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Hydroxyapatite-Supported Palladium-Catalyzed Efficient Synthesis of (*E*)-2-Alkene-4-ynecarboxylic Esters. Intense Fluorescene Emission of Selected Compounds

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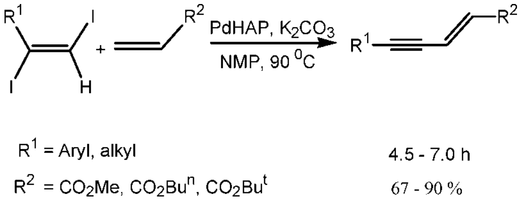
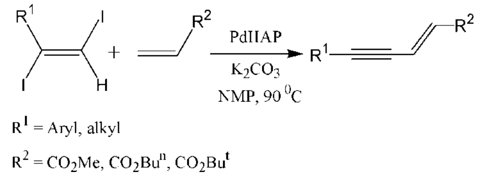


A simple procedure for the synthesis of substituted (*E*)-2-alkene-4-ynecarboxylic esters has been achieved using hydroxyapatite-supported palladium as efficient catalyst surface. The catalyst is recycled, and the turnover number (TON) based on Pd is 16000. A naphthyl-substituted derivative gives very intense fluorescence emission.

Catalysis by palladium anchored on a heterogeneous support for carbon−carbon coupling has received tremendous attention in recent times.[1] The main advantages of heterogeneous catalysts compared to their homogeneous counterparts are ease of separation, reusability, improved efficiency due to stable active site and better steric control of a reaction intermediate.[2] These qualities of heterogeneous catalysts made them very promising for applications in industry.

Hydroxyapatite, a Ca−phosphate complex, is found to be one of the best active heterogeneous supports cabable of accommodating a variety of metals and metal salts.[3] One of these hydroxyapatite-supported palladium complexes, nonstoichiometric PdHAP containing Pd^{2+}, has been used very successfully for the Heck and Suzuki coupling reactions.[4] We now report here a facile synthesis of *(E)*-2-alkene-4-ynoate system by the coupling of *vicinal*-diiodoalkenes with conjugated carboxylic esters catalyzed by nonstoichiometric PdHAP (Scheme 1). The TEM image of our fresh and used nonstoichiometric PdHAP catalyst did not show discrete particles (see the Supporting Information) corresponding to Pd(0).[3c]

SCHEME 1. Coupling of Diiodoalkenes and Conjugated Alkenes



The stereodefined 2-en-4-ynoate moiety or its derivatives are of considerable interest in organic synthesis because of their presence in many natural products of promising biological activities[5] and their potential as advanced materials for electronic and photonic applications.[6] This unit is usually synthesized by homogeneous Pd- or Pd/Cu- or Cu-catalyzed coupling of alkyne or an organometallic alkyne and a vinyl halide.[7–9] Recently, we reported a Pd nanoparticle-catalyzed coupling of *vic*-diiodoalkenes and conjugated alkenes to build up this unit.[10] However, none of these methods[7–9] including ours[10] offered satisfactory catalytic recyclability and large turnover number (TON). To accommodate these two prime criteria for industrial applications, we considered a heterogeneous HAP-based catalyst for this important reaction.

The experimental procedure is very simple. A stirred mixture of *vic*-diiodoalkene, acrylic ester in *N*-methylpyrrolidone (NMP) was heated at 90−100 °C in the presence of PdHAP and K$_2$CO$_3$ for a certain period of time (TLC). Standard workup provided the product. The catalyst, PdHAP, was recycled up to three times without appreciable loss of efficiency (see the Experimental Procedure and Table 5).

Several substituted *vic*-diiodoalkenes underwent coupling with acrylic esters under the catalysis of PdHAP by this procedure to produce the corresponding enynecarboxylic esters in high yields. The results are summarized in Table 3.

Both aryl- and alkyl-substituted diiodoalkenes participated in this reaction. The coupling is stereoselective, giving (*E*)-esters in all reactions. The Br, Cl, and F substituents on the aromatic ring (entries 5−9, Table 3) of the aryl group did not interfere in the coupling with diiodoalkenes. The corresponding *vic*-dibromoalkenes (entry 17, Table 3) also coupled with acrylic

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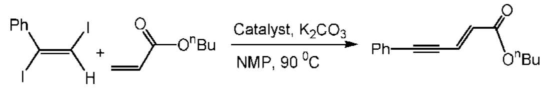
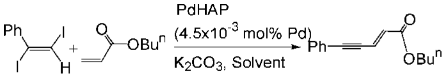
TABLE 1. Standardization of Catalyst System



entry	catalyst system	palladium loadings (mol%)	time (h)	yield (%)	TON
1[a]	PdCl$_2$, TBAB, Na$_2$CO$_3$	2.0	7.0	78	39
2	stoichiometric PdHAP	6×10^{-3}	10.0	15	2500
3	nonstoichiometric PdHAP	4.5×10^{-3}	6.0	75	16666
4	PdCl$_2$(PhCN)$_2$	2.0	10.0		
5	Pd/C (10%)	0.37	10.0	55	148
6	Pd/CuO (5%)	0.47	10.0	50	107
7	Pd/ZnO (5%)	0.47	10.0	40	86

[a] The reaction in entry 1 was carried out in H$_2$O.

TABLE 2. Standardization of Solvent



entry	solvent	T (°C)	time (h)	yield (%)
1	H$_2$O	90	8.0	
2	THF	70	8.0	35
3	toluene	90	8.0	
4	DMF	90	8.0	60
5	NMP	90	6.0	75
6	CH$_3$CN	75	8.0	

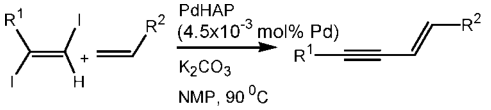
esters; however, the reaction time was longer and yield was lower compared to diiodo counterparts.

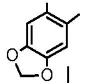
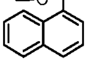
To explore potential of these enynecarboxylic esters for useful applications, the absorption and fluorescence properties of these compounds were studied.[12] The five compounds showed very promising absorption and fluorescence, as highlighted in Table 4, Figure 1, and Figure 2.

To determine the most suitable catalyst, a variety of heterogeneous Pd catalysts as shown in Table 1 were investigated. As evident from the results, nonstoichiometric PdHAP was found to be the best one with a TON of 16666.[11] Similarly, a study of solvent system (Table 2) compatible with PdHAP showed NMP as the most effective.

However, except for alkyl-substituted enyne esters, all products showed considerable emission. In general, increased conjugation in the system leads to increasing red shift in emission spectrum. This can be explained by lower Franck−Cordon energy gap due to increased delocalization of the π network.[6] Among these five fluorescent enyne esters, the naphthyl derivative (entry 1, Table 4) was found to be the best showing a $\lambda_{\max}$ at 333 nm (Figure 1) and λ_{em} 443 nm (methanol) (Figure 2). A solvent study with regard to emission was done with the naphthyl derivative, and it was found that it showed lesser λ_{em} in nonpolar solvent like cyclohexane compared to that in highly polar methanol solvent (Figure 3). This indicated that the emissive state of naphthyl derivative is strongly dependent on solvent. The intense fluorescence of the naphthyl derivative may be attributed to the structural rigidity of naphthalene moiety which significantly reduces the nonradiative mechanism leading to high quantum yield, 0.22 (determined using a fluorescent probe, coumarin 480, C 480, exciton in cyclohexane with a

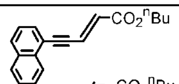
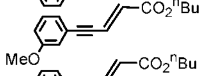
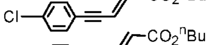
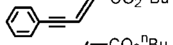
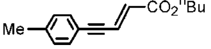
TABLE 3. Coupling of Diiodoalkenes with Activated Alkenes



entry	R^1	R^2	time (h)	yield (%)[a]	ref
1	C$_6$H$_5$	CO$_2$Bu^n	6.0	75	10
2	C$_6$H$_5$	CO$_2$Bu^t	7.0	72	
3	*p*-Me-C$_6$H$_4$	CO$_2$Me	6.5	78	10
4	*p*-Me-C$_6$H$_4$	CO$_2$Bu^n	6.0	83	
5	*p*-Cl-C$_6$H$_4$	CO$_2$Me	5.0	85	10
6	*p*-Cl-C$_6$H$_4$	CO$_2$Bu^n	5.5	90	
7	*o*-Br-C$_6$H$_4$	CO$_2$Bu^n	4.5	82	
8	*o*-Br-C$_6$H$_4$	CO$_2$Bu^t	5.0	78	
9	*p*-F-C$_6$H$_4$	CO$_2$Bu^n	6.0	68	
10	*m*-MeO-C$_6$H$_4$	CO$_2$Me	7.0	75	10
11	*m*-MeO-C$_6$H$_4$	CO$_2$Bu^n	6.0	85	
12		CO$_2$Me	5.5	67	10
13		CO$_2$Bu^n	4.5	80	10
14	n-C$_4$H$_9$	CO$_2$Bu^n	5.5	72	
15	n-C$_6$H$_{13}$	CO$_2$Me	6.0	75	
16	n-C$_6$H$_{13}$	CO$_2$Bu^n	6.5	70	10
17	C$_6$H$_5$	CO$_2$Bu^n	16.0	15	10[b]

[a] Yields refer to those of purified products characterized by IR and ^{1}H and ^{13}C NMR spectroscopic data. [b] This substrate is a dibromoalkene.

TABLE 4. Absorption and Emission Data of Enyne Compounds in Methanol

entry	compounds	absorption λmax (nm)	emission λem (nm)
1		333	443
2		298	450
3		300	456
4		296	452
5		303	430

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(11) Lower yield of product and TON with the use of stoichiometric PdHAP (entry 2, Table 1) compared to nonstoichiometric PdHAP (entry 3, Table 1) is probably due to the relatively less efficiency of stoichiometric PdHAP in coupling reactions as this catalyst surface has a lower concentration of phosphate anions, which are necessary to statibilize the resulting higher oxidation state of palladium.4.

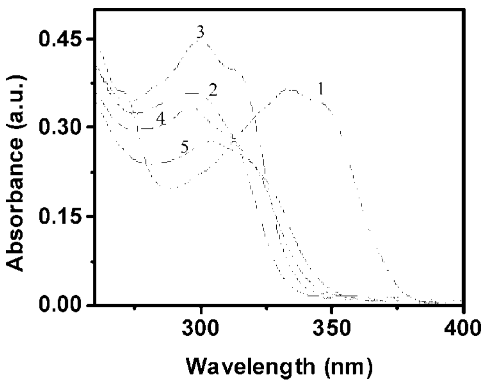


FIGURE 1. Absoption spectra of five selected enynes designated by their entries in Table 4.

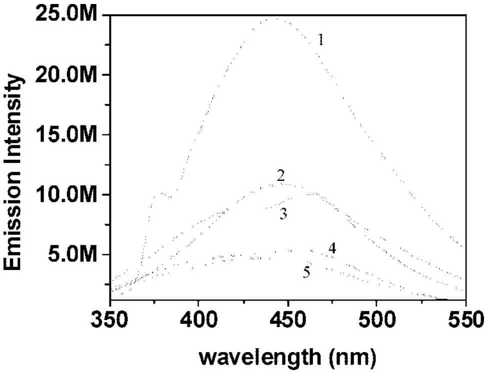


FIGURE 2. Emisssion spectra of five selected enynes.

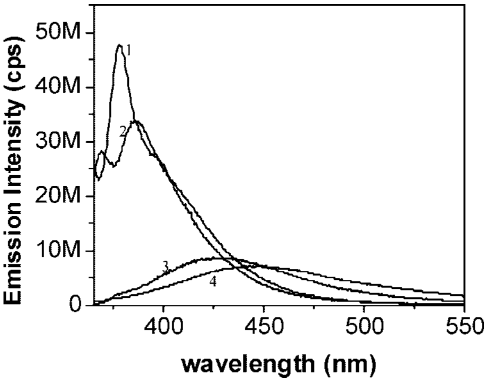
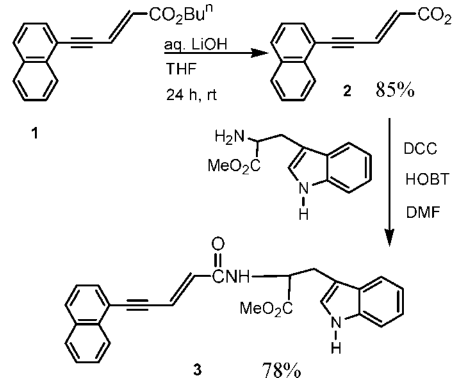


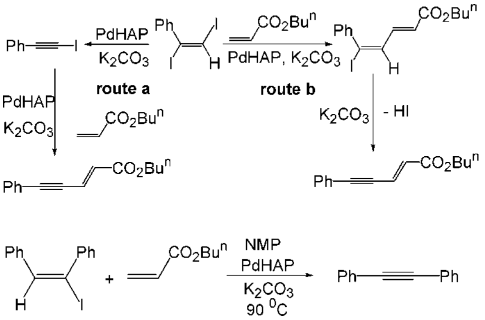
FIGURE 3. Comparison of emission of the naphthyl derivative in different solvents ((1) cyclohexane; (2) CCl_4; (3) CH_3CN; (4) methanol).

reported quantum yield of 1.05).[13] Certainly, these enyne esters, particularly the naphthalene derivative with excellent fluorescence emission, may be considered as a good biomarker through tagging with a biologically active unit. To check the feasibility of this hypothesis, the (*E*)-5-naphthalene-1-ylpent-2-en-4-ynoic acid butyl ester **1** was hydrolyzed to give the corresponding acid **2** which was coupled with a tryptophan moiety to give the corresponding peptide **3** (Scheme 2). This class of compounds might have promising biological activities.[14] A systematic and detailed investigation to find the useful applications of a series of these peptides will constitute our next endeavor.

SCHEME 2. Synthesis of Peptide



SCHEME 3. Possible Reaction Pathway



It may be predicted that this PdHAP-catalyzed coupling does not proceed via the traditional Pd^0/Pd^{II} cycle as no Pd(0) was detected in the fresh and used catalyst, and it is more likely that it goes via the Pd^{II}/Pd^{IV} state, as reported in other PdHAP-catalyzed Heck reactions.[4] Two alternative routes were considered for this reaction (Scheme 3). In route a, the diiodoalkene on treatment with PdHAP under the reaction conditions produces the iodoalkyne which then couples with acrylic ester to provide the product. The intermediate iodoalkyne isolated as the sole product in a separate experiment using PdHAP, produced the en-yne carboxylic ester on reaction with *n*-butyl acrylate. Thus, route a is obviously the most probable path. Route b demonstrates initial Heck coupling followed by HI elimination to give the product. The selective Heck coupling with terminal iodide group at the first step may be rationalized by steric reasons and the subsequent preferential HI elimination over further Heck coupling was supported by a model experiment with iododiphenylethylene, as outlined in Scheme 3. Hence, operation of route b is also not ruled out.

In conclusion, we have developed a convenient and efficient procedure for the synthesis of (*E*)-2-alkene-4-ynecarboxylic esters by a simple reaction of *vic*-diiodoalkenes with acrylic esters catalyzed by hydroxyapatite-supported palladium complex. In addition to excellent stereoselectivity, good yields of products and simple operation, the most attractive features of this methodology are recylability of catalyst and high turnover number (>16000). Fluorescence properties of the enyne esters indicate the possible application of this type of compounds as fluorescent markers. One of these compounds showed remarkable fluorescence with very high quantum yield and is endowed with potential to be used as a biomarker.

Experimental Section

General Experimental Procedure for the Synthesis of Enyne Esters. Representative Procedure for 5-Phenylpent-2-en-4-

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TABLE 5. Recyclability of the Catalyst

cycle no.	time (h)	yield (%)	TOF (h^{-1})
1	6	75	2778
2	6	72	2667
3	8	60	1667
4	12	20	370

ynoic Acid Butyl Ester (Entry 1, Table 3). To a stirred mixture of 1,2-diiodovinylbenzene (3.56 g, 10 mmol) and butyl acrylate (3.84 g, 30 mmol) in *N*-methylpyrrolidone (NMP, 12 mL) were added PdHAP (30 mg, 0.00045 mmol of Pd) and potassium carbonate (3.5 g, 25 mmol). The mixture was then heated at 90−100 °C (oil bath) for 6 h (TLC). After being cooled, the reaction mixture was extracted with Et_2O (5 × 10 mL). The ether extract was washed with water and brine and dried (Na_2SO_4). Evaporation of solvent left the crude product which was purified by column chromatography over silica gel (ether−hexane 5:95) to afford the pure product (1.7 g, 75%) 5-phenyl-1-pent-2-en-4-ynoic acid butyl ester as a yellow oil. The spectroscopic data (IR, ^{1}H NMR and ^{13}C NMR) are in good agreement with the reported values.[10] The remaining catalyst, PdHAP, was reused for three subsequent reactions without much loss of efficiency (Table 5).

Many of these products are known compounds and were easily identified by comparison of their spectroscopic data with those reported (see references in Table 3). The unknown compounds were properly characterized by their spectroscopic data (IR, ^{1}H NMR, ^{13}C NMR, HRMS). The purity of all compounds was also checked by ^{1}H NMR, ^{13}C NMR, and HRMS.

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Supporting Information Available: Characterization data (IR, ^{1}H and ^{13}C NMR, and HRMS spectroscopic data) of the products in entries 2, 4, 6−9, 11, 14, and 15, Table 3. Copies of ^{1}H and ^{13}C NMR spectra of all products listed in Table 3. This material is available free of charge via the Internet at http://pubs.acs.org.

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