Novel Role of Carbon Dioxide as a Selective Agent in Palladium-Catalyzed Cyclotrimerization of Alkynes

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Carbon dioxide was found as a selective agent to promote the palladium-catalyzed cyclotrimerization of alkynes in water. Both aryl and alkylacetylenes afforded the corresponding cyclotrimerization products regioselectively in high yields using PdCl₂, CuCl₂, and CO₂ as the catalytic system. However, *tert*-butylacetylene bearing a bulky group gave a dimerization product. Mechanism of this reaction was also discussed.

Keywords carbon dioxide, a selective agent, palladium, cyclotrimerization, alkyne

In the earlier reports on carbon dioxide (CO₂), most of the studies concerned the use of CO₂ as raw materials¹ or reaction media² in organic synthesis. So the development of new routes to apply CO₂ to the modern organic synthesis is considered to be one of the most challenges for the synthetic chemists. Although CO₂ has been displayed to be a selective agent in the earlier reports as either a raw material or reaction media,¹⁻³ few examples succeeded in applying CO₂ only as a selective agent to shift the reaction selectivity in organic synthesis.⁴ Very recently, we found that CO₂ could be used as a selective agent to improve the diiodination of alkynes^{4b} and homocoupling of aryl halides,^{4c} respectively. The results encouraged us to investigate and broaden this role of CO₂ in organic synthesis.

Transition metal mediated [2+2+2] cyclotrimerization of alkynes has been an area of extensive investigation, and utilized efficiently in the synthesis of aromatic compounds and many natural products.⁵⁻¹² Recently, a novel palladium-catalyzed cyclotrimerization of alkynes has been reported,¹² which is useful for the regioselective synthesis of symmetric benzene derivatives in C₆H₆/n-BuOH. Unfortunately, phenylacetylene could not undergo the cyclotrimerization reaction, and only red oil was obtained. On the other hand, harmful solvents such as benzene or dichloromethane were used in all cases.5-12 Thus, development of new and environmentally benign procedures for the palladium-catalyzed cyclotrimerization of alkynes is still an attractive area. Herein we reported our new results of using CO₂ as a selective agent in the palladium-catalyzed cyclotrimerization of alkynes (Scheme 1 and Table 1).

Our recent studies showed that the solvent effects played an important role in influencing the selectivity (chemo-, stereo-, and regio-selectivity) of the Pd(II)-

Scheme 1

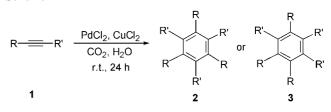


 Table 1
 Palladium-catalyzed cyclotrimerization of alkynes^a

Entry	Alkyne	Isolated yield/%		
1^b	PhC≡CH (1a)	$7 (2a)^{c}$		
2^d	PhC≡CH (1a)	31 (2a) ^c		
3	PhC≡CH (1a)	90 (2a)		
4	p -MeC ₆ H ₄ C \equiv CH (1b)	95 (2b)		
5	$PhC \equiv CMe (1c)$	91 (3)		
6	n -C ₅ H ₁₁ C \equiv CH (1d)	87 (2d)		
7^e	n -C ₅ H ₁₁ C \equiv CH (1d)	с		
8	$n-\mathrm{C}_{3}\mathrm{H}_{7}\mathrm{C}\equiv\mathrm{C}(n-\mathrm{C}_{3}\mathrm{H}_{7})(\mathbf{1e})$	99 (2e)		

^{*a*} Reaction conditions: alkyne **1** (1 mmol), PdCl₂ (5 mol%), CuCl₂ (2 equiv.), CO₂ (1.0 MPa), and H₂O (5 mL) at room temperature for 24 h. ^{*b*} Without both CuCl₂ and CO₂. ^{*c*} The product was red oil and unidentified. ^{*d*} Without CO₂. ^{*e*} Without CuCl₂.

catalyzed processes.¹²⁻¹⁵ Indeed, we found that cyclotrimerization of phenylacetylene (**1a**) occurred regioselectively by altering the reaction solvent from benzene to water in the presence of PdCl₂ and CuCl₂, although the yield of the corresponding cyclotrimerization product **2a** was low (1,3,5-triphenylbenzene, 31% yield), and some red oil was still obtained (Entry 2 in Table 1). Cyclotrimerization of **1a** could occur in the absence of CuCl₂, but the yield of **2a** was decreased to 7% and a large amount of red oils were obtained (Entry 1). It is

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interesting to note that the presence of CO_2 can enhance the yields of the palladium-catalyzed cyclotrimerization of alkynes. For example, the yield of **2a** increased sharply to 90% by using 5 mol% of PdCl₂, 2 equiv. of CuCl₂ and 1.0 MPa of CO₂ as the catalytic system (Entry 3).

In the presence of 5 mol% of $PdCl_2$, 2 equiv. of CuCl₂ and 1.0 MPa of CO₂, the palladium-catalyzed cyclotrimerization reactions of other alkynes were carried out smoothly in excellent yields. Cyclotrimerization of p-MeC₆H₄C \equiv CH (1b), C₅H₁₁C \equiv CH (1d), and $C_3H_7C \equiv CC_3H_7$ (1e) afforded the corresponding symmetric benzenes 2b, 2d, and 2e in 95%, 87% and 99% yields, respectively (Entries 4, 6, and 8). Whereas for cyclotrimerization of PhC=CCH₃ (1c), unsymmetrical benzene **3** was obtained in 91% yield [1,2,4-trimethyl-3, 5,6-triphenylbenzene (3), Entry 5]. The results also showed that CuCl₂ played a crucial role in the cyclotrimerization of alkylacetylene 1d (Entries 6 and 7).¹² With its absence, only red oil was obtained (Entry 7), whereas in the presence of 2 equiv. of CuCl₂, 87% yield of the corresponding symmetric cyclotrimerization product 2d was obtained.

Surprisingly, *tert*-butylacetylene (**1f**), a highly bulky alkyne, was dimerized to afford 98% yield of **4** (1,4-di(*tert*-butyl)buta-1,3-diyne) in water, whereas only 1,3, 5-tri(*tert*-butyl)benzene was found using benzene as the reaction solvent¹² (Scheme 2). The results also showed that CO₂ improved the dimerization reaction. In the absence of CO₂, only 37% yield of **4** was obtained (Entry 1 in Scheme 2), whereas the yield of **4** was increased to 98% with the aid of 1.0 MPa of CO₂ (Entry 2).

Scheme 2

Bu ^t —	$= -H = \frac{5 \text{ mol% PdCl}_2}{\text{CuCl}_2 (2 \text{ equiv.})}$ 1f $\frac{1}{H_2 O (5 \text{ mL}), \text{ r.t., 12 h}}$	→ ^t Bu <u>——</u> tBu 4
Entry	Pressure of CO ₂ /MPa	Isolated yield of 4/%
1	0	37
2	10	98

Based upon the above results, several points were noteworthy: (1) Compared with our previous results,¹² the effect of solvents affected the selectivity of the reaction. In benzene, phenylacetylene did not undergo the cyclotrimerization reaction and *tert*-butylacetylene gave 1,3,5-tri(*tert*-butyl)benzene, whereas in water phenylacetylene was cyclotrimerized to 1,3,5-triphenylbenzene and *tert*-butylacetylene was dimerized to 1,4-di(*tert*butyl)buta-1,3-diyne. (2) The presence of CO₂ can improve the reaction. With its presence, the yield of 1,3,5triphenyl-2,4,6-trimethylbenzene was increased from 31% to 90%. (3) The structure of alkynes influenced both the chemoselectivity and regioselectivity of the reaction to some extent. (4) CuCl₂ can also affect the yields of the reaction.¹²

To further explore the role of CO₂, some controlled

reactions were carried out in the presence of various Lewis and Brönsted acids, and the results are summarized in Table 2. The results showed that the acidity of Lewis or Brönsted acids played a crucial role in the chemoselectivity of the cyclotrimerization reaction. With the increase of the acidity from $Al_2(SO_4)_3$ to NaH_2PO_4 , the yield of **2a** was increased from 27% to 57%. However, the yield was decreased to 41% using aqueous NaH_2PO_4 saturated solution (5 mL) as the reaction solvent. The results showed distinctly that the acidity of CO_2 was not the single factor to improve the palladium-catalyzed cyclotrimerization reaction.

Table 2Palladium-catalyzed cyclotrimerization of $1a^a$

Entry	Lewis or Brönsted acid	Isolated yield of 2a/%
1	Al_2SO_4	27^b
2	Yb(OTf) ₃	33^b
3	NH ₄ Cl	35^b
4	Na ₂ HPO ₄	35^b
5	NaH ₂ PO ₄	57^b
6 ^{<i>c</i>}	NaH ₂ PO ₄	41^b

^{*a*} Reaction conditions: **1a** (1 mmol), PdCl₂ (5 mol%), CuCl₂ (2 equiv.), Lewis or Brönsted acid (2 equiv.), and H₂O (5 mL) at room temperature for 24 h. ^{*b*} The product was red oil and unidentified. ^{*c*} Aqueous NaH₂PO₄ saturated solution (5 mL) as the reaction solvent.

To elucidate how CO_2 promoted the palladiumcatalyzed cyclotrimerization reaction results, a possible mechanism was proposed as shown in Scheme 3.⁵⁻¹² In

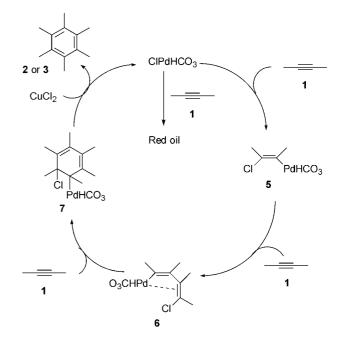
Scheme 1

PdCl₂

$PdCl_2$	+	H_2O	<u> </u>	CIPd(OH)	+	HCI	(1)

+ $CuCl_2$ \leftarrow $CuPdCl_4$ (2)

 $ICI_2 + CO_2 + H_2O \longrightarrow CIPdHCO_3 + HCI (3)$



water, $PdCl_2$ was partly changed to ClPd(OH) species [Eq. (1)],⁸ which led to decreasing complex of catalysts with alkynes to give the desired products **2**. Trace of **2** was obtained in the absence of $CuCl_2$ and CO_2 due to poor solubility of the catalysts in H₂O. The presence of $CuCl_2$ could not only regenerate the palladium species *in situ* but also increase the solubility of catalysts due to the generation of $CuPdCl_4$ [Eq. (2)]. The formation of $ClPdHCO_3R$ from the reaction of CO_2 with $PdCl_2$ and H_2O decreased the complex of the catalysts with alkynes,¹⁶ which resulted in the shift from the chemoselectivity to the cyclotrimerization reaction besides the acidity of H_2CO_3 by the reaction of CO_2 with water [Eq. (3)].⁴ A dimerization product **4** was obtained from *tert*-butylacetylene **1f** due to the steric hindrances.

In conclusion, we have developed a new general and environmentally benign protocol to synthesize some benzene derivatives. Currently, further efforts associated with this new role of carbon dioxide in organic synthesis are in progress in our laboratory.

Experimental

All ¹H NMR spectra were recorded on an INOVA-400 (Varian) spectrometer with CDCl₃ as solvent. All reagents were used directly as obtained commercially.

Typical procedure for the palladium-catalyzed cyclotrimerization of alkynes

Alkyne 1 (1 mmol) was added to a mixture of $PdCl_2$ (5 mol%), $CuCl_2$ (2 equiv.), and H_2O (5 mL) in HF-25 autoclave. Liquid CO₂ was then transferred into the autoclave to 1.0 MPa. The reaction mixture was stirred at room temperature for 24 h. After the gas was vented, the residue was extracted (ether), dried (anhydrous Na₂-SO₄) and then purified by flash column chromatography (hexane/ethyl acetate). Under the above reaction conditions, alkyne 1 was consumed completely detected by GC analysis.

1,3,5-Triphenylbenzene (**2a**): A white solid, m.p. (uncorrected) 174—177 °C (lit.¹⁷ 176 °C); ¹H NMR (CDCl₃, 400 MHz) δ : 7.30—7.36 (m, 11H), 7.51—7.53 (m, 7H); MS *m/z* (%): 306 (M⁺, 100).

1,3,5-Tri(p-methylphenyl)benzene (2b): A white solid, m.p. (uncorrected) 175—178 °C (lit.¹⁷ 178 °C); ¹H NMR (CDCl₃, 400 MHz) δ : 2.37 (s, 9H), 7.16 (d, J=8.4 Hz, 6H), 7.27 (s, 3H), 7.60 (d, J=8.4 Hz, 6H); MS m/z (%): 348 (M⁺, 100).

1,3,5-Tripentylbenzene (2d): A colorless oil; ¹H NMR (CDCl₃, 400 MHz) δ : 0.88 (t, J=7.6 Hz, 9H), 1.24—1.32 (m, 12H), 1.55—1.61 (m, 6H), 2.38 (t, J= 4.8 Hz, 6H), 6.39 (s, 3H); MS m/z (%): 288 (M⁺, 8) 262 (7), 241 (16), 227 (12), 205 (23), 192 (19), 171 (11), 149 (33), 135 (37), 113 (18), 99 (67), 91 (100).

Hexapropylbenzene (2e): A white solid, m.p. (uncorrected) 101-104 °C (lit.¹⁸ 102-102.5 °C); ¹H NMR (CDCl₃, 400 MHz) δ : 1.02 (t, J=7.6 Hz, 18H), 1.48–1.54 (m, 12H), 2.45 (t, J=4.8 Hz, 12H); MS m/z (%): 330 (M⁺, 5), 301 (9), 287 (18), 273 (8), 259 (11),

217 (15), 175 (8), 133 (25), 119 (56), 105 (100).

1,2,4-Trimethyl-3,5,6-triphenylbenzene (3): A white solid, m.p. (uncorrected) 223—225 °C (lit.¹⁹ 224 °C); ¹H NMR (CDCl₃, 400 MHz) δ : 1.71 (s, 6H), 2.03 (s, 3H), 6.95—7.44 (m, 15H); MS *m*/*z* (%): 348 (M⁺, 100).

1,4-Di(*tert*-butyl)buta-1,3-diyn (4): A white solid, m.p. (uncorrected) 129—132 °C (lit.²⁰ 131 °C); ¹H NMR (CDCl₃, 400 MHz) δ : 1.23 (s, 18H); MS *m*/*z* (%): 162 (M¹, 8), 161 (25), 133 (37), 119 (55), 91 (100).

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