation 5),<sup>6</sup> which release a bromonium ion, likewise NBS. The presence of phenolic OH is necessary to promote this bromination; anisole was inert for the bromination. Both the two bromine atoms in **1c** are capable of taking part in the transformation. (3) We tested the reaction of dibromides **1d** and **1f** with phenol (2 equiv) at 100 °C for 2 days according to the conditions in the literature<sup>6</sup> affording dibenzoylmethane (89%) and barbituric acid (81%), respectively, along with *p*-bromophenol (91%) in both the cases (Equation 6). Dibromides **1d** and **1f** were protonated by the phenolic proton, which may play a critical role to prevent a reverse reaction regenerating the dibromides.



Equation 3 (from ref. 3b)



Equation 4 (from ref. 4a)



Equation 5 (from ref. 5)



#### Equation 6

On the basis of the above observations, we have a tentative scenario that the reaction starts with liberation of a bromonium ion from dibromides 1, which is presumably trapped by iodide ion to prevent a recombination leading to 1. The resulting bromomalononitrile anion undergoes a Michael addition to 2 affording cyclopropanes 3 via intramolecular cyclization.

The different behavior of dibromides **1a** and **1b** was marked by a cyclic voltammetric study, which revealed that the redox potentials of **1a** and **1b** in DMF vs.  $Ag/Ag^+$  were shown at -0.62 V and -1.39 V, respectively, reflecting the yields of cyclopropanes.

In summary, the cyclopropanation of electron-deficient alkenes were achieved by using a combination of active methylene dibromides and LiI under mild conditions.<sup>7</sup>

#### **Typical Reaction Procedure (Entry 5, Table 1)**

To a mixture of **1b** (77 mg, 0.50 mmol) and LiI (67 mg, 0.50 mmol) in DMF (1 mL), **2b** (70  $\mu$ L, 0.60 mmol) was added, and the mixture was stirred for 1 h. The product was extracted with Et<sub>2</sub>O, washed with H<sub>2</sub>O and brine, and dried over Na<sub>2</sub>SO<sub>4</sub>. The solvent was removed under reduced pressure, and the product was purified by chromatography on SiO<sub>2</sub> (elution with hexane–EtOAc = 2:1, then EtOAc) affording **3bb** (124 mg, 94%, dr = 51:49).

# Ethyl 1,2,2-Tricyano-3-phenylcyclopropanecarboxylate<sup>4a</sup> (3bb) <sup>1</sup>H NMR (200 MHz, CDCl<sub>3</sub>): $\delta$ = 1.21 (t, *J* = 7.2 Hz, 3 H<sub>a</sub>), 1.47 (t,

<sup>1</sup>H NMR (200 MHz, CDCl<sub>3</sub>):  $\delta = 1.21$  (t, J = 7.2 Hz, 3 H<sub>a</sub>), 1.47 (t, J = 7.2 Hz, 3 H<sub>b</sub>), 3.98 (s, 1 H<sub>a</sub>), 4.04 (s, 1 H<sub>b</sub>), 4.25 (q, J = 7.2 Hz, 2 H<sub>a</sub>), 4.52 (q, J = 7.2 Hz, 2 H<sub>b</sub>), 7.29-7.46 (m, 5 H<sub>a</sub>), 7.50 (s, 5 H<sub>b</sub>).

# Diethyl 2,2-Dicyano-3-phenylcyclopropane-1,1-dicarboxylate (3cb)

<sup>1</sup>H NMR (200 MHz, CDCl<sub>3</sub>):  $\delta$  = 1.19 (t, *J* = 7.2 Hz, 3 H, CH<sub>3</sub>), 1.39 (t, *J* = 7.2 Hz, 3 H, CH<sub>3</sub>), 3.95 (s, 1 H, CH), 4.23 (q, *J* = 7.2 Hz, 2 H, CH<sub>2</sub>), 4.32 (q, *J* = 7.0 Hz, 2 H, CH<sub>2</sub>), 7.35–7.40 (m, 5 H, Ph).

#### 1,1-Dicyano-2,2-dibenzoyl-3-phenylcyclopropane (3db)

<sup>1</sup>H NMR (200 MHz, CDCl<sub>3</sub>):  $\delta$  = 4.38 (s, 1 H), 7.20–7.64 (m, 7 H), 7.68–7.77 (m, 2 H), 7.98–8.08 (m, 2 H). <sup>13</sup>C NMR (50 MHz, CDCl<sub>3</sub>):  $\delta$  = 16.5, 41.2, 56.0, 110.0, 112.3, 127.5, 128.4, 128.7, 128.9, 129.1, 129.1, 129.4, 129.5, 133.7, 134.7, 135.1, 187.7, 188.0 (one aromatic carbon is overlapping).

# 1,1-Cyano-6,6-dimethyl-2-phenylspiro[2.5]octane-4,8-dione (3eb)

<sup>1</sup>H NMR (200 MHz, CDCl<sub>3</sub>): δ = 1.21 (s, 6 H, 2 × CH<sub>3</sub>), 2.60–2.83 (m, 4H), 4.12 (s, 1 H), 7.10–7.20 (m, 2 H), 7.30–7.40 (m, 3 H). <sup>13</sup>C NMR (50 MHz, CDCl<sub>3</sub>): δ = 22.1, 28.5, 29.0, 30.2, 44.3, 49.4, 53.2, 54.4, 109.5, 111.0, 127.1, 128.4, 128.8, 128.9, 195.9, 198.0.

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## 1,1-Dicyano-*N*,*N*'-dimethyl-2-phenyl-5,7-diazaspiro[2.5]oc-tane-4,6,8-trione (3fb)

 $^1H$  NMR (200 MHz, CDCl<sub>3</sub>):  $\delta$  = 3.33 (s, 3 H, CH<sub>3</sub>), 3.49 (s, 3 H, CH<sub>3</sub>), 4.30 (s, 1 H), 7.24–7.34 (m, 2 H), 7.38–7.46 (m, 3 H). Anal. Calcd for  $C_{16}H_{12}N_4O_3$ : C, 62.33; H, 3.92; N, 18.17. Found: C, 62.00; H, 3.71; N, 17.87.

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