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Olefin Ring Closing Metathesis and Hydrosilylation Reaction in Aqueous Medium by Grubbs Second Generation Ruthenium Catalyst

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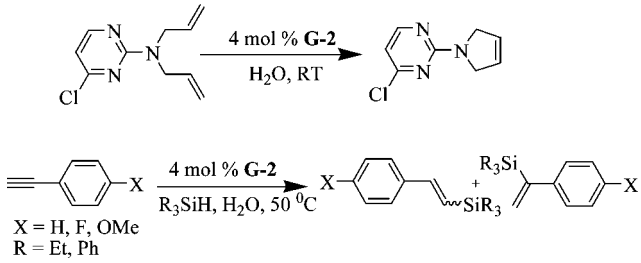
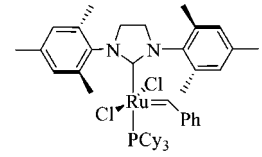


The Grubbs second generation ruthenium catalyst was shown to catalyze various olefin ring closing metathesis and hydrosilylation reactions in aqueous medium. Reactions proceeded in pure water without any additives or cosolvents, in a short period of time. We found that inhomogeneity of the reaction mixture does not prevent high conversion (70−95%) of the products in both reactions.

The advent of Grubbs catalyst has fueled the widespread application for various organic transformations, importantly olefin metathesis[1] and very recently hydrosilylation reaction.[2] Olefin metatheses, such as ring-closing metathesis (RCM) and cross-metathesis (CM), are extensively used as a dominant tool for the carbon−carbon bond forming reaction in the synthesis of several small molecules,[3] biomolecules,[4] and macromolecules[5] in the drug discovery and polymer industry. Similarly, the hydrosilylation reaction of alkynes to generate vinylsilanes, powerful intermediates in organic synthesis,[6] is a simple and widely used protocol.

Both of these reactions are generally carried out in organic solvents and their potential utility in aqueous medium is largely untapped, despite their profound allure for biomolecule synthesis[4] and green chemistry.[7] Although there are few protocols for olefin metathesis reactions in aqueous medium,[8−11] surprisingly to the best of our knowledge there is no description of the hydrosilylation reaction in aqueous medium. Pioneers in this field, Grubbs et al., prepared water soluble *N*-heterocyclic-carbene-based olefin metathesis ruthenium catalyst.[9] Although this work led the way to advance the metathesis reaction in aqueous medium, the reaction still needs 12−24 h to complete. Blechert et al. used Grubbs second generation ruthenium catalyst for the RCM reactions; however, they used a mixture of organic solvents and water with extended reaction time.[10] Recently, Raines and co-workers reported olefin metathesis in homogeneous aqueous medium using second generation Hoveyda−Grubbs catalyst and claimed it as a green protocol.[11] They did not use pure water as a reaction medium; instead they used organic solvents with some percentage of water in it and very often deuterated solvents, which does not justify the protocol to be truly environmentally friendly. Thus, the majority of the reported aqueous RCM methods used a mixture of organic solvent and small amounts of water or expensive and toxic deuterated solvents, e.g., C_6D_6, as cosolvents with exotic ruthenium complexes as catalysts. Consequently, we decided to develop simple and environmentally benign RCM and hydrosilylation protocols exclusively in aqueous medium.



G-2

FIGURE 1. Grubbs second generation ruthenium catalyst.

Engaged in the development of greener synthetic pathways,[12] herein we report an expeditious and benign ring-closing metathesis in pure aqueous medium (without using any organic or deuterated solvent) with conventional Grubbs second generation ruthenium (G-2) catalyst (Figure 1).

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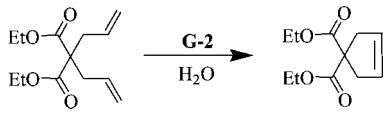
TABLE 1. Optimization of Reaction Conditions with G-2 in Water



entry	G-2	temp (°C)	reaction time (h)	conversion (%)
1	1 mol %	rt	6	35
2	2 mol %	rt	6	55
3	4 mol %	rt	6	90
4	4 mol %	45	1	80
5	4 mol %	45	1.5	95

Initially the RCM reaction of diethyl 2,2-diallylmalonate with Grubbs second generation ruthenium catalyst in aqueous medium was investigated to establish the feasibility of our strategy and to optimize the reaction conditions (Table 1).

First the reaction was conducted with 1 mol % of catalyst and a moderate 35% conversion was observed at room temperature (rt). As the catalyst amount was increased to 4 mol %, a good conversion (90%) was achieved in 6 h. However, when the mixture was warmed at 45 °C, the reaction proceeded expeditiously with 80% conversion within 1 h, which was further increased to 95% by extending the reaction time by another 30 min.

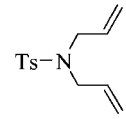
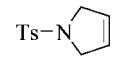
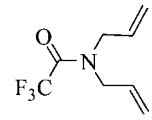
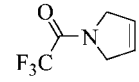
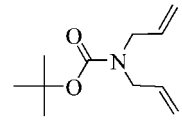
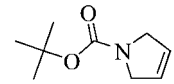
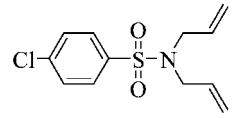
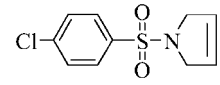
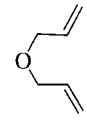
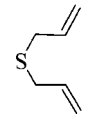
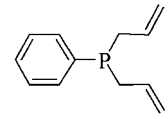
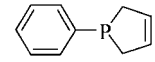
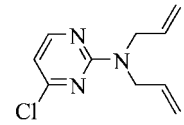
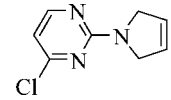
With the above optimized reaction conditions, ring-closing metathesis of a series of dienes with Grubbs second generation ruthenium catalyst was probed solely in aqueous medium (Table 2). A variety of substrates such as diallylamines (entries 1−4), diallyl ether (entry 5), and diallyl thioether (entry 6) were successfully metathesized to from respective cyclic products with high conversion.

Excellent conversions were observed for various *N*-substituted allylamines within 2 h. In the case of diallyl ether and thioether, although the conversion is high, the decrease in yield is due to volatility of the ensuing cyclic products. The pyrimidine-based diene (entry 8), an extensively used building-block in drug discovery, also underwent RCM reaction in aqueous medium with high yield, proving the suitability of this protocol for assembly of biomolecules.

While metathesis remains the most imperative application for the Ru-catalyst, a growing number of other reactions are also mediated by this procedure. Selective formation of the β-(*E*) isomer of vinylsilane by hydrosilylation of alkyne has proven to be a difficult task,[2] and in view of the fact that hydrosilylation reaction has not been reported in aqueous medium, we set out to attempt the regioselective hydrosilylation of alkyne in aqueous medium using G-2. Selective formation of the β-(*E*) isomer of a range of vinylsilanes in high yields occurred with use of this protocol and the results are summarized in Table 3.

Grubbs second generation ruthenium catalyst was found to be capable of catalyzing these reactions in water, achieving good conversion. We observed that warming equimolar quantities of alkyl silane and alkynes at 50 °C in aqueous medium in the presence of G-2 resulted in the rapid consumption of starting materials (as monitored by GC-MS and ^{1}H NMR). The reaction was complete within 4 h in the case of triethylsilane and was complete in 6 h for triphenylsilane. Among the three isomeric vinylsilane products, namely β-(*Z*), β-(*E*) and α, the predominant regioselective formation of the β-(*E*) isomer as a major product was very satisfying. Heterocyclic 6-ethynylquinoxaline also reacts efficiently with triethylsilane yielding corresponding silylated product in 80% yield. An attempt to hydrosilylate 2-ethynylpyridine was not successful, which may be due to its instability under our reaction conditions. Aliphatic alkynes can also be hydrosilylated; however, due to competitive metathesis reaction, a mixture of products was formed.

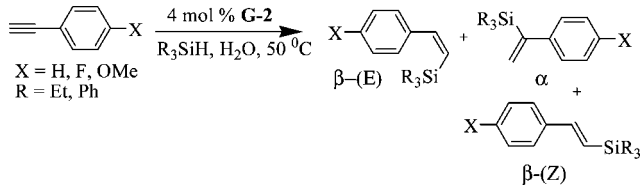
TABLE 2. RCM Reaction of Dienes Catalyzed by G-2 in Water[a]

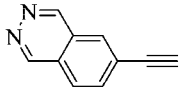
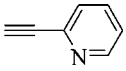
Entry	Diene	Product	Yield (%)
1			95
2			96
3			92
4			95
5			70[b]
6			72[b]
7			NR
8			96

[a] Reactions were performed at 45 °C with 4 mol % catalyst G-2 in water for 2 h. [b] GC yield.

In conclusion, we have developed a simple and sustainable protocol for olefin ring closing metathesis and selective hydrosilylation reactions that proceed exclusively in aqueous medium without any additives or cosolvents. It is remarkable that the inhomogeneity of the reaction mixture does not prevent high conversion of the products in both reactions. These reactions will be very useful in drug discovery as various biomolecules, enzymes, and polysaccharides have stronger affinity toward water than organic solvent and can be easily metathesized and hydrosilylated. Also, the use of commercially available Grubbs second generation ruthenium complex as a catalyst and mild reaction conditions are additional eco-friendly attributes of this aqueous protocol.

TABLE 3. Hydrosilylation of Alkynes Catalyzed by G-2 in Water[a]



Alkyne	Silane	Yield (%)	Isomer Ratio[b]		
			β–(E)	α	β–(Z)
1-Ethynylbenzene	Et_3SiH	85	85	12	03
1-Ethynyl-4-F-benzene	Et_3SiH	83	87	06	07
1-Ethynyl-4-MeO-benzene	Et_3SiH	84	76	05	19
1-Ethynylbenzene	Ph_3SiH	70	80	20	00
1-Ethynyl-4-F-benzene	Ph_3SiH	68	85	06	09
1-Ethynyl-4-MeO-benzene	Ph_3SiH	70	86	04	10
	Et_3SiH	80	90	10	00
	Et_3SiH	NR			
Cyclohexylacetylene	Et_3SiH	35[c]	[d]		
1-Pentyne	Et_3SiH	30[c]	[d]		

[a] Reactions were performed at 50 °C with 4 mol % catalyst G-2 in water. [b] Determined by ^1H NMR spectroscopy and GC-MS. [c] GC yield. [d] Mixture of products.

Experimental Section

A typical experimental procedure for olefin ring closing metathesis reaction follows: The diene (1 mmol) and Grubbs second generation ruthenium catalyst (4 mol %) were added to a 10 mL glass tube filled with 2 mL of water and the reaction mixture was stirred for 2 h at 45 °C. After completion of the reaction, the reaction mixture was quenched with ether and product was purified by column chromatography.

Spectral data of a representative compound are given below.

2,5-Dihydro-1-tosyl-1*H*-pyrrole. ^1H NMR (300 MHz, $CDCl_3$): δ 2.38 (3H, s), 4.21 (4H, s), 5.45 (2H, s), 7.35 (2H, d), 7.81 (2H, d) ppm. ^{13}C NMR ($CDCl_3$): δ 21.5, 54.8, 125.4, 127.4, 129.7, 134.4, 143.3 ppm. MS: (M^+) 223, 155, 139, 91, 68, 51, 41. Anal. Calcd for $C_{11}H_{13}NO_2S$: C, 59.17; H, 5.87; N, 6.27. Found: C, 59.12; H, 5.80; N, 6.19.

A typical experimental procedure for hydrosilylation reaction of alkyne follows: The alkyne (1 mmol), silane (1 mmol), and Grubbs second generation ruthenium catalyst (4 mol %) were added to a 10 mL glass tube filled with 2 mL of water and the reaction mixture was stirred at 50 °C. The reaction was complete within 4 h in the case of triethylsilane and was complete in 6 h for triphenylsilane. After completion of the reaction, the reaction mixture was quenched with ether and product was purified by column chromatography.

Spectral data of a representative compound are given below.

***β*-(*E*)-Triethyl(styryl)silane.** ^1H NMR (300 MHz, $CDCl_3$): δ 0.52 (6H, m), 0.95 (9H, m), 5.79 (1H, d, J = 12 Hz), 7.31 (5H, m), 7.53 (1H, d, J = 12 Hz) ppm.; MS: (M^+) 218, 189, 161, 131, 105, 59. Anal. Calcd for $C_{14}H_{22}Si$: C, 76.99; H, 10.15. Found: C, 76.89; H, 10.20.

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Supporting Information Available: Experimental procedures and NMR and MS data of the reported compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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