

# Solvent and ligand partition reaction pathways in nickel-mediated carboxylation of methylenecyclopropanes

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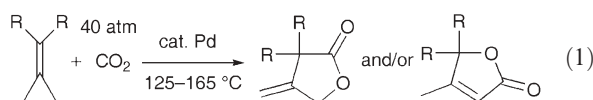
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Methylenecyclopropanes are carboxylated with gaseous carbon dioxide in the presence of a stoichiometric amount of a nickel complex; the reaction pathways are significantly influenced by the reaction solvent and the amine ligand.

The incorporation of carbon dioxide into organic compounds presents an important challenge in chemistry, as reduction of greenhouse gases has emerged as a pressing global issue. In addition, due to its abundance as a raw material and innocuous nature, the development of methods to activate intrinsically inert carbon dioxide and to fix it into organic compounds becomes of practical value to synthetic chemists.<sup>1</sup> On the other hand, a number of transition metal-mediated processes involving the carbon–carbon bond cleavage of methylenecyclopropanes have been reported.<sup>2</sup> Methylenecyclopropanes are unique in that coordination of their carbon–carbon double bonds to low-valent transition metals triggers cleavage at either the proximal Csp<sup>2</sup>–Csp<sup>3</sup> bond or the distal Csp<sup>3</sup>–Csp<sup>3</sup> bond of the cyclopropane core.<sup>3</sup> There has been, however, only one example of carboxylation of methylenecyclopropanes with carbon dioxide; a palladium-catalysed reaction at relatively high temperature forms unsaturated five-membered ring lactones through a sequence involving oxidative addition of the distal carbon–carbon bond to palladium, insertion of carbon dioxide and, finally, reductive elimination (eqn. 1).<sup>4</sup>



It has been reported recently that low-valent nickel species mediate the coupling of carbon dioxide with various unsaturated hydrocarbons under mild conditions,<sup>5</sup> which encouraged us to explore a new nickel-mediated carboxylation reaction of methylenecyclopropanes. Notably, it was found that diverse reaction pathways are partitioned in response to reaction conditions, such as a reaction solvent and the amine ligand employed, affording products essentially different from those obtained in the palladium case mentioned above.

A solution of benzylidenecyclopropane (**1a**, 1.1 equiv), Ni(cod)<sub>2</sub> (1 equiv, cod = cycloocta-1,5-diene) and an amine ligand (2.2 equiv) was stirred at 0 °C for 4 h under an atmosphere of carbon dioxide (1 atm). An aqueous workup followed by methylation with Me<sub>3</sub>SiCHN<sub>2</sub> afforded a mixture of methyl esters of the carboxylated products. The distribution of these products

varied significantly as a function of reaction solvent and amine ligand (Table 1). When 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU, 2.2 equiv) was used as the amine ligand in toluene solvent, cyclopropane derivative **2a** was obtained along with a small amount of the branched  $\alpha,\beta$ -unsaturated ester **3a**<sup>6</sup> (73%, **2a** : **3a** : **4a** = 93 : 7 : 0, entry 1). In contrast, the use of more polar solvents favoured the formation of **3a** (entries 2–5). In particular, the reaction with DBU in *N*-methyl-2-pyrrolidinone (NMP) gave **3a** in 78% yield as the major product (**2a** : **3a** : **4a** = 6 : 94 : 0). Here, the formation of the linear  $\gamma,\delta$ -unsaturated ester **4a** was not observed. However, to our surprise, use of 7-methyl-1,5,7-triazabicyclo-[4.4.0]dec-5-ene (MTBD) instead of DBU altered the reaction course to favour production of the linear  $\gamma,\delta$ -unsaturated ester **4a**;<sup>7</sup> the reaction with MTBD in NMP gave **4a** in 52% yield exclusively (entry 8). At a higher CO<sub>2</sub> pressure of 5 atm, the yield was improved (67%, **2a** : **3a** : **4a** = 0 : 1 : 99, entry 9). Suppression of the formation of **4a** with DBU, and of **2a** and **3a** with MTBD suggests different mechanisms operate with DBU and MTBD (*vide infra*).

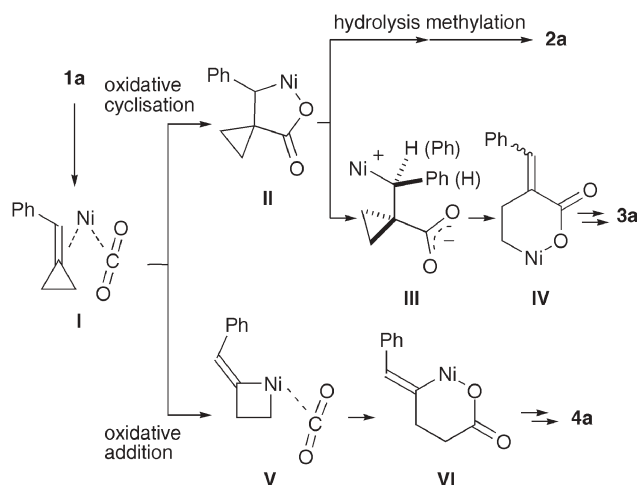
The partitioning of the various reaction pathways can be explained by assuming the mechanism shown in Scheme 1. Initially, nickel(0) forms the  $\pi$ -complex **I** with the carbon–carbon double bond of methylenecyclopropane and carbon dioxide. For the formation of the products **2a** and **3a**, oxidative cyclisation occurs to give the nickelacycle **II**.<sup>8</sup> Direct hydrolysis of **II** followed by methylation with Me<sub>3</sub>SiCHN<sub>2</sub> affords **2a**. Alternatively, the

**Table 1** Nickel-mediated carboxylation of **1a** with CO<sub>2</sub> under various conditions<sup>a</sup>

Entry	Solvent	Amine	Yield (%) <sup>b</sup>	Ratio <sup>c</sup>		
				<b>2a</b>	<b>3a</b>	<b>4a</b>
1	toluene	DBU	73	93	7	0
2	THF	DBU	77	40	60	0
3	DMF	DBU	68	23	77	0
4	CH <sub>3</sub> CN	DBU	66	4	96	0
5	NMP	DBU	78	6	94 <sup>d</sup>	0
6	toluene	MTBD	27	0	0	> 99
7	THF	MTBD	40	0	0	> 99
8	NMP	MTBD	52	0	0	> 99
9	NMP	MTBD	67 <sup>e</sup>	0	1	99

<sup>a</sup> Conditions: **1a** (1.1 equiv), CO<sub>2</sub> (1 atm), Ni(cod)<sub>2</sub> (1.0 equiv), amine (2.2 equiv), solvent, 0 °C, 4 h; hydrolysis with diluted HCl; then methylation with TMSCHN<sub>2</sub>, MeOH. <sup>b</sup> Combined yields. <sup>c</sup> Ratio determined by <sup>1</sup>H NMR. <sup>d</sup> E : Z = 94 : 6. <sup>e</sup> CO<sub>2</sub> (5 atm).

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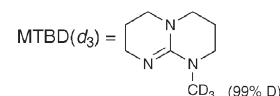
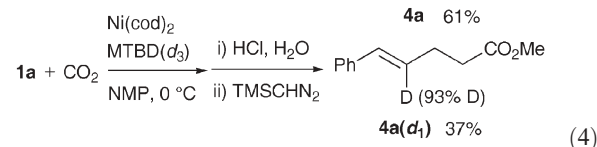
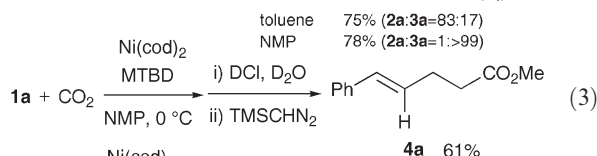
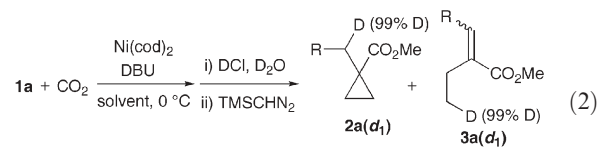


**Scheme 1** Proposed mechanism for the carboxylation reaction of **1a**.

intermediate **II** may undergo  $\beta$ -carbon elimination to give the six-membered nickelacycle **IV**, probably through the dissociated ionic complex **III**, which would allow a *syn* (or *synclinal*) conformation of the nickel–carbon linkage with the cleaving carbon–carbon bond.<sup>9</sup> Hydrolysis and methylation then leads to the production of **3a**. We assume that  $\beta$ -carbon elimination occurs more easily with the ionic intermediate **III** than with the nickelacycle **II** and that a polar solvent such as NMP facilitates the formation of the ionic intermediate to favour the formation of **3a**.<sup>10,11</sup> On the other hand, when MTBD is used as the amine ligand, the proximal carbon–carbon bond *cis* to the phenyl group of **1a** undergoes oxidative addition giving the nickelacycle **V**.<sup>12,13</sup> Insertion of carbon dioxide into the nickel– $sp^3$  carbon linkage gives **VI**. The corresponding *E* product **4a** is selectively produced by subsequent protonolysis and methylation.<sup>14</sup>

We quenched the reactions forming **2a**, **3a** and **4a** with DCl/D<sub>2</sub>O (2 M) in order to support the intermediacy of **II**, **IV** and **VI**. With the products **2a** and **3a** obtained, deuterium atoms were

incorporated at the expected positions (eqn. 2), whereas no deuterium incorporation was observed with **4a** (eqn. 3). In contrast, when MTBD(*d*<sub>3</sub>) having a CD<sub>3</sub> group was used as the base, the vinylic position of product **4a** was deuterated (eqn. 4). These contrasting results shown in eqns. 3 and 4 can be explained by assuming that the intermediate nickelacycle **VI** abstracts a proton from the methyl group of MTBD prior to an aqueous workup.



Under these optimised conditions, a structurally diverse set of methylenecyclopropanes **1** was examined (Table 2).<sup>†</sup> The reactions of (arylmethylidene)cyclopropanes **1b–1f** in toluene produced the corresponding cyclopropane derivatives **2b–2f** with moderate to good selectivities, except in the case of **1d** (entries 1–5). The chlorophenyl moiety of **1f** remained intact in the presence of nickel(0). The alkylidene cyclopropane derivative **1g** gave the ring-opening product **3g** as the major product, even when toluene was used as solvent (entry 6).<sup>15</sup> All the reactions in NMP gave the branched  $\alpha,\beta$ -unsaturated esters **3** selectively (entries 7–12). The

**Table 2** Nickel-mediated carboxylation of **1** with CO<sub>2</sub>

Entry	<b>1</b> (R)	Conditions <sup>a</sup>	Yield (%) <sup>b</sup>	Ratio <sup>c</sup>		
				<b>2</b>	<b>3</b> ( <i>E</i> : <i>Z</i> ) <sup>d</sup>	<b>4</b>
1	<b>1b</b> (4-MeC <sub>6</sub> H <sub>4</sub> )	A	75	78	22	0
2	<b>1c</b> (2-MeC <sub>6</sub> H <sub>4</sub> )	A	77	92	8	0
3	<b>1d</b> (4-MeOC <sub>6</sub> H <sub>4</sub> )	A	78	51	49 (91 : 9)	0
4	<b>1e</b> (4-FC <sub>6</sub> H <sub>4</sub> )	A	79	89	11	0
5	<b>1f</b> (4-ClC <sub>6</sub> H <sub>4</sub> )	A	79	93	7	0
6	<b>1g</b> (Ph(CH <sub>2</sub> ) <sub>2</sub> )	A	70	20	80 (63 : 35)	0
7	<b>1b</b>	B	70	1	99 (93 : 7)	0
8	<b>1c</b>	B	72	3	97 (97 : 3)	0
9	<b>1d</b>	B	79	1	99 (91 : 9)	0
10	<b>1e</b>	B <sup>e</sup>	81	1	99 (93 : 7)	0
11	<b>1f</b>	B <sup>e</sup>	87	8	92 (93 : 7)	0
12	<b>1g</b>	B	68	0	> 99 (56 : 44)	0
13	<b>1b</b>	C	58	0	3	97
14	<b>1c</b>	C	55	0	4	96
15	<b>1d</b>	C	40	0	1	99
16	<b>1e</b>	C	66	0	1	99
17	<b>1f</b>	C	64	0	0	> 99
18	<b>1g</b>	C	37	0	6	94

<sup>a</sup> Common conditions: **1** (1.1 equiv), CO<sub>2</sub>, Ni(cod)<sub>2</sub> (1.0 equiv), amine (2.2 equiv), 0 °C, 4 h; then workup. Conditions A: 1 atm of CO<sub>2</sub>, DBU, in toluene; conditions B: 1 atm of CO<sub>2</sub>, DBU, in NMP; conditions C: 5 atm of CO<sub>2</sub>, MTBD, in NMP. <sup>b</sup> Combined yields. <sup>c</sup> Ratio determined by <sup>1</sup>H NMR. <sup>d</sup> Obtained as a mixture of *E* and *Z* isomers. The ratio given in parentheses if determined. <sup>e</sup> 6 h.

use of MTBD as the amine ligand resulted in highly selective formation of the *E* linear  $\gamma,\delta$ -unsaturated esters **4**, although the yields were moderate (entries 13–18).

In conclusion, we have described the nickel-mediated carboxylation of methylenecyclopropanes with carbon dioxide. Three types of carboxylated products, which are all different from that obtained by the palladium-catalysed reaction,<sup>4</sup> are prepared exclusively or preferentially depending on the reaction solvent and the amine ligand employed.

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## Notes and references

† **General procedure:** To a stirred suspension of Ni(cod)<sub>2</sub> (82.5 mg, 0.30 mmol) in a freshly distilled solvent (3 mL) in a Schlenk-type flask under a nitrogen atmosphere at 0 °C was added an amine ligand (0.66 mmol). The mixture was degassed by a freeze–pump–thaw method, and then carbon dioxide was introduced. Substrate **1** (0.33 mmol) was added to the resulting pale yellow suspension at 0 °C. After the reaction mixture was stirred at 0 °C for 4 h, diluted HCl aq. (2 M) was added to the reaction mixture. The aqueous layer was extracted with ethyl acetate. The combined organic layer was washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated. The residue was treated with TMSCHN<sub>2</sub> in Et<sub>2</sub>O/MeOH. The solvent was removed under reduced pressure and the residue was purified by preparative thin-layer chromatography (hexane : ethyl acetate) to give the product.

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- 7 Production of **4a** was not observed with other amines like DBN, TMEDA, 2,2'-bipyridyl, 1,2-dimethylimidazole and 2-methyl-2-oxazoline.
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- 10 The branched ester **3a** was obtained as the major product (72%, **2a** : **3a** : **4a** = 20 : 80 : 0) when the reaction was carried out initially in toluene for 4 h and then CH<sub>3</sub>CN was added to the reaction mixture which was further stirred for an additional 4 h prior to an aqueous workup.
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- 14 Product **4a** can result from carboxylation of 1-phenylbuta-1,3-diene, to which **1a** may possibly isomerise in the presence of nickel(0). The present reaction conditions, however, caused no carboxylation reaction of 1-phenylbuta-1,3-diene prepared independently.
- 15 The contrasting results obtained with **1g** and (arylmethylidene)-cyclopropanes **1a–1f** are accounted for by assuming the more stable nature of the nickel–benzylic carbon linkage of **II**.