COMMUNICATION

Electrocatalytic Cyclopropanation of Active Methylene Compounds

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Abstract

The development of novel strategies to access cyclopropanes has become increasingly important due to the vital role of these three-membered ring structures in synthetic intermediates, natural products, and pharmaceuticals. Herein, we present an electrocatalytic method for the synthesis of cyclopropanes through intermolecular dehydrogenative annulation of active methylene compounds and arylalkenes. This electrochemical process requires no chemical oxidants, allowing for a speedy access to various functionalized cyclopropanes from inexpensive and readily available materials.

Keywords: Electrochemistry; Cyclopropane; Catalyst; Alkene; Organic electrosynthesis

1. Introduction

The cyclopropane ring has a wide range of applications in synthesis, natural products and pharmaceuticals [1—7], but is most often formed by alkene cyclopropanation — a process that typically utilizes dangerous diazo compounds [8—10]. To reduce the risk associated with diazo compounds [11], alternative strategies that involve easily accessible and stable materials have been developed. These approaches involve the use of precursors such as ylides, hydrazones, alkynes, triazoles, and other functionalized materials to generate metal-carbene species, and ultimately produce cyclopropane units [12—18]. Although these alternative strategies are advantageous, the development of efficient and cost-effective methods for constructing cyclopropanes from easily available materials remains a challenge [19]. Cyclopropanation directly from methylene compounds is an ideal strategy because it reduces synthetic manipulation, and employs stable and readily available materials. However, such a strategy remains difficult.

Organic electrochemistry enables dehydrogenative transformations through H_2 evoluation without need for external chemical oxidants [20,21]. In this context, we have recently developed an organoelectrocatalytic strategy to achieve intramolecular cyclopropanation of active methylene compounds [22]. These electrochemical dehydrogenative annulation reactions require no sacrificial chemical oxidants and produces H_2 as the side product. With our continued interests in developing sustainable electrochemical technologies for organic synthesis [23—29], we report herein the electrocatalytic intermolecular cyclopropanation of active methylene compounds (Fig. 1).

2. Results and discussion

The electrocatalytic annulation of styrene **1** with dimethyl malonate was chosen as a model to optimize the electrolysis conditions (Table 1). Note that the phenothiazine-based catalyst used in the electrocatalytic intramolecular cyclopropanation reaction was not efficient for this more challenging intermolecular reaction because it reacted with the

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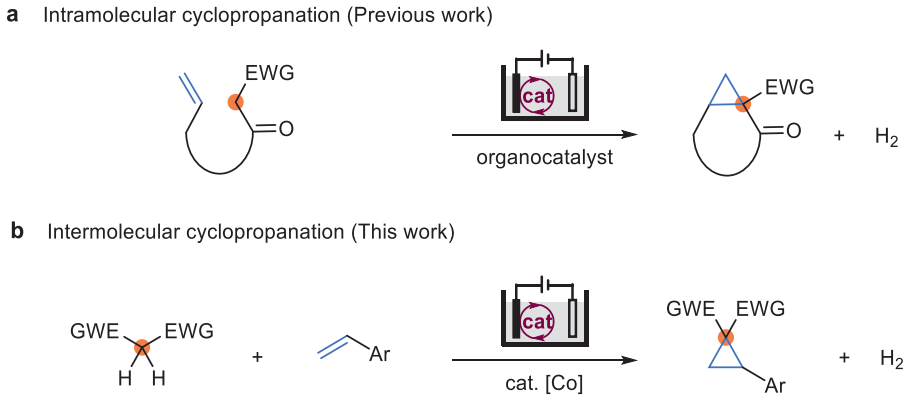
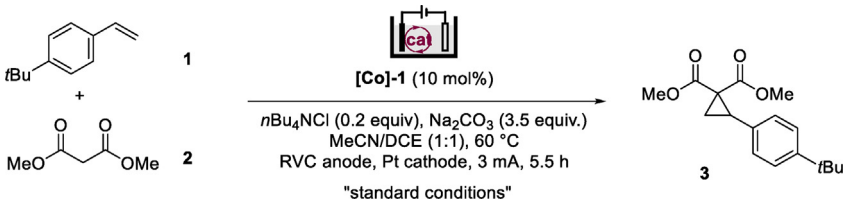


Fig. 1. Electrocatalytic cyclopropanation of active methylene compounds. a. Electrocatalytic intramolecular cyclopropanation. b. Electrocatalytic intermolecular cyclopropanation. EWG, electron withdrawing group.

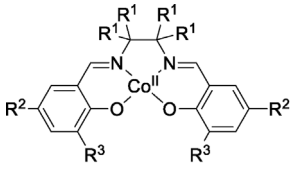
1,3-dicarbonyl starting material, leading to catalyst inactivation [22,30]. Hence, we resorted the cobalt-salen complexes that are known to be efficient for electrocatalytic oxidation of active methylene compounds [31,32]. Reaction screening revealed that the desired cyclopropane product **3** could be obtained in 82% yield under the optimal conditions involving **[Co]-1** (10mol%) as the catalyst, nBu$_4$NCl

Table 1. Optimization of reaction conditions[a].

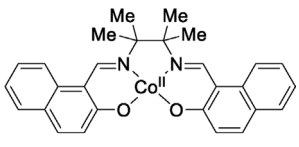


Entry	Deviation from standard condition	Yield of **3** (%)[b]
1	none	82[c]
2	no electricity	0
3	no **[Co]-1**	0
4	no Na_2CO_3	0
6	at RT	21
8	graphite plate as anode	33
9	K_2CO_3 as base	9
10	Cs_2CO_3 as base	66
11	MeCN/MeOH (1:1)	0
12	MeCN as solvent	61
13	**[Co]-2** as catalyst	59
16	**[Co]-3** as catalyst	38
17	**[Co]-4** as catalyst	82

[a] Standard reaction conditions: RVC anode, Pt cathode, **1** (0.2 mmol), **2** (0.5 mmol), Na_2CO_3 (3.5 equiv.), MeCN/DCE (1:1, 5.0 mL), 3.0 mA, 5.5 h (3.1 F·mol^{-1}).
[b] Yield determined by ^{1}H-NMR analysis using 1,3,5-trimethoxybenzene as the internal standard.
[c] Isolated yield.



[Co]-1 (R^1 = Me, R^2 = *t*Bu, R^3 = H)
[Co]-2 (R^1 = Me, R^2 = R^3 = *t*Bu)
[Co]-3 (R^1 = H, R^2 = R^3 = *t*Bu)



[Co]-4

(0.2 equiv) as the electrolyte, and Na_2CO_3 as a basic additive in a mixed solvent of MeCN/DCE (1:1). The electrolysis was conducted at 60 °C with a reticulated vitreous carbon (RVC) anode, a Pt cathode, and a constant current of 3 mA in a simple undivided cell. Control experiments showed that electricity, the cobalt catalyst, Na_2CO_3, and heating were critical for the formation of **3**. Yield reduction was observed with a graphite plate as the anode, K_2CO_3 or Cs_2CO_3 as the base, and MeCN/MeOH (1:1) or MeCN as the solvent. While **[Co]-2** and **[Co]-3** were less efficient than **[Co]-1** in catalyzing the cyclopropanation reaction, **[Co]-4** was equally effective.

The scope of the electrocatalytic cyclopropanation reaction was investigated (Fig. 2). The phenyl ring of the styrene tolerated substituents of various electronic properties at the para (**4**—**12**), meta (**13** and **14**), and ortho (**15** and **16**) positions. The phenyl ring can be replaced with other (hetero)aryl groups, such as naphthene (**17**), pyridine (**18** and **19**), thiophene (**20**), thiazole (**21**), and benzothiazole (**22**). A conjugated diene also reacted at the terminal alkene regioselectively (**23**). The current reaction conditions were not compatible with alkyl-substituted alkenes, 1,1- and 1,2-disubstituted alkenes. A brief investigation of the active methylene compounds revealed that cyanoesters (**24** and **25**) and cyanoamides (**26**—**28**) were also suitable substrates.

The electrocatalytic cyclopropanation could be scaled up to gram scale (Fig. 3). Hence, the reaction of 8.0 mmol of alkene **24** with dimethyl malonate **2** (2.5 equiv) provided 1.68 g of the cyclopropane product **6** (68% yield).

Although more studies are needed to elucidate the details of the mechanism of this electrocatalytic cyclopropanation reaction, we have proposed a possible one based on observations in this study and previous reports on cobalt catalysis (Fig. 4) [31,33—35].The [Co^{II}] catalyst loses an electron to the anode to give [Co^{III}], which oxidizes the active methylene compounds with the help of a base to regenerate [Co^{II}] and produce an electrophilic carbon radical. The latter C-radical adds to the arylalkene to afford a benzylic carbon radical. The benzylic radical combines with [Co^{II}] to give a [Co^{III}] organometallic intermediate, which is

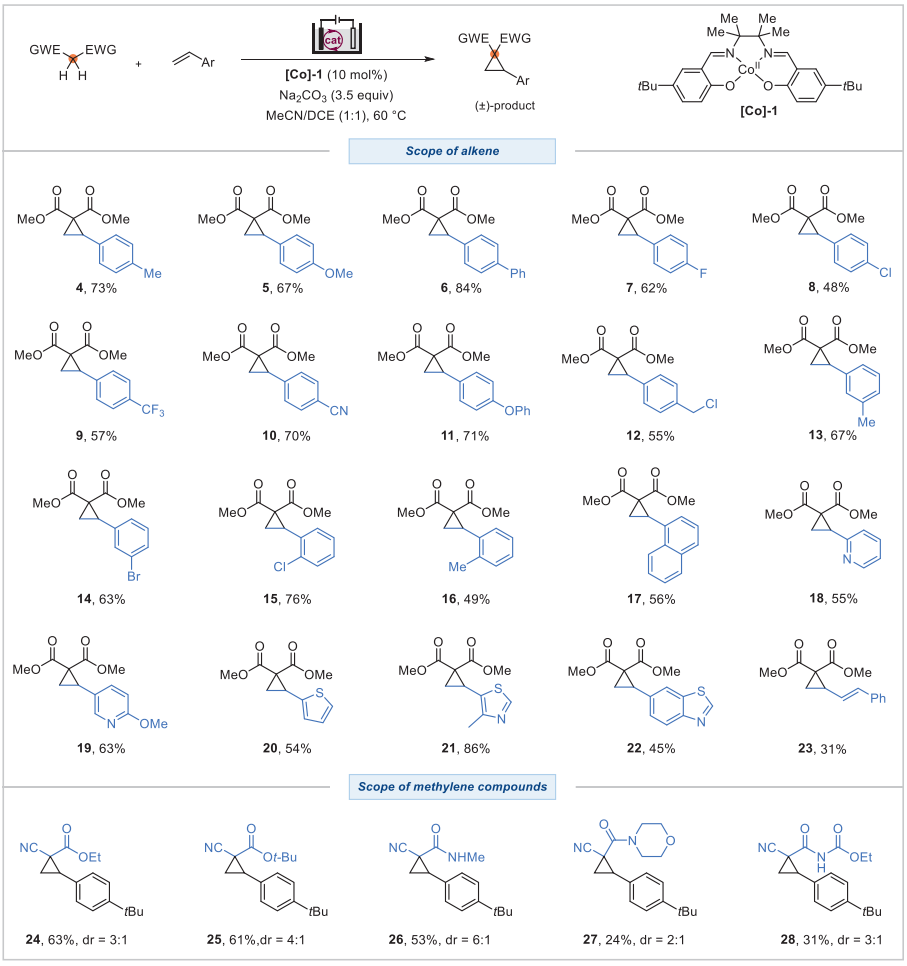


Fig. 2. Reaction conditions: RVC anode, Pt cathode, alkene (0.2 mmol), active methylene compound (0.5 mmol), MeCN/DCE (1:1, 5 mL), 3.0 mA, 60 °C, 5.5—10.0 h. Yields of isolated products are reported.

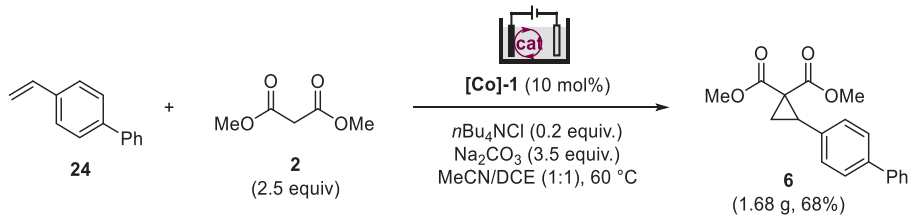


Fig. 3. Reaction scale-up.

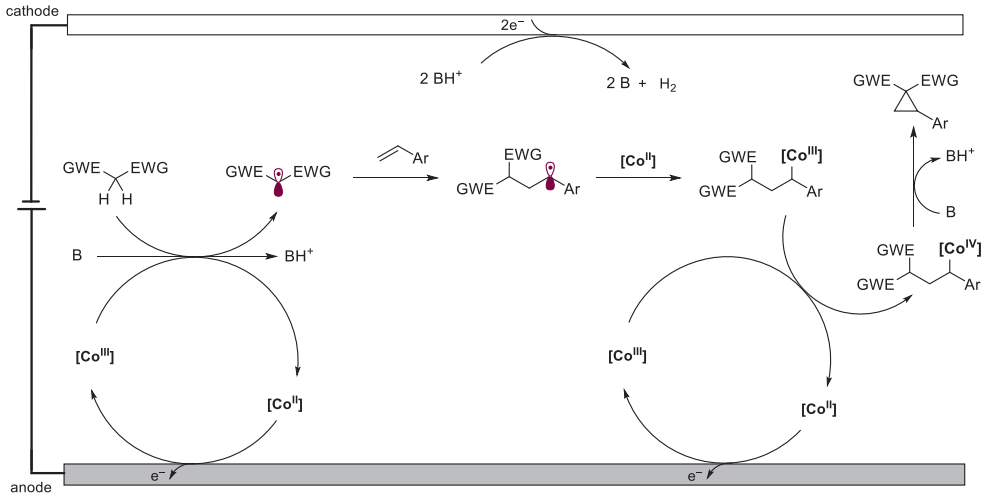


Fig. 4. Mechanistic proposal.

oxidized by [Co^{III}] catalyst to give a [Co^{IV}] species. This high valent Co^{IV} complex is reactive toward nucleophiles [33−35] and undergoes cyclization to give the final cyclopropane product.

3. Conclusions

In summary, we have developed an electrocatalytic method to achieve intermolecular cyclopropanation directly from active methylene compounds without prefunctionalization. The method is currently limited to arylalkenes. Research is ongoing to develop new catalysts to allow the cyclopropanation of alkylalkenes.

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电催化活性亚甲基化合物的环丙烷化反应

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摘要

由于三元环结构在中间体、天然产品和药物的合成中发挥着重要作用，这使得开发新的策略以获得环丙烷已变得越来越重要。在此，我们提出了一种通过活性亚甲基化合物和芳基烯烃的分子间脱氢环化合成环丙烷的电催化方法。该电化学过程不需要化学氧化剂，允许从廉价和简单易得的原料中快速获得各种官能团化的环丙烷。

关键字：电化学；有机电合成；催化剂；环丙烷；烯烃