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Efficient Metallo–Ene Reactions in Organoaqueous Phase

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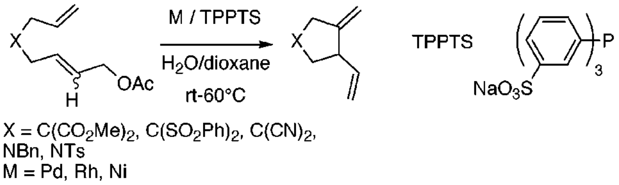
ABSTRACT



The easily prepared catalyst systems $PdCl_2$, $RhCl_2(COD)_2$, $NiCl_2{\cdot}6H_2O$, or $Ni(COD)_2$/TPPTS have been found to form a C–C bond in organoaqueous medium. Intramolecular metallo–ene reactions have been efficiently realized. Metal selectivity has been discovered.

Organic synthesis in water has recently received much attention, not only because unique reactivity and selectivity are often exhibited in water but also because it is an economical and environmentally friendly solvent.[1] Water-soluble complex catalysts such as Rh, Ru, and Pd catalysts have been intensively investigated for C−H and C−C bond formations.[1,2] The industrial applications in the fields of hydrogenation and hydroformylation have already indicated the wide scope of this type of catalyst. In our continuing search for water-soluble complex catalysts,[3] we have focused on investigating new C−C bond formation reactions in organoaqueous medium. The development of routes for the synthesis of five-membered rings continues to attract attention due to the wide variety of natural products containing this structural unit.[4] We turned our attention to intramolecular metallo−ene reactions, which have been widely described by Oppolzer[5] and proceed with a high level of atom economy.[6,7] The ene reactions involve the addition of a group possessing a π-bond to a group possessing an allylic leaving group and are regio- and stereoselective as well as entropically favored.[8] In the presence of Pd(0) or Rh(I) catalysts, anhydrous conditions usually need the use of acetic acid at 70−120 °C.[9] A few catalytic examples of nickel catalysts[10] have been reported, but they are limited to the use of diphenylphosphinobutane. To our knowledge, metallo−ene reactions have never been described in organoaqueous media. In this report, we wish to disclose our preliminary results in

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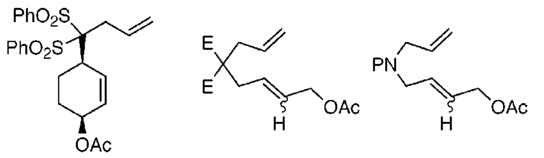
organoaqueous conditions using TPPTS as a water-soluble ligand.[11] We first prepared various dienyl acetates such as cyclic compound **1** which was obtained from regioselective Pd(0) alkylation of *cis*-chloroacetoxycyclohexene (Scheme 1).[12] Dienyl acetates **2a**, **2b**, **3a**, and **3b** derived respectively from dimethyl malonate, bis(phenylsulfonyl)methane, and protected allylamine were prepared in a two-step synthesis according to a literature procedure.[13] The diene **2c** was synthesized by two sequential alkylations, one by phase transfer[14] and one catalyzed by 5 mol % of palladium(0).

Scheme 1



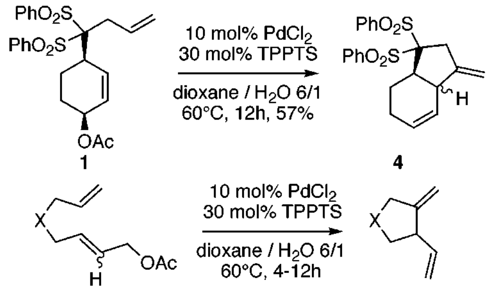
1

2a E = CO_2Me
2b E = SO_2Ph
2c E = CN

3a P = Bn
3b P = Ts

The ene reaction was then investigated and optimized by mixing 10 mol % of $PdCl_2$ and 30 mol % of TPPTS ligand in a mixture of dioxane and water. The cyclized products were formed at a temperature of 60 °C (Scheme 2). Lower temperatures or the use of other cosolvents such as CH_3CN or THF led to poor yields. Cyclization of **1** gave a 1:1 mixture of diastereomers **4** in a 57% yield. More efficiently, the formation of five-membered ring alkenes **5a** and **5b** respectively occurred with 88% and 80% yield. The nitrile-containing substrate **2c** was inert to the reaction conditions. Prolonged heating led to many degradation products. Nitrogen-substituted compound **3a** did not react, probably because of the free doublet of the nitrogen atom that may chelate to palladium intermediates[8] and inhibit the catalytic cycle. Indeed, the tosyl-protected aminodiene **3b** could be cyclized in a moderate yield of 50%.

Scheme 2



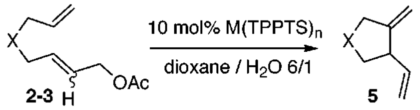
1

4

2a X = $C(CO_2Me)_2$
2b X = $C(SO_2Ph)_2$
2c X = $C(CN)_2$
3a X = NBn
3b X = NTs

5a X = $C(CO_2Me)_2$ 88%
5b X = $C(SO_2Ph)_2$ 80%
5c X = $C(CN)_2$ < 5%
5d X = NBn <5%
5e X = NTs 56%

Table 1. Metal-Catalyzed Ene Reaction in Organoaqueous Media



2-3

5

entry	**2**−**3**, X =	conditions (catalyst, *T*, *t*)	yield (%)
1	**2a**, $C(CO_2Me)_2$	$Rh(TPPTS)_3Cl$, 60 °C, 6 h	57
2	**3a**, $C(CO_2Me)_2$	$Rh(TPPTS)_3Cl$, 60 °C, 24 h	50
3	**3b**, NBn	$Rh(TPPTS)_3Cl$, 60 °C, 3 h	62
4	**2a**, $C(CO_2Me)_2$	$Ni(TPPTS)_3$, rt, 12 h	99
5	**3b**, NBn	$Ni(TPPTS)_3$, rt, 12 h	<5
6	**2b**, $C(SO_2Ph)_2$	$Ni(TPPTS)_3$, rt−60 °C, 12 h	0%
7	**2c**, $C(CN)_2$	$Ni(TPPTS)_3$, rt−60 °C, 12 h	0%

As palladium−ene catalysis seemed to be limited to dimethyl malonate and bis(phenylsulfonyl)methane derivatives and needed a high temperature, we then turned our attention to other transition metals such as rhodium and nickel. The known hydrosoluble complexes[15] $Rh(TPPTS)_3Cl$ and $Ni(TPPTS)_3$ have been prepared using respectively $[Rh(COD)Cl]_2$/TPPTS and NaCl as the depolymerization agents in a water/THF mixture and $NiCl_2{\cdot}6H_2O$/TPPTS and $NaBH_4$ as the reductive agents[16] in a water/ethanol mixture. As exemplified in Table 1, the Rh(I)-catalyzed reaction was successful at 60 °C with the dienyl acetate **2a** in 57% yield (entry 1). In contrast to the previous palladium-catalyzed reaction, cyclization of the benzyl-protected amino compound **3a** could be performed after 24 h at 60 °C in 50% yield (entry 2). The reaction of **3b** led to **5e** in the same manner as the Pd(0)/TPPTS catalyst (entry 3). We were pleased to see that the cyclization conducted in the presence of Ni(0) catalyst occurred at room temperature. Five-membered ring **5a** was cleanly isolated in 99% yield (entry 4). Unfortunately, the sulfonated derivative **3b** could not be transformed to **5d** (entry 5). No reactions were observed with **2b** and **2c**, even at higher temperatures (entries 6 and 7). We tried $Ni(OAc)_2{\cdot}4H_2O$ as another Ni(II) precursor and enhanced the ligand ratio to stabilize the catalyst without success.

The low reproducibility due to the oxygen sensitivity of the Ni(0) catalyst and undesirable presence of boron residues prompted us to find another method. We prepared the catalyst system without reductive agent by heating a mixture of $Ni(COD)_2$ and TPPTS (Ni/L 1/5) at 80 °C in neat water. As documented in Table 2, the Ni(0)-catalyzed reaction was first tested with 3 mol % of the catalyst at room temperature in

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[11] TPPTS: trisodium salt of 3,3′,3″-phosphanetriylbenzenesulfonic acid.

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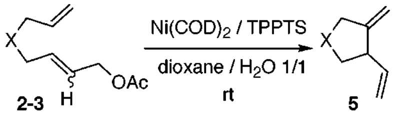
Table 2. Ni(0)-Catalyzed Ene Reaction in Organoaqueous Media



2-3 **5**

entry	**2−3**, X =	catalyst (mol %)	yield (%) (conversion)
1	**2a**, $C(CO_2Me)_2$	3	nd (34)
2	**2a**, $C(CO_2Me)_2$	10	92 (100)
3	**2b**, $C(SO_2Ph)_2$	10	65 (100)
4	**2c**, $C(CN)_2$	30	51 (100)
5	**3b**, NBn	10	45 (65)[a]

[a] 35% of starting material was recovered.

a 1/1 mixture of dioxane and water. Compound **2a** was cleanly cyclized but with only 34% conversion (entry 1).

The advantage of this protocol was the easy experimental setup and workup. The formation of the cyclized product was clean, and the catalyst was removed by simple filtration over a neutral silica bed. The reaction was successfully performed using 10 mol % of Ni(0) leading to the pentacyclic diene **5a** in 92% isolated yield (entry 2). Cyclization under anhydrous conditions was only performed with palladium catalyst in acid acetic at 80 °C, giving **5a** in 77% yield.[9d] Sulfonated derivative **5b** was obtained in nonoptimized 65% yield (entry 3). The dinitrile diene **2c** could only be cyclized in the presence of 30 mol % of Ni(0), which once again may be due to a chelation between the nitrile group and the catalyst (entry 4). The nitrogenated compound reacted very cleanly under mild conditions leading to 65% conversion and 45% yield (entry 5).

Table 3. Metal Selectivity in Organoaqueous Ene Reaction

diene, X =	$Pd(TPPTS)_2$	$RhCl(TPPTS)_3$	$Ni(TPPTS)_3$
5a, $C(CO_2Me)_2$	88%	57%	99%
5c, $C(CN)_2$	0%		51%
5d, NBn	<5%	50%	
5e, NTs	56%	62%	65%

Table 3 displays selected metallo−ene reactions in the presence of palladium, rhodium, and nickel catalysts. The palladium catalyst showed higher efficiency with malonic derivatives bearing nonchelating groups. The nitrogen-substituted compounds were selectively cyclized in the presence of rhodium. The use of nickel led to the best results as all the dienyl acetates were cleanly cyclized at room temperature.

In summary, water-soluble catalysts, easily prepared from Pd(II), Rh(I), Ni(II), and Ni(0) precursors and TPPTS ligand, have proven to be very efficient in intramolecular metallo−ene reactions in organoaqueous media. The reactions were conducted in the absence of acetic acid with palladium and rhodium. A new water-soluble nickel catalyst was easily prepared from $Ni(COD)_2$ without reducing agent. This inexpensive metal, combined with environmentally friendly water and mild conditions, showed comparable and sometimes higher efficiency than metals in anhydrous conditions. A major benefit consists of the facile separation of the functionalized five-membered ring substrates from the catalyst. Recycling tests and other catalytic applications are currently under investigation and will be reported in due course.

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Supporting Information Available: General experimental procedures for metallo−ene reactions. This information is available free of charge via the Internet at http://pubs.acs.org.

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