

Cu-exchanged phosphotungstic acid: An efficient and reusable heteropoly acid for the cyclopropanation of alkenes via C-H insertion

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Abstract

Alkenes undergo smooth cyclopropanation with ethyl diazoacetate using a catalytic amount of Cu-exchanged phosphotungstic acid (Cu-TPA) in dichloromethane under mild reaction conditions to afford cyclopropanecarboxylates in high yields with moderate selectivity. The catalyst is recycled and reused for three to four subsequent runs with a minimal decrease of activity.

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1. Introduction

The cyclopropanation of alkenes is an important transformation in organic synthesis because of its versatile applications in natural products synthesis [1]. The cyclopropane ring is frequently found in various biologically active compounds [2]. They are also very useful intermediates for the construction of new C–C bond [3]. The metal catalyzed cyclopropanation of alkenes with ethyl diazoacetate (EDA) is one of the most simple and direct approaches for the preparation of cyclopropanes [4–6]. The copper complexes have primarily been used as catalysts for the cyclopropanation of alkenes with diazo compounds [7–10]. Subsequently, rhodium and ruthenium complexes have also been reported for this transformation [11–20]. In recent reports iron Lewis acids have been found to give *cis*-cyclopropanes predominantly [21,22]. However, most of these catalysts are expensive and also difficult to recycle which limit their use in large-scale synthesis. Therefore, the introduction of new methods involving simple, inexpensive and recyclable catalysts for an efficient and selective cyclopropanation continues to be a challenging endeavor in organic synthesis.

In recent years, the use of solid acids as heterogeneous catalysts has received considerable interest in different areas of

organic synthesis [23]. The heterogeneous solid acids are advantageous over conventional homogeneous acid catalysts as they can be easily recovered from the reaction mixture by simple filtration and can be reused after activation or without activation, thereby making the process economically viable. In many cases, heterogeneous catalysts can be recovered with only minor change in activity and selectivity so that they can be conveniently used in continuous flow reactions. Among various heterogeneous catalysts, heteropoly acids are most attractive, because of their unique properties such as well-defined structure, Bronsted acidity, possibility to modify their acid–base and redox properties by changing their chemical composition (substituted HPAs), ability to accept and release electrons, high proton mobility, etc. [24–27]. However, there have been no examples of the use of copper salt of heteropoly acid for the cyclopropanation of alkenes via carbene insertion.

2. Experimental

2.1. General methods

Melting points were recorded on a Buchi R-535 apparatus and are uncorrected. IR spectra were recorded on a PerkinElmer FT-IR 240-c spectrophotometer using KBr optics. ¹H NMR and ¹³C spectra were recorded on Gemini-200 spectrometer (200 MHz) in CDCl₃ using TMS as internal standard. Mass spectra were

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recorded on a Finnigan MAT 1020 mass spectrometer operating at 70 eV. Column chromatography was performed using E. Merck 60–120, mesh silica gel. All solvents were distilled, dried over CaH₂ and stored under nitrogen prior to use. Starting materials and reagents used in the reactions were obtained commercially from Aldrich, Lancaster, and Fluka were used without purification, unless otherwise indicated.

2.2. Catalyst preparation

The copper salt of the H₃PW₁₂O₄₀ was prepared as precipitate by adding 0.18 g of barium hydroxide (to neutralize the three protons) to the aqueous solution containing 2.0 g of H₃PW₁₂O₄₀. Later 0.16 g of CuSO₄·5H₂O was added to replace Ba with Cu by eliminating the Ba as BaSO₄. Thus the Cu_{1.5}PW₁₂O₄₀ salt was recovered from the solution by recrystallization. The catalyst mass was dried at 120 °C for 12 h in an oven and finally calcined at 300 °C for 2 h. The retention of Keggin structure after exchange of Cu ions is confirmed by XRD and FT-IT analysis.

2.3. General procedure

To a stirred solution of alkene (3 mmol) and Cu-TPA (5 mol%) in dichloromethane (5 mL), ethyl diazoacetate (1 mmol) was added slowly in a drop wise manner. The resulting mixture was stirred at 27 °C for the appropriate time (Table 1). After completion, as indicated by TLC, the catalyst was removed by simple filtration and washed with ether (3 mL × 10 mL). The combined organic extracts were dried over anhydrous Na₂SO₄, concentrated *in vacuo* and purified by column chromatography on silica gel (Merck, 100–200 mesh ethyl acetate: hexane, 1:9) to afford pure cyclopropane carboxylate. The structure of cyclopropanes was established by comparing their NMR, IR and mass spectra with known compounds. The spectral data of all the products were identical with those of authentic samples [7–20,16,28].

2.3.1. Spectral data for selected products

2.3.1.1. 2,3-Diphenyl-cyclopropanecarboxylic acid ethyl ester (3l). Liquid, IR (KBr): $\nu=3024, 2924, 2853, 1733, 1448, 1459, 1307, 1191, 1170, 1039, 964, 751, 694$ cm⁻¹; ¹H NMR (200 MHz, CDCl₃): $\delta=1.03$ (t, 3H, $J=7.1$ Hz), 2.37 (dd, 1H, $J=5.0, 9.6$ Hz), 2.88 (dd, 1H, $J=6.9, 9.6$ Hz), 3.17 (dd, 1H, $J=5.2, 6.9$ Hz), 4.93 (q, 2H, $J=7.1$ Hz), 7.11–7.32 (m, 10H); EIMS: $m/z=266$ (M⁺), 194, 142, 116, 91, 43.

2.3.1.2. trans-Ethyl 2-phenylcyclopropane-1-carboxylate (3a). Liquid, IR (KBr): $\nu=2985, 2931, 2865, 1720, 1605, 1458, 1369, 1257, 1153, 1070, 1045, 935, 780, 697$ cm⁻¹; ¹H NMR (200 MHz, CDCl₃): $\delta=1.02$ (t, 3H, $J=6.9$ Hz), 1.25 (ddd, 1H, $J=4.4, 6.4, 8.4$ Hz), 1.53 (ddd, 1H, $J=4.4, 5.2, 9.2$ Hz), 1.85 (ddd, 1H, $J=4.2, 5.2, 8.4$ Hz), 2.45 (ddd, 1H, $J=4.2, 6.4, 9.2$ Hz), 3.99–4.05 (m, 2H), 7.05–7.32 (m, 5H); EIMS: $m/z=190$ (M⁺), 162, 141, 115, 91, 43.

2.3.1.3. cis-Ethyl 2-phenylcyclopropane-1-carboxylate (4a). Liquid, IR (KBr): $\nu=3059, 2982, 2933, 1728, 1607, 1454,$

1381, 1265, 1086, 961, 795, 694 cm⁻¹; ¹H NMR (200 MHz, CDCl₃): $\delta=0.98$ (t, 3H, $J=7.1$ Hz), 1.33 (ddd, 1H, $J=5.1, 7.8, 8.7$ Hz), 1.70 (ddd, 1H, $J=5.1, 5.6, 7.4$ Hz), 2.05 (ddd, 1H, $J=5.6, 7.8, 9.3$ Hz), 2.59 (ddd, 1H, $J=7.4, 8.7, 9.3$ Hz), 3.90 (q, 2H, $J=7.1$ Hz), 7.19–7.28 (m, 5H); EIMS: $m/z=190$ (M⁺), 163, 91, 55.

2.3.1.4. endo-Bicyclo [6.1.0] nonane-9-carboxylic acid ethyl ester (3g). Liquid, IR (KBr) $\nu=2984, 2923, 2855, 1726, 1449, 1378, 1150$ cm⁻¹; ¹H NMR (200 MHz, CDCl₃): $\delta=1.10$ –1.95 (m, 18H), 4.02–4.19 (q, 2H, $J=7.1$ Hz); EIMS: $m/z=196$ (M⁺), 151, 108, 97, 81, 67, 55, 41.

2.3.1.5. exo-Bicyclo [6.1.0] nonane-9-carboxylic acid ethyl ester (4g). Liquid, IR (KBr): $\nu=2923, 2854, 1723, 1463, 1211, 1180, 1145$ cm⁻¹. ¹H NMR (200 MHz, CDCl₃): $\delta=0.91$ –1.18 (m, 3H), 1.21–1.82 (m, 13H), 2.0–2.15 (m, 2H), 4.02–4.11 (q, 2H, $J=7.1$ Hz); EIMS: $m/z=196$ (M⁺), 122, 108, 97, 81, 79, 67, 55, 41.

3. Results and discussion

In continuation of our research program on the catalytic applications of heteropoly acids, we herein report a mild, selective and efficient method for the cyclopropanation of alkene with ethyl diazoacetate by means of carbene insertion. In a model experiment, styrene was treated with ethyl diazoacetate in the presence of 10 mol% of Cu-TPA in dichloromethane. The reaction was complete in 2.5 h at room temperature and the product, ethyl 2-phenyl-1-cyclopropanecarboxylate was isolated as a mixture of **3a** and **4a** in 90% yield (entry **a**, Table 1, Scheme 1).

However, the product was obtained as a mixture of **3a** *trans*- and **4a** *cis*-isomers, favoring *trans*-diastereomer **3a**. The diastereomers **3a** and **4a** could be easily separated by column chromatography and were characterized by comparison of their NMR spectra with authentic samples [11]. Both electron rich and electron deficient styrene derivatives gave cyclopropane carboxylates in high yields. In all cases, the reaction proceeds smoothly at room temperature with high *trans*-selectivity. α -And β -substituted styrene derivatives such as α -methyl styrene and β -methyl styrene gave the corresponding cyclopropane carboxylates in excellent yields but low selectivity with approximately 1:1 ratio of *cis/trans*-isomers (entries **j** and **k**, Table 1). Surprisingly, stilbene gave *trans*-product exclusively (entry **l**, Table 1).

In addition, treatment of cyclohexene with ethyl diazoacetate gave ethyl bicyclo [4.1.0] heptane-7-carboxylate in 95% yield (Scheme 2). In case of cyclohexene, the product was obtained as a mixture of *endo*- and *exo*-isomers, favoring *endo*-isomer. Similarly, cyclooctene, indene and dihydronaphthalene worked well for this cyclopropanation (entries **g**, **h** and **i**, Table 1). No allylic insertion was observed in the reactions of cycloalkenes with ethyl diazoacetate. In the absence of catalyst, no reaction was observed between alkene and EDA. The advantage of the use of Cu-TPA is that it can be easily recovered and recycled

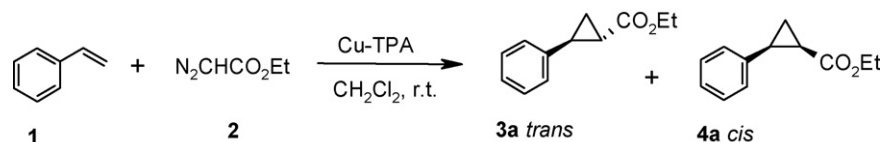
Table 1
Cu(TPA) catalyzed cyclopropanation of alkenes

Entry	Alkene	Product ^a		Time (h)	Yield (%) ^b	<i>trans:cis</i> ^c
a	R=Ph	R=Ph		2.5	90	2.4:1
b	R=4-Me-Ph	R=4-Me-Ph		2.5	86	2.4:1
c	R=4-OMe-Ph	R=4-MeO-Ph		2.0	82	2.4:1
d	R=2-naphthyl	R=2-naphthyl		2.5	89	2.4:1
e	R=n-hexyl	R=n-hexyl		2.5	92	2.4:1
f				2.0	95	2.4:1 ^d
g				2.0	95	2.4:1 ^d
h				3.0	85	2.4:1 ^d
i				3.0	80	2.4:1 ^d
j				3.0	88	1:1
k				3.0	89	1:1
l				3.5	80	-

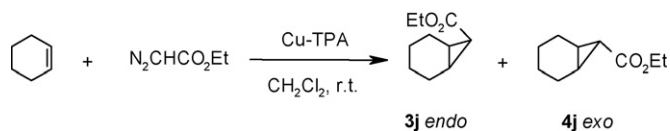
^aAll products were characterized by ¹H NMR, IR and mass spectrometry.

^bYield refers to pure products after chromatography.

^cThe ratios were determined by ¹H NMR. ^dRatio of endo:exo



Scheme 1. Cyclopropanation of styrene.



Scheme 2. Cyclopropanation of cyclohexene.

Table 2
The effects of various catalysts in the preparation of **3a/4a**

S. no.	Cu(II)salts	<i>trans:cis</i>	Time (h)	Yield (%) ^a
1	Cu(BF ₄) ₂	1.2:1	0.5	90
2	Cu(II)TFA	1.8:1	12	55
3	Cu(OTf) ₂	1.4:1	12	40
4	Cu(OAc) ₂	1.8:1	12	35
5	CuSO ₄	1.2:1	12	30
6	Cu(TPA)	2.4:1	2.5	90

^a Isolated yield after purification.

in subsequent runs. The scope and generality of this process is illustrated Table 1.

Since the reaction mixture is heterogeneous, the catalyst could be easily separated by simple filtration. The recovered catalyst was further washed with ether, dried at 60 °C under reduced pressure and reused in three to four successive runs with only a minimal decrease in activity. For example, styrene and ethyl diazoacetate in the presence of 10 mol% of Cu-TPA in dichloromethane gave 90, 87, 85 and 80% yields over four cycles. The chemoselectivity for cyclopropane formation over carbene dimerization was achieved by the use of an excess of alkene and slow addition of the carbene source e.g. ethyl diazoacetate to the reaction mixture. No formation of side products such as diethyl fumarate or diethyl maleate was observed when the reaction was carried out using Cu-TPA. A variety of alkenes including vinyl arenes and few cyclic and acyclic olefins underwent smooth cyclopropanation with ethyl diazoacetate under identical conditions. In most cases, the products were obtained

Table 3
Optimization of reaction conditions for the reaction of styrene with ethyl diazoacetate

S. no.	Catalyst (mol%)	Solvent	Yield (%)	Time (h)
1	5	CH ₂ Cl ₂	90	2.5
2	5	THF	–	–
3	5	Toluene	–	–
4	5	CH ₃ CN	–	–
5	1	CH ₂ Cl ₂	70	4.0
6	5	CH ₂ Cl ₂	90	2.5
7	10	CH ₂ Cl ₂	90	2.0
8	15	CH ₂ Cl ₂	90	2.0

in high yields and with high *trans*-selectivity. The effects of various copper(II) salts were screened in the cyclopropanation of styrene with ethyl diazoacetate and the results are presented in Table 2.

To optimize the reaction conditions, we carried out the cyclopropanation of styrene with ethyl diazoacetate in various solvents by varying the amount of catalyst and the results are summarized in Table 3. The best result was obtained using 5 mol% of the catalyst in dichloromethane.

4. Conclusion

In summary, we have developed an efficient protocol for the cyclopropanation of olefins with ethyl diazoacetate using copper exchanged heteropoly acid (Cu-TPA) as a heterogeneous catalyst. This method offers significant advantages such as high conversions, mild conditions, ease of recovery and reusability of the catalyst, which makes it a useful and attractive strategy for the preparation of cyclopropane carboxylates. The use of heterogeneous catalyst makes this method quite simple, more convenient and environmentally friendly.

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