A Room Temperature Kharasch Reaction Catalyzed by Pd(0) in a Heterogeneous Aqueous System

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Abstract: The palladium-catalyzed Kharasch reaction of alkenes and alkynes is enhanced by the use of a heterogeneous aqueous system, without the use of hydrophilic co-solvents or phase transfer catalysts. The Pd(0)-catalyzed reaction of terminal alkenes with bromotrichloromethane in water goes to completion within 2 h at room temperature, whereas no reaction occurs in benzene otherwise under the same conditions. The Pd(0) catalyst in aqueous media also effects the radical addition of iodoperfluoroalkanes toward terminal alkenes and alkynes at room temperature.

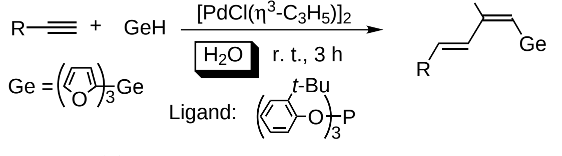
Keywords: biphasic catalysis; Kharasch reaction; palladium; radical reactions; water as solvent

In recent years, organic reactions in aqueous media have received increasing attention for environmental and safety reasons.[1] In particular, water-soluble ligands have allowed the rapid development of transition metal-catalyzed reactions.[2] Efficient recycling of rare metal catalysts is also achieved with such ligands. Phase-transfer catalysts and surfactants also play an important role in a number of transition metal-catalyzed reactions in aqueous media, by homogenizing the reaction system to retain contact between hydrophobic substrates and the catalyst in the aqueous phase.[3]

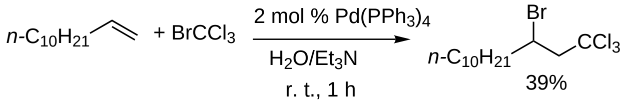
One typically thinks that water is a poor choice for hydrophobic substrates without homogenization. However, we have already reported a remarkable rate acceleration of Pd(0)-catalyzed hydrogermylation of alkynes in aqueous system without the use of phase-transfer catalysts or water-soluble ligands (Scheme 1).[4] In spite of the heterogeneous conditions, the reaction in water proceeds much faster than the reaction under neat conditions. This intriguing phenomenon in a heterogeneous aqueous system inspired us to explore other reactions employing water as the solvent. Herein we report beneficial effects in heterogeneous aqueous media on the palladium-catalyzed Kharasch-type radical addition.[5]

The Kharasch addition reaction generally requires rather harsh reaction conditions. The Pd(0)-catalyzed Kharasch-type radical addition was reported by Tsuji et al. and the original procedure required heating (> 40 °C).[6,7] We have revisited their pioneer work to investigate the effect of a heterogeneous aqueous system. We then found that the palladium-catalyzed coupling of 1-dodecene with bromotrichloromethane proceeded at room temperature in a heterogeneous aqueous system (Scheme 2).[8] In contrast, no observable reaction took place in benzene as the solvent at room temperature.

Several palladium sources, ligands, and bases were examined to optimize the reaction conditions (Table 1). Among the palladium sources we examined, $PdCl_2(PhCN)_2$ proved to be the best, presumably as a result of its solubility in 1-dodecene. It is notable that palladium-carbon coupled with dppf exhibited a weak activity. As for the ligand, dppf could effect a smooth radical addition reaction. Other bidentate phosphine ligands such as dppe and dppp were not effective (entries 7 and 8). A water-soluble phosphine, the trisodium salt of tris(*m*-sulfonatophenyl)phosphine (tppts), lowered the yield of the reaction (entry 15).

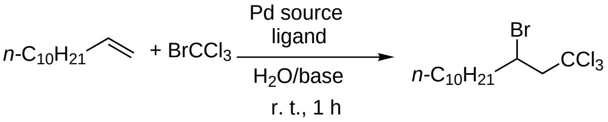


Scheme 1. Pd(0)-catalyzed hydrogermylation of alkynes with tri(2-furyl)germane in water.



Scheme 2. Initial attempt at the Pd(0)-catalyzed Kharasch reaction in water. Dodecene (1.0 mmol), $BrCCl_3$ (3.0 mmol), $Pd(PPh_3)_4$ (0.02 mmol), water (5 mL), and Et_3N (2.0 mmol) were employed.

Table 1. Optimization of the reaction conditions.[a]



Entry	Pd source	Ligand	Base	Time [h]	Yield [%]
1	$PdCl_2(PPh_3)_2$	dppf	Et_3N	1	54
2	Pd_2dba_3[b]	dppf	Et_3N	1	53
3	$[PdCl(C_3H_5)]_2$	dppf	Et_3N	1	45
4	$PdCl_2(PhCN)_2$	dppf	Et_3N	1	68
5	Pd/C[c]	dppf	Et_2NH	1	16
6	$PdCl_2(PhCN)_2$	dppf	Et_2NH	1	89
7	$PdCl_2(PhCN)_2$	dppe	Et_2NH	1	10
8	$PdCl_2(PhCN)_2$	dppp	Et_2NH	1	45
9	$PdCl_2(PhCN)_2$	dppf	1-methylpyrrolidine	1	82
10	$PdCl_2(PhCN)_2$	dppf	pyridine	1	0
11	$PdCl_2(PhCN)_2$	dppf	K_2CO_3	1	33
12	$PdCl_2(PhCN)_2$	dppf	pyrrolidine	2	89
13	$PdCl_2(PhCN)_2$	dppf	Et_2NH	2	93
14	$PdCl_2(PhCN)_2$	–	Et_2NH	2	21
15	$PdCl_2(PhCN)_2$	tppts[d]	Et_2NH	2	18

[a] Conditions: 1-dodecene (1.0 mmol), bromotrichloromethane (1.5 mmol), water (5 mL), a base (1.0 mmol), 0.02 mmol of a palladium source and 0.02 mmol of a ligand.

[b] $Pd_2dba_3 \cdot CHCl_3$ (0.01 mmol) was used.

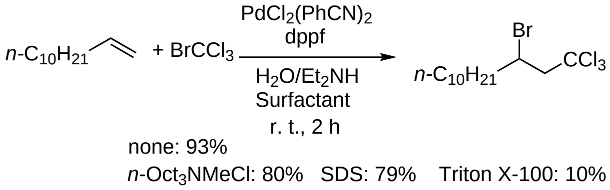
[c] Pd on carbon (5%) was employed.

[d] tppts (0.04 mmol) was employed; tppts = trisodium salt of tris(*m*-sulfonatophenyl)phosphine.

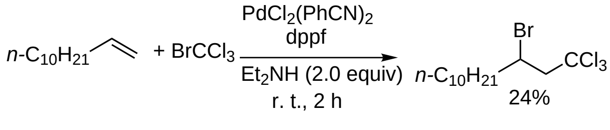
The presence of a base was required in this reaction as reported by Tsuji, and Et_2NH was the best among K_2CO_3, Et_3N, pyridine, pyrrolidine, and 1-methylpyrrolidine (entries 9 – 13). From these optimizations, we chose $PdCl_2(PhCN)_2$/dppf as the catalyst and Et_2NH as the base for the aqueous Kharasch addition reaction at room temperature.[9]

The Kharasch addition reaction of $BrCCl_3$ with a variety of alkenes proceeds efficiently in the heterogeneous aqueous system (Table 2). Several characteristics of this protocol are noteworthy. Functional groups such as ester or ketone groups are tolerated during the reaction. Diallyl ether or diallylamine afforded the dihydrofuran or pyrrolidine derivatives in good yields via the radical addition – 5-*exo* radical cyclization sequence. Unfortunately, the use of internal alkenes such as 4-dodecene provided the desired adduct in only 11% yield in spite of the prolonged reaction time at room temperature. Moreover, the use of a solid alkene, 1-docosene, afforded the adduct in a decreased yield (entry 3).[10] We also tried to decrease the amount of the catalyst. With a reduced catalyst loading (0.2 mol %), the reaction still took place to provide the product in 40% yield (entry 2).

It is particularly noteworthy that the use of toluene, Et_3N, or wet toluene as the solvent provided none of the desired product at room temperature, even with the optimized catalyst system [$PdCl_2(PhCN)_2$/dppf]. The use of surfactants to homogenize the reaction mixture decreased the yield of the adduct (Scheme 3). In addition, a water-soluble phosphine ligand was not effective (Table 1, entry 15). The reaction of a water-soluble substrate such as allyl alcohol afforded none of the product. Furthermore, a solvent-free system was also inferior to the heterogeneous aqueous conditions. Without the addition of water, the desired product was obtained in only 24% yield under otherwise the same reaction conditions (Scheme 4). Consequently, a heterogeneous system, which consists of a hydrophobic substrate, a water-insoluble catalyst, and water, seems to be crucial for the successful progress of the Kharasch addition at room temperature.

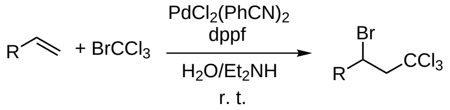


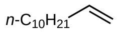
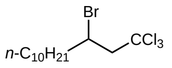
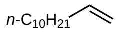
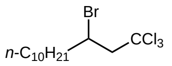
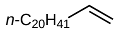
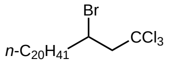
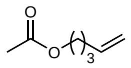
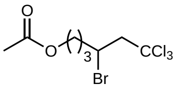
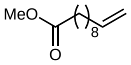
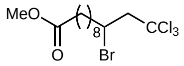
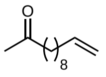
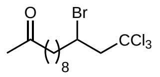
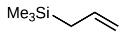
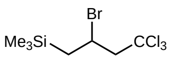
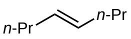
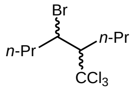
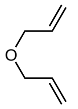
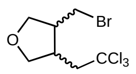
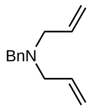
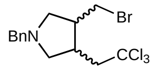
Scheme 3. Effect of surfactants.



Scheme 4.

Table 2. Pd(0)-catalyzed radical addition of $BrCCl_3$ to alkenes in water.[a]



Entry	Alkenes	Time [h]	Products	Yield [%]
1		2		93
2[b]		2		40
3		2		39
4		10		75
5		10		70
6		10		75
7		12		63
8		15		11 (63/37)[d]
9[c]		10		80 (*cis*/*trans* = 82/18)[d]
10		10		43% (*cis*/*trans* = 72/28)[e]

[a] Conditions: alkenes (1.0 mmol), bromotrichloromethane (1.5 mmol), water (5 mL), Et_2NH (1.0 mmol), $PdCl_2(PhCN)_2$ (0.02 mmol) and dppf (0.02 mmol).

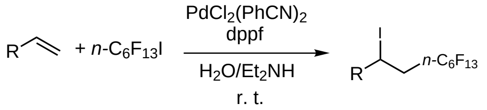
[b] The palladium catalyst $PdCl_2(PhCN)_2$/dppf (0.2 mol %) was employed.

[c] The reaction employed diallyl ether (5.0 mmol) and $BrCCl_3$ (1.0 mmol) otherwise the same reaction conditions.

[d] The diastereomeric ratio was determined on the basis of the ^1H NMR spectrum.

[e] The diastereomeric ratio was estimated on the basis of the ^{13}C NMR spectrum.

Table 3. Pd(0)-catalyzed radical addition of $n\text{-}C_6F_{13}I$ to alkenes in water.[a]



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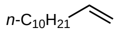
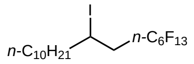
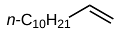
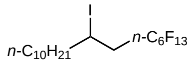
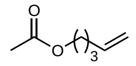
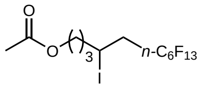
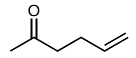
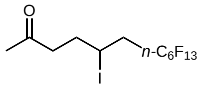
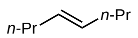
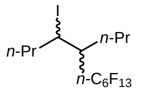
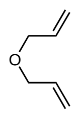
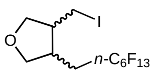
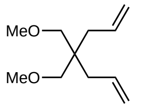
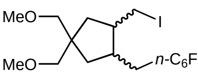
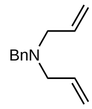
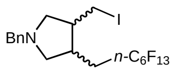
1		1		98
2[b]		1		54
3		3		96
4		3		79
5		15		37 (63/37)[c]
6		5		99 (*cis*/*trans* = 88/12)[c]
7		6		99 (*cis*/*trans* = 89/11)[d]
8		6		89 (*cis*/*trans* = 68/32)[d]

[a] Conditions: alkenes (1.0 mmol), $n\text{-}C_6F_{13}I$ (1.5 mmol), water (5 mL), Et_2NH (1.0 mmol), $PdCl_2(PhCN)_2$ (0.02 mmol) and dppf (0.02 mmol).

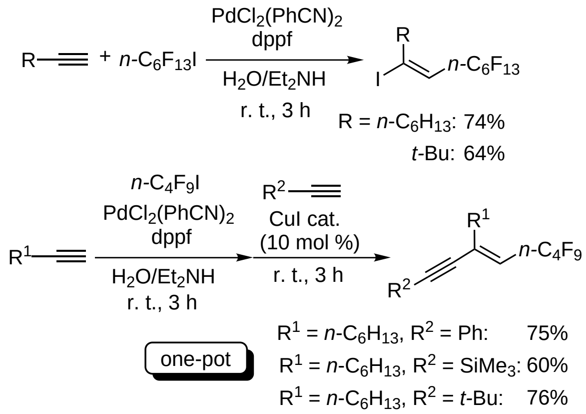
[b] The palladium catalyst $PdCl_2(PhCN)_2$/dppf (0.2 mol %) was employed.

[c] The diastereomeric ratio was determined on the basis of the ^1H NMR spectrum.

[d] The diastereomeric ratio was estimated on the basis of the ^{13}C NMR spectrum.

The use of tridecafluorohexyl iodide instead of $BrCCl_3$ as a radical source furnished the desired products in excellent yields.[11] Table 3 shows the results of the addition reaction of tridecafluorohexyl radical in water. The reaction of alkenes with $n\text{-}C_6F_{13}I$ proceeded in better yields than those with $BrCCl_3$. Water again played a crucial role in this reaction. Without water, the reaction of diallyl ether with $n\text{-}C_6F_{13}I$ afforded the cyclization product in only 22% yield, whereas a quantitative yield was achieved in water.

The use of an alkyne as a radical acceptor in the perfluoroalkyl radical addition furnished a vinylic iodide with high stereoselectivity. None of the *Z*-isomer was present in the crude reaction mixture. The iodide thus obtained is a useful synthetic intermediate. For instance, additions of the second alkyne and copper iodide (10 mol %), after the Pd(0)-catalyzed Kharasch reaction, effected a Sonogashira coupling in a one-pot procedure without isolation of the intermediary alkenyl iodide (Scheme 5).[12,13]



Scheme 5. Addition of perfluoroalkyl iodide to alkynes and the subsequent one-pot Sonogashira coupling in water.

In conclusion, we have developed the room temperature Kharasch reaction of alkenes and alkynes in a heterogeneous aqueous system. It is typically thought that water is a poor choice for hydrophobic substrates and that homogenization is necessary. However, we have found that surfactants lowered the efficiency of the reaction. Our results suggest that the heterogeneous aqueous system can be excellent media for reactions with substrates insoluble in water.[14]

Experimental Section

Typical Procedure

$PdCl_2(PhCN)_2$ (7.7 mg, 0.02 mmol), dppf (11.1 mg, 0.02 mmol), and 1-dodecene (168 mg, 1.0 mmol) were placed in a flask, and the mixture was stirred for 5 min at room temperature. Diethylamine (0.1 mL, 1.0 mmol) and water (5 mL) were introduced and the mixture was stirred vigorously (1500 rpm). To the mixture was added bromotrichloromethane (0.15 mL, 1.5 mmol) dropwise via a syringe. After stirring for 2 h, the mixture was extracted with hexane (10 mL × 3). The organic layers were dried over Na_2SO_4 and concentrated. Purification of the residual oil afforded 3-bromo-1,1,1-trichlorotridecane; yield: 341 mg (0.93 mmol, 93%).

Acknowledgements

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References and Notes

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