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Ruthenium-Catalyzed Yne-Ene Cross Metathesis Immobilization of Functionalized Alkynes

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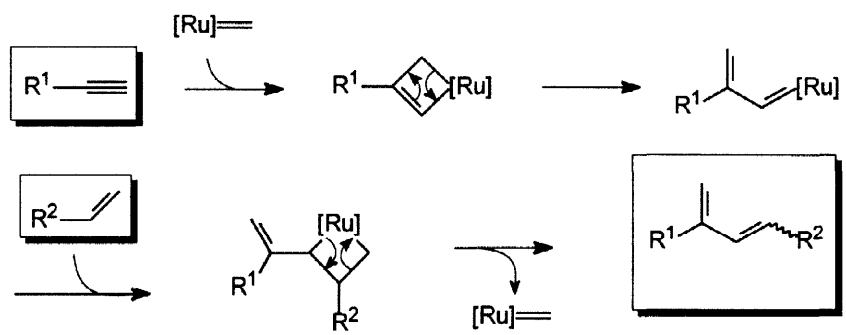
Abstract: Ruthenium initiator **1** efficiently catalyzes the crossed metathesis[1] between functionalized terminal alkynes and allylsilyl polystyrene **2**. This selective yne-ene metathesis yields polymer-supported 1,3-dienes and represents a novel catalytic immobilization method.

Selective catalytic cross-coupling reactions involving solid phase-supported substrates represent an interesting alternative to common immobilization techniques used in solid-phase organic chemistry.[2] Recently,[3,4] we reported the ruthenium-catalyzed crossed metathesis of functionalized alkenes with modified polystyrene resins containing terminal double bonds employing Grubbs' ruthenium initiator[5] $Cl_2(PCy_3)_2Ru{=}CHPh$ (**1**, Cy = cyclohexyl). This catalyst allows the immobilization process to proceed under mild, neutral reaction conditions without a requirement for activated substrates. A variety of functional groups



Scheme 1 Proposed pathway for the yne-ene metathesis reaction.

are tolerated. Herein, we describe the catalytic cross-coupling between functionalized terminal alkynes and allylsilyl polystyrene **2** *via* a more selective Ru-catalyzed crossed yne-ene metathesis reaction. During

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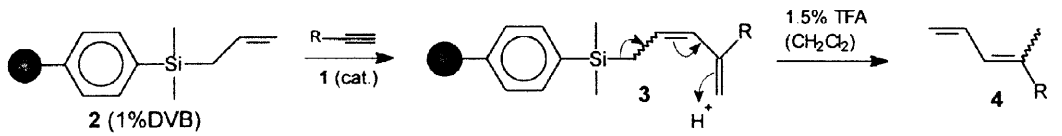
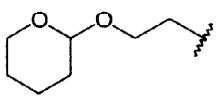
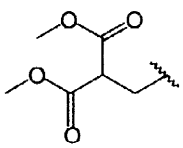
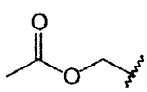
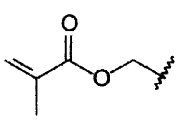
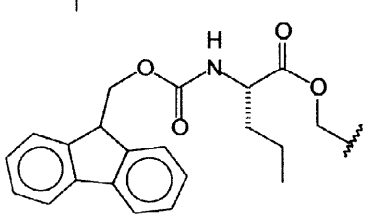
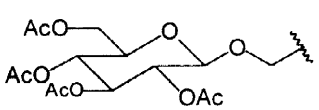
the yne-ene metathesis[6] a terminal alkyne and a terminal alkene are selectively converted into a 1,3-diene. A proposed reaction pathway is given in Scheme 1. In contrast to the crossed metathesis of two terminal alkenes, where homodimerization of both reactants represents a major drawback, no homodimerization of an alkyne takes place in the presence of the alkene component when using **1**. Therefore, Ru-catalyzed cross-coupling of alkynes with a polymer-supported alkene should require only equimolar amounts of the alkyne component. In addition, the reaction would give direct access to solid-phase bound 1,3-dienes representing substrates for subsequent Diels-Alder transformations.

These novel features prompted us to investigate the catalytic immobilization of various functionalized terminal alkynes. We used allylsilyl polystyrene **2**, since cross-coupling products can be released by mild acidic cleavage of the C-Si bond, thus, allowing a straightforward characterization of the binding reaction (Table 1). The resin (**2**) employed throughout this study was obtained as described[4] and had a silicon content of 0.9 mmol g^{-1}. Cross metathesis was performed in refluxing dichloromethane using 0.05 mmol of **1** and 1.2 mmol of terminal alkyne per gram of **2**. Products **3a-f** were filtered off after 18 hours and washed thoroughly. Loadings were calculated from the amount of soluble cleavage products **4a-f** released from **3a-f** by treatment with trifluoroacetic acid (1.5% in CH_2Cl_2).[7] The results of the binding reactions performed are compiled in Table 1. As indicated, protodesilylation of metathesis products **3a-f** proceeds *via* a conjugate mechanism resulting in the formation of soluble 1,3-dienes **4a-f**. E.g., 0.50 mmol of **4a** (*E*:*Z* = 1:1) was released per gram of **3a**. This modification level corresponds to 56% yield based on the silicon content of **2**. However, it has to be considered, that a certain amount of allylsilyl moieties is not available for the binding reaction due to intramolecular metathetical self-dimerization on the resin surface.[4] The Ru-catalyzed binding of dimethyl propargylmalonate yields **3b** with a loading of 0.50 mmol g^{-1}. The binding of propargyl esters yields polymer-supported allyl acetates like **3c** (0.50 mmol g^{-1}, from propargyl acetate) representing interesting materials for further Pd(0)-catalyzed modifications. Propargyl methacrylate was converted to **3d** (0.44 mmol g^{-1}). No side products resulting from reactions of the disubstituted methacrylic double bound could be detected. Notably, in both **4c** and **4d** the *E*-isomers clearly predominate as confirmed by NOE measurements. In order to test the applicability of the yne-ene metathesis to the binding of highly functionalized molecules Fmoc-protected norvaline propargyl ester was synthesized and subjected to cross metathesis under standard conditions. The amount of **4e** formed upon protodesilylation revealed a loading of 0.35 mmol g^{-1}. The loading was confirmed by reacting **3e** with 10 mol% $Pd(PPh_3)_4$ in the presence of excess morpholine resulting in the formation of the free carboxylic acid Fmoc-Nva-OH. Like propargylic esters propargylic glycosides are also viable substrates for catalytic binding as demonstrated by the formation of **3f** with 0.55 mmol g^{-1}. It should be noted, that all of **4a-f** are obtained in high purity. Only small amounts of polar material (residual catalyst, silanols[4]) had to be removed prior to characterization.

Table 1 Results of the Ru-catalyzed cross-coupling of functionalized terminal alkynes to allylsilylpolystyrene **2** and subsequent protodesilylation of coupling products **3a-f** resulting in the formation of soluble **4a-f**.



cleavage product	R	cleavage yield[a]	*E,Z*-isomer ratio[b] (**4**)
4a		0.51 mmol/g	1:1
4b		0.50 mmol/g	2:1
4c		0.50 mmol/g	6:1 (*E:Z*)
4d		0.52 mmol/g	8:1 (*E:Z*)
4e		0.35 mmol/g	3:1
4f		0.55 mmol/g	4:1 (*E:Z*)

[a] Isolated yields of cleavage product **4** per gram of resin **3**. [b] Identity of major isomer was determined by NOE analysis only in cases where isomer ratio >3:1.

In summary, we have introduced a reaction system allowing the selective catalytic binding of terminal alkynes to an olefinic matrix. Although, allylsilyl polystyrene resin **2** was chosen in this study for practical reasons (mild cleavage), replacement by other polymer-supported terminal olefins should not pose problems as can be concluded from reactions using soluble alkene components.[6] Diels-Alder transformations of the polymer-supported 1,3-dienes resulting from the immobilization process are currently under investigation.

ACKNOWLEDGEMENTS

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7. All new compounds gave satisfactory spectral and analytical data (^{1}H-NMR, ^{13}C-NMR, HRMS, IR) . For example, the spectral data for the *E*-isomer of **4d** are given: ^{1}H-NMR (400MHz, $CDCl_3$) δ 6.58 (1H, ddd, J = 17.0, 10.5, 10.5 Hz, $\underline{H}C=CH_2$), 6.14 (1H, s, $\underline{H}_2C=CH$), 6.09 (1H, d, J = 10.5 Hz, $\underline{H}C\text{-}CH=CH_2$), 5.58 (1H, s, $\underline{H}_2C=CH$), 5.25 (1H, d, J = 17.0 Hz, $\underline{H}_2C=CH$), 5.15 (1H, d, J = 10.5 Hz, $\underline{H}_2C=CH$), 4.60 (s, 2H, $\underline{H}_2C\text{-}O$), 1.96 (3H, s, $\underline{H}_3C\text{-}C(=CH_2)\text{-}CO$), 1.82 (3H, s, $\underline{H}_3C\text{-}C(C_3H_4)\text{-}CH_2\text{-}O$); NOE (400MHz): 6.58 ↔ 1.82 ppm (8%); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 136.05, 132.16, 128.23, 125.59, 118.06, 69.57, 29.66, 18.37, 14.37; HRMS: 166.09938 (M^+), calcd 166.0994 ($C_{10}H_{14}O_2^+$); IR (neat): 2956, 2927 (s), 2854, 1781, 1721 (vs), 1638, 1453, 1377, 1318, 1294, 1258, 1220, 1160 (vs) cm^{-1}.