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Ruthenium-Catalyzed Multicomponent Reaction: Access to α -Silyl- β -Hydroxy Vinylsilanes, Stereodefined 1,3-Dienes and Cyclohexenes

Prof. Dr. Barry M. Trost^a, Dr. Dennis C. Koester^a, and Dr. Ehesan U. Sharif^a

^aDepartment of Chemistry, Stanford University, Stanford, California 94305-5080, USA

Abstract

The synthesis of α -silyl- β -hydroxyl vinylsilanes was achieved in a ruthenium-catalyzed multicomponent reaction (MCR). The utility of these substrates was explored in further synthetic manipulations giving rise to stereodefined olefins and cyclohexene derivatives in one-pot. A MCR with four components and five subsequent reactions was uncovered leading to a valuable cyclohexene derivatives. The application of the substrates was demonstrated by their use in epoxidation reactions, Prins cyclizations and Diels-Alder reactions.

Graphical abstract

It's as easy as 1,2,3: A Ru-catalyzed MCR leading to α -silyl- β -hydroxyl olefins and stereodefined 1,3-dienes is reported. These valuable products were further functionalized through cross-coupling and oxidation strategies to access structural motifs found in many natural products. Notably, the three-component coupling can be extended to perform five synthetic operations in one pot.

Keywords

Multicomponent Reaction; Catalysis; Stereoselectivity; Dienes; Ruthenium

The demand for new chemical entities requires organic chemists to develop innovative solutions for synthetic problems. Multicomponent reactions (MCRs) have emerged as a powerful tool in medicinal chemistry.^{1–5} The application of MCRs in the synthesis of small drug-like molecules bears obvious advantages over step-wise approaches. High atom-economy, operational simplicity, high modularity, great functional group tolerance and high resource efficiency illustrate the major advantages of MCRs. The synthesis of linear

aliphatic compounds with a high degree of structural diversity in a one-pot operation by MCRs is somewhat underdeveloped. We aimed for the development of a strategy to access a variety of stereodefined chemical motifs in a simple one-pot operation. Herein, we wish to report on a Ru-catalyzed MCR giving access to α -silyl- β -hydroxyl vinylsilanes, geometrically defined 1,3-dienes and cyclohexene derivatives in one-pot involving the bifunctional silyl-propargyl boronate **1** (Scheme 1). The fact that three completely different molecular scaffolds can be obtained from the same starting materials by simply controlling the reaction parameters is highly remarkable.^{6,7} The reported MCR is initiated by a Ru-catalyzed hydrosilylation of propargyl boronates **1** followed by direct allylation of aldehydes leading to α -silyl- β -hydroxyl vinylsilanes **4**.⁸ The propargyl boronate **1** is readily available and has been synthesized in multi-100 kg scale by a research group at BI.⁹ It has found application in the copper- and zinc-catalyzed asymmetric propargylation of aldehydes, ketones, imines and trifluoroketones.^{10–14} Therefore, it is quite astonishing that the hydrosilylation of **1** can be performed in presence of an aldehyde without the generation of the propargyl alcohol as by-product. Benzyldimethyl silane was chosen as the hydrosilylation agent because of its excellence in Hiyama cross-coupling which will be discussed later in this report. In the initial experiments propargyl boronate **1**, benzyldimethylsilane **2** and aldehyde **3** were mixed with the Ru-catalyst. The only product that could be isolated was a single diastereomer of the desired α -silyl- β -hydroxyl olefin **4** verifying the clean timing of the events. A screening of the reaction conditions with hexanal as aldehyde electrophile revealed [CpRu(MeCN)₃]PF₆ as the superior catalyst. Dichloromethane was identified as the solvent of choice in this three component reactions. A good yield of 71% with complete diastereocontrol could be achieved in this process. The scope of aliphatic aldehydes is depicted in Scheme 1.

Formaldehyde prills were successfully employed in the transformation to furnish unsubstituted products such as **4a** in good yields. Branched and cyclic aliphatic aldehydes were converted to the desired products **4b–4e**. However, chiral aldehydes such as citronellal led to a 1:1 mixture of diastereomers **4e**. Electron-withdrawing groups such as esters are well tolerated in the process, setting the stage for further synthetic modifications (*vide infra*). α,β -Unsaturated aldehydes bearing electron-withdrawing substituents are viable substrates to give rise to products such as **4h**. Different ynals were also found to be effective substrates in a sequential protocol leading to propargyl alcohols **4i** and **4j**.

Aryl aldehydes were also investigated as substrates for the multicomponent reaction (Scheme 2). Substitution on the aromatic core was well tolerated. Sterically encumbered *ortho*-TMS-acetylene benzaldehyde proved to be compatible with the reaction conditions in a slightly modified one-pot protocol. Electron-withdrawing and electron-donating substituents on the aromatic core were equally well tolerated. The products **4n**, **4p**, **4q** and **4r** bear handles for further synthetic manipulation in cross-coupling reactions. The pinacolato-borane and the benzyldimethylsilyl group in **4p** could be utilized as handles in iterative cross-coupling reactions. Disubstituted aromatics performed well under the optimized reaction conditions and even free phenols such as **4r** was synthesized from bromosalicylaldehyde. Heteroaromatic aldehydes are viable substrates giving rise to

coupling products such as **4s**. Gratifyingly, ferrocenecarboxaldehyde was transformed to the desired product **4t** in 68%.

The regio- and stereocontrol of the hydrosilylation contrasts with the typical behavior of the Ru-catalyzed process, which is *trans*-selective.¹⁵ The hydrosilylation of TMS-substituted alkynes with [CpRu(MeCN)₃]PF₆ was experimentally and theoretically investigated by Wu and co-workers.¹⁶ His results indicate a clear preference the β-*syn* addition, whereas the hydrosilylation with [Cp*Ru(MeCN)₃]PF₆ proceeds in an α-*anti* addition. These results suggest that the investigated [CpRu]-catalyzed MCR of benzyldimethylsilane with propargyl boronate **1** to proceed through intermediate INT-**4** (Scheme 3). The diastereoselectivity of the subsequent allylation reaction can be explained through a closed chair-like transition-state. The *syn*-product can be rationalized as the result of TS-*syn*-**4**. The formation of the *anti*-product would require the reaction to go through transition state TS-*anti*-**4** which features a major steric clash between the benzyldimethylsilyl-group and the substituent on the aldehyde. Therefore, the *syn*-product is exclusively observed.

A number of pharmaceutically active natural products bear scaffolds potentially accessible by using our newly developed method (Figure 1). 1,3-Dienes with a (*Z*)-configured internal olefin are found in complex natural products such as palytoxin and haemoxiphidone. Steroid based natural products such as nebrosteroid **E**¹⁷ and heterocyclic compounds such as mycothiazole^{18–21} contain (*Z*)-configured olefins. Since the geometry of the internal double bond can be controlled through the reaction conditions *cis*-dehydrocoumurrayin²² and (*E*)-dehydroostol could be accessed through our strategy (Figure 1).

Valuable stereodefined olefins were accessed through our one-pot MCR giving rise to various structural motifs. Aliphatic aldehydes can be employed with catalytic amounts of Lewis acid selectively leading to the (*Z*)-diene (Scheme 4).²³ Trienes and tetraenes with defined olefin geometry can be synthesized from hexenal and hexadienal under the optimized reaction conditions for the MCR without the addition of external Lewis acid. Dienynes with could also be synthesized employing 1 mol% of Ho(OTf)₃ as Lewis acid. Even sensitive functionalities such as aromatic pinacolato boronates and heteroatomics such as thiophene were smoothly converted to the desired (*Z*)-olefins. The geometry of the double bond was determined from the coupling constants of the vinylic protons (for details see supporting information).

(*E*)-Olefins could be accessed by two different strategies (Scheme 5). The first strategy is the addition of base after the completion of the hydrosilylation-allylation sequence to the same flask. α,β-Unsaturated aldehydes, ynals and aromatic aldehydes were competent substrates to furnish (*E*)-olefins. It was found that NaOMe generated from MeOH and NaBH₄ can be employed as base in these transformations. Secondly, we found that (*Z*)-olefins could be easily isomerized to the thermodynamically more stable (*E*)-olefins by employing iodine and light in a quantitative yield and in a one-pot fashion (*vide infra*). The configuration of the olefin could be assigned through the coupling constants of the vinylic protons (for details see supporting information).

The selectivity for the respective olefin can be rationalized through the transition states depicted in Scheme 6. An acid-catalyzed process is known to involve an *anti*-elimination and therefore gives rise to the (*Z*)-olefins **5**. The base-mediated elimination proceeds through a siloxane intermediate and delivers olefins **6** with an (*E*)-geometry exclusively.

Homoallylic alcohols, however, can also be accessed with our newly developed strategy (Scheme 7). The effect of a chiral phosphoric acid on the diastereoselectivity of the reaction was investigated employing a chiral aldehyde.²⁴ A carbohydrate-derived aldehyde was subjected to the standard reaction conditions furnishing **7a**. The allylation would not occur in the absence of external Lewis acid. When adding Ho(OTf)₃ as achiral Lewis acid the homoallyl alcohol **7a** was observed in 63% yield in a 6:1 dr.²³ Employing the catalytic amounts of the chiral phosphoric-acid instead of Ho(OTf)₃ led to the formation of a single diastereomer of homoallyl alcohol **7a**. Ho(OTf)₃ also allowed for the formation of homoallyl alcohol **7b**. Istatin could also be engaged as an electrophile in the allylation reaction furnishing homoallyl alcohol **7c**. The product formation is thought to proceed through a sequence of hydrosilylation of the alkyne, allylation of the aldehyde, [1,3]-Brook rearrangement²⁵ and cleavage of the *O*-silyl group.

The synthetic utility of α -silyl- β -hydroxy vinylsilanes was demonstrated in a highly diastereoselective Prins cyclization (Scheme 8). We realized that an electron-withdrawing group in α -position to the hydroxyl-group was crucial to obtain the desired reactivity. Presumably, the destabilization of a positive charge α to the electron-withdrawing functionality is the reason for the Prins cyclization to be favored over the potential Peterson olefination.^{20,26–28} Accordingly, we optimized the reaction conditions for the ester-substituted substrate **4f**. The Prins cyclization occurs at –30 °C after the addition of stoichiometric amounts of TMSOTf leading to the desired pyrane products **8a** and **8b** in excellent yields and selectivity. The selectivity for the *syn*-pyrane is determined by the configuration of the initial α -silyl- β -hydroxy vinylsilane, which can be stereospecifically transformed into the product. Aromatic aldehydes were found to perform equally well as α,β -unsaturated aldehydes in accordance with Panek's work.²⁶

The dienes proved to be competent substrates in various functionalization reactions (Scheme 9). The benzyldimethylsilyl-group could be utilized in a Hiyama cross-coupling reaction.^{15,29} Even highly sterically demanding *o*-iodo-ethylbenzoates were cross-coupled to diene **9** in good yields. Notably, the double bond geometry was retained during this process. By the choice of the aldehyde in the Ru-catalyzed MCR and the cross-coupling partner, the 1,3-(*Z*)-diene motif can be integrated in a variety of different molecular scaffolds. The selective epoxidation of the internal double-bond allows for a rapid access to biologically important vinyl epoxides³⁰ such as phebalosin. The core of diepoxides such as spatol³¹ might also be accessed through a double epoxidation. Therefore, we examined the epoxidation of the dienes giving access to powerful building blocks. The (*Z*)-1,2-substituted olefin can be epoxidized in the presence of the 1,1'-disubstituted vinyl-silane to give rise to valuable vinyl-epoxides such as **10**. By simply modifying the protocol, diepoxide **11** can be obtained in excellent yields and good diastereoselectivity of 5:1.

We envisioned the application of the generated dienes in an electrocyclic Diels-Alder reaction (Scheme 10).^{32,33} When we subjected the isolated (*Z*)-olefin to thermal Diels-Alder conditions using microwave irradiation, we found that the desired product **12a** was formed in 65% yield from the diene. A one-pot sequence starting from **1**, **2** and **3** led to the formation of the cyclization product in an overall 41% yield over 3 steps. The discovery of the quantitative isomerization reaction prompted us to investigate the application of the (*E*)-dienes in the desired Diels-Alder reaction. Interestingly, we could demonstrate an iterative multicomponent-one-pot protocol to carry out five synthetic operations in one flask generating highly complex products from simple starting materials in a highly selective fashion. A sequence consisting of hydrosilylation, allylation, elimination, isomerization, and a subsequent Diels-Alder reaction was attempted. Before we examined the one-pot sequence, we probed the Diels-Alder reaction of the isomerized (*E*)-olefins. We were pleased to find that the reaction could be carried out at low temperature in CH₂Cl₂ with the Lewis acid Et₂AlCl leading to the product **12b** in 76% yield. Notably, the five-step one-pot sequence could be performed with improved efficiency furnishing **12b** in 52% yield without the need of intermediate purification.

In summary, we have developed a Ru-catalyzed MCR leading to valuable α -silyl- β -hydroxyl olefins and stereodefined 1,3-dienes from the same simple starting materials. The reaction proceeds under very mild reaction conditions and exhibits a great scope of aliphatic, aromatic and heteroaromatic aldehydes. The newly developed approach allows access to α -silyl- β -hydroxyl vinylsilanes in complete diastereoselectivity. The geometry of the 1,3-dienes can be remotely controlled by the choice of either mildly basic or Lewis acidic reaction conditions leading to (*E*)- or (*Z*)-dienes, respectively. Homoallyl alcohols can be accessed through with high diastereocontrol a [1,3]-Brook rearrangement. The α -silyl- β -hydroxyl vinylsilanes readily undergo further functionalization to yield valuable pyrane derivatives in excellent yield and selectivity. The 1,3-dienes can be cross-coupled, oxidized and employed in electrocyclic reactions. Most notably a protocol for a five-step one-pot sequence was established furnishing highly complex cyclohexene derivatives in high yields and selectivities from very simple starting materials.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Figure 1.
Potentially Accessible Natural Product Scaffolds.

Scheme 1.

Scope of Aliphatic Aldehydes for the Reaction Sequence to α -Silyl- β -Hydroxyl Vinylsilanes.^a

(a) Conditions: **1** (0.25 mmol), **2** (0.30 mmol), **3** (0.50 mmol), $[\text{CpRu}(\text{MeCN})_3]\text{PF}_6$ (5 mol %), CH_2Cl_2 (1.0 mL), rt, 3–16 h. (b) Isolated yield. (c) 10 eq. of **3**, (d) 2.5 eq. of **3**, (e) DCE as solvent, (f) 1.0 eq of **2**, (g) reaction performed on 1.0 mmol scale, (h) reaction performed sequentially. $[\text{Si}] = \text{SiMe}_2\text{Bn}$, SiEt_3

Scheme 2.

Scope of Aromatic Aldehydes for the Reaction Sequence to α -Silyl- β -Hydroxyl Vinylsilanes.^a

(a) Conditions: **1** (0.25 mmol), **2** (0.30 mmol), **3** (0.50 mmol), $[\text{CpRu}(\text{MeCN})_3]\text{PF}_6$ (5 mol %), CH_2Cl_2 (1.0 mL), rt, 3–16 h. (b) Isolated yield. (c) 10 eq. of **3**, (d) 2.5 eq. of **3**, (e) DCE as solvent, (f) 1.0 eq of **2**, (g) reaction performed on 1.0 mmol scale, (h) reaction performed sequentially. [Si] = SiMe_2Bn , SiEt_3

Scheme 3.

Rationale for the Diastereoselectivity in the MCR.

Scheme 4.

Scope for the one-pot formation of (Z)-1,3-dienes.^a

(a) Conditions: **1** (0.25 mmol), **2** (0.30 mmol), **3** (0.50 mmol), $[\text{CpRu}(\text{MeCN})_3]\text{PF}_6$ (5 mol %), LA (0–5 mol %), CH_2Cl_2 (1.0 mL) at rt, 3–16 h, isolated yield. (b) 5 mol% $\text{In}(\text{OTf})_3$ (c) no external LA (d) 1 mol% $\text{Ho}(\text{OTf})_3$ (e) 5 mol% $\text{Ho}(\text{OTf})_3$ (f) 2 mol% $\text{In}(\text{OTf})_3$

Scheme 5. Scope for the One-Pot Formation of (*E*)-1,3-Dienes.^a

(a) Conditions: **1** (0.25 mmol), **2** (0.30 mmol), **3** (0.50 mmol), $[\text{CpRu}(\text{MeCN})_3]\text{PF}_6$ (5 mol %), LA (5–10 mol %), CH_2Cl_2 (1.0 mL) at rt, 3–16 h, isolated yield.

Scheme 6.
Rational for the Stereoselective Olefin Formation

Scheme 7. Scope for the One-Pot Formation of Homoallyl alcohols.^a

(a) Conditions: **1** (0.25 mmol), **2** (0.30 mmol), **3** (0.50 mmol), [CpRu(MeCN)₃]PF₆ (5 mol %), LA (0–5 mol %), CH₂Cl₂ (1.0 mL) at rt, 3–16 h, isolated yield.

Scheme 9.

Application of 1,3-Dienes in a Hiyama Coupling and Selective Epoxidation Strategy.

Scheme 10.

Isomerization and Application of the MCR Incorporating a Diels-Alder Reaction.