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Diastereo- and Enantioselective Ruthenium-Catalyzed Hydrohydroxyalkylation of 2-Silyl-butadienes: Carbonyl *syn*-Crotylation from the Alcohol Oxidation Level

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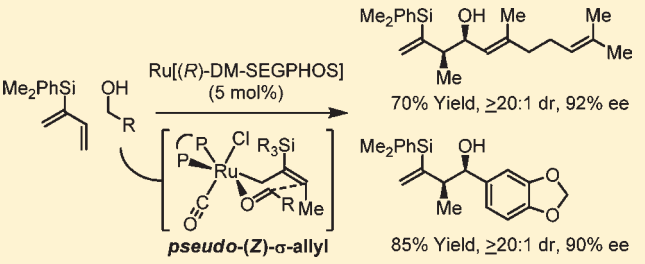
Supporting Information

ABSTRACT: Exposure of alcohols **2a**−**2j** to 2-silyl-butadienes in the presence of ruthenium complexes modified by (*R*)-SEGPHOS or (*R*)-DM-SEGPHOS results in redox-triggered generation of allylruthenium−aldehyde pairs, which combine to form products of carbonyl crotylation **4a**−**4j** in the absence of stoichiometric byproducts and with high levels of *syn*-diastereo- and enantioselectivity. In the presence of isopropanol under otherwise identical conditions, aldehydes **3a**−**3j** are converted to an equivalent set of adducts **4a**−**4j**. Whereas reactions conducted using conventional heating require 48 h, microwave irradiation enables full conversion in only 4 h. Finally, as illustrated in the conversion of adduct **4a** to compounds **6a** and **6b**, diastereoselective hydroboration−Suzuki cross-coupling with aryl and vinyl halides followed by Fleming−Tamao oxidation enables generation of *anti*, *syn*-stereotriads found in numerous polyketide natural products.



INTRODUCTION

Roughly 20% of top-selling small molecule therapeutic agents are polyketides,[1,2] and it is estimated that polyketides are 5 times more likely to possess useful drug activity as compared to other families of natural products.[3] Among methods for polyketide construction,[4] the addition of chirally modified crotylmetal reagents to carbonyl compounds ranks as one of the foremost strategies used for the generation of polypropionate substructures.[5−8] However, the most broadly utilized protocol of this type, Brown's crotylation,[5b,c] generates superstoichiometric quantities of a secondary alcohol byproduct, isopinocampheol, which frequently complicates product isolation and has prevented implementation of this technology at the process level.[9] Consequently, efforts toward asymmetric carbonyl crotylation protocols continue unabated.[6−8]

Recently, we reported a catalytic method for *anti*-diastereo- and enantioselective carbonyl crotylation from the alcohol or aldehyde oxidation level employing α-methyl allyl acetate as the crotyl donor.[10c,d] This transformation represents one among a broad, new class of catalytic C−C couplings in which hydrogen exchange between alcohols and π-unsaturated reactants triggers generation of electrophile−nucleophile pairs that combine to form products of carbonyl addition.[11,12] Whereas chirally modified iridium complexes promote such transformations with excellent control of diastereo- and enantioselectivity,[10,11c,11d] enantioselective ruthenium-catalyzed processes have proven elusive.[13] For example, in ruthenium-catalyzed butadiene−alcohol C−C couplings, products of carbonyl crotylation appear as mixtures of *syn*- and *anti*-diastereomers (Figure 1).[13a]

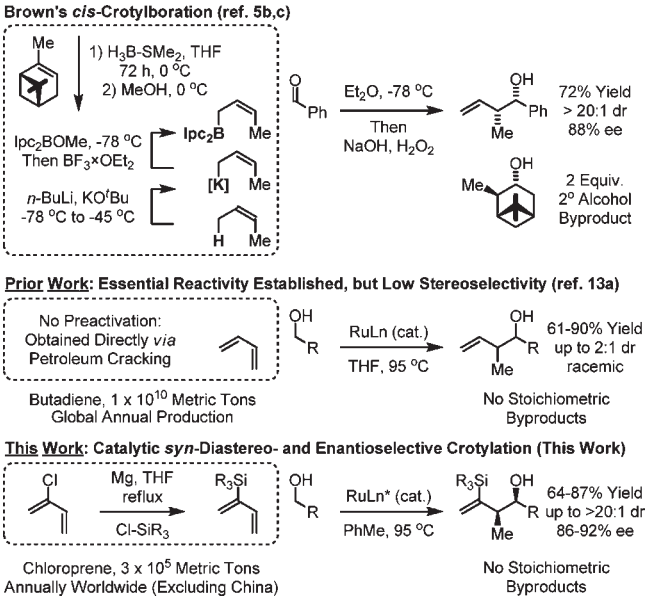


Figure 1. *syn*-Diastereo- and enantioselective carbonyl crotylation in the absence of stoichiometric byproducts via ruthenium-catalyzed hydrohydroxyalkylation of 2-silyl-butadienes.

The low levels of diastereoselectivity associated with butadiene mediated crotylations are attributed to incomplete partitioning of

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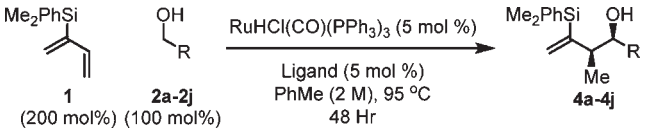
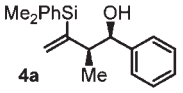
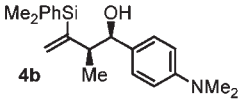
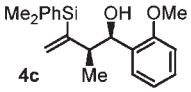
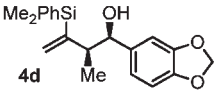
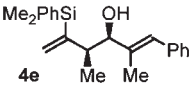
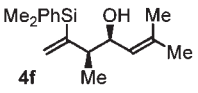
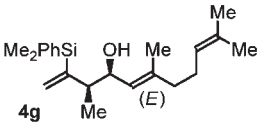
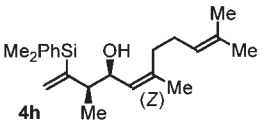
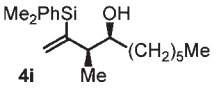
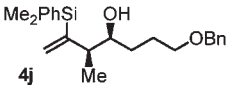
Table 1. *syn*-Diastereo- and Enantioselective Carbonyl Crotylation from the Alcohol Oxidation Level[a]



Entry	Product	Ligand	Yield [%]	ee [%]	*syn*:*anti*
1	 **4a**	A	81	87	13:1
2	 **4b**	A	87	90	≥ 20:1
3	 **4c**	A	84	90	≥ 20:1
4	 **4d**	B	85	90	≥ 20:1
5	 **4e**	B	70[b]	90	11:1
6	 **4f**	A	67[b,c]	90	≥ 20:1
7	 **4g**	A	70[b]	92	≥ 20:1
8	 **4h**	A	64[b,c]	86	≥ 20:1
9	 **4i**	A	65[b-d]	88	≥ 20:1
10	 **4j**	A	66	86	≥ 20:1

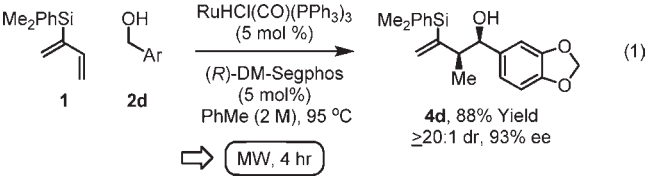
[a] Ligand A = (*R*)-DM-SEGPHOS, ligand B = (*R*)- SEGPHOS. Yields are of isolated material. Diastereoselectivity was determined through ^{1}H NMR analysis of crude reaction mixtures. Enantiomeric excess was determined by chiral stationary phase HPLC analysis. See the Supporting Information for details. (b) 250 mol % **1**. (c) THF. (d) 7 mol % catalyst.

(*Z*)- and (*E*)-σ-crotylruthenium intermediates, which react stereospecifically through closed transition structures to deliver *syn*- and *anti*-diastereomers, respectively. It was reasoned that 2-silyl-substituted butadienes, readily prepared from chloroprene, would enforce generation of "*pseudo*-(*Z*)-σ-crotylruthenium" isomers, potentially generating products of carbonyl *syn*-crotylation.[14] Here, we report that upon exposure of primary alcohols **2a**−**2j** to 2-silyl-butadiene **1** in the presence of chirally modified ruthenium catalysts, products of carbonyl crotylation **4a**−**4j** are formed with high levels of *syn*-diastereo- and enantioselectivity. Under related transfer hydrogenation conditions employing isopropanol as terminal reductant, aldehydes **3a**−**3j** are converted to an equivalent set of carbonyl crotylation products **4a**−**4j** with comparable levels of stereoselectivity (Table 2).

RESULTS AND DISCUSSION

In an initial set of experiments, a range of 2-silyl-substituted dienes were assayed for their ability to engage in efficient, *syn*-diastereoselective carbonyl crotylation from the alcohol oxidation level. Such dienes are conveniently prepared from the Grignard reagent derived from chloroprene, which itself is generated in situ from 3,4-dichloro-1-butene.[15] It was found that upon exposure of the 2-silyl-substituted butadiene **1** to aliphatic alcohol **2j** in the presence of $RuHCl(CO)(PPh_3)_3$, *rac*-BINAP, in THF solvent at 95 °C, the desired product of *syn*-crotylation **4j** was obtained as a single diastereomer in 25% yield. It should be noted that large alkyl substituents (for example, mesityl) at the 2-position of butadiene also enforce *syn*-diastereoselectivity. Encouraged by these results, an assay of chiral ligands was undertaken. Remarkably, although a racemic background reaction is catalyzed by $RuHCl(CO)(PPh_3)_3$, the catalyst modified by (*R*)-DM-SEGPHOS [(*R*)-(+)-5,5-bis(di[3,5-xylyl]phosphino)-4,4-bi-1,3-benzodioxole] promotes the reaction in 34% yield, >20:1 dr, and 84% ee. In an effort to exclude triphenylphosphine, and potentially eliminate a competing background reaction, the phosphine-free precatalyst $RuCl_2(CO)$(cymene) was assayed in combination with (*R*)-DM-SEGPHOS. However, conversion was low. In toluene, a less Lewis basic solvent, using $RuHCl(CO)(PPh_3)_3$ as precatalyst, the yield of **2j** was significantly improved (66% yield, >20:1 dr, 86% ee). Under these conditions, diene **1** was coupled to a diverse range of alcohols **2a**−**2j**. The products of crotylation **4a**−**4j** were formed in good yields and with excellent control of *syn*-diastereo- and enantioselectivity (Table 1).

Reactions conducted using conventional heating typically require 48 h to reach full conversion. However, microwave irradiation promotes a dramatic increase in rate. For example, in a microwave reactor under otherwise standard conditions, the coupling of 2-silyl-butadiene **1** to alcohol **2d** is complete in only 4 h. The reaction product **4d** is isolated in 88% yield with complete *syn*-diastereoselectivity (>20:1 dr) and exceptional levels of enantioselectivity (93% ee) (eq 1).



The reductive coupling of 2-silyl-butadiene **1** to aldehydes was attempted next. Toward this end, formic acid, 1,4-butanediol, and isopropanol were assayed as terminal reductants under conditions otherwise identical to those established for reactions conducted from the alcohol oxidation level. Using isopropanol

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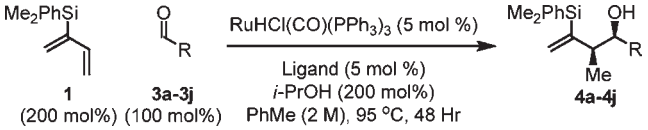
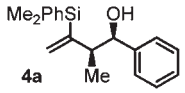
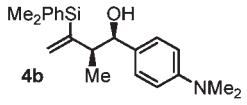
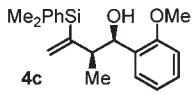
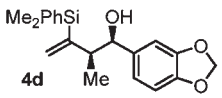
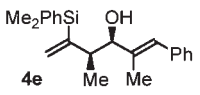
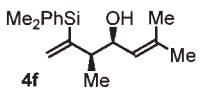
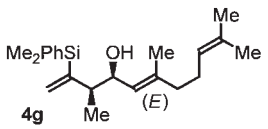
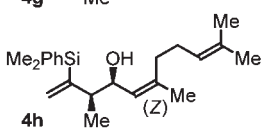
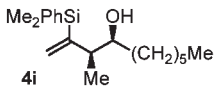
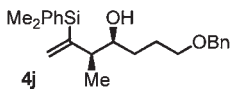
Table 2. *syn*-Diastereo- and Enantioselective Carbonyl Crotylation from the Aldehyde Oxidation Level[a]

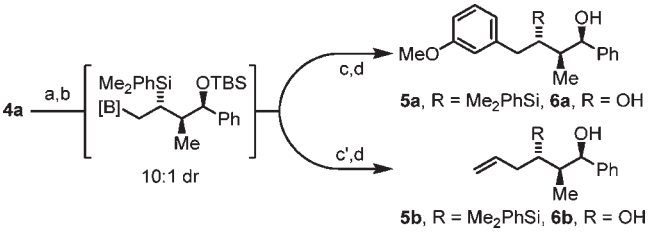


Entry	Product	Ligand	Yield [%]	ee [%]	*syn*:*anti*
1	 **4a**	A	76	88	12:1
2	 **4b**	A	80	93	19:1
3	 **4c**	A	71	88	≥ 20:1
4	 **4d**	B	91	90	≥ 20:1
5	 **4e**	B	75[b]	93	11:1
6	 **4f**	A	56[b,c]	90	≥ 20:1
7	 **4g**	A	71[b]	91	≥ 20:1
8	 **4h**	A	66	84	≥ 20:1
9	 **4i**	A	53[b-e]	84	≥ 20:1
10	 **4j**	A	50[b,d,e]	84	≥ 20:1

[a] Ligand A = (*R*)-DM-SEGPHOS, ligand B = (*R*)- SEGPHOS. Yields are of isolated material. Diastereoselectivity was determined through ^{1}H NMR analysis of crude reaction mixtures. Enantiomeric excess was determined by chiral stationary phase HPLC analysis. See the Supporting Information for details. (b) 250 mol % **1**. (c) THF. (d) 7 mol % catalyst. (e) 72 h.

(200 mol %) as terminal reductant, diene **1** participates in highly regio-, diastereo-, and enantioselective couplings to aldehydes **3a**−**3j** to furnish an identical set of homoallylic alcohols **4a**−**4j** in roughly equivalent isolated yields (Table 2).

Scheme 1. Diastereoselective Hydroboration Enables Formation of *anti,syn*-Stereotriads[a]



[a] Reagents: (a) TBSCl (120 mol %), imidazole (150 mol %), DMF, 25 °C, 81% yield; (b) 9-BBN (300 mol %), THF, 55 °C; (c) 3-bromoanisole (250 mol %), NaOH (330 mol %), $Pd(PPh_3)_4$ (10 mol %), THF−H_2O, 70 °C, 75% yield **5a** (over two steps); (c′) vinyl bromide (250 mol %), NaOH (330 mol %), $Pd(PPh_3)_4$ (10 mol %), THF−H_2O, 70 °C, 56% yield **5b** (over two steps); (d) KH (600 mol %), ^{t}BuOOH (600 mol %), TBAF (300 mol %), NMP, 70 °C, 86% yield **6a**, 77% yield **6b**.

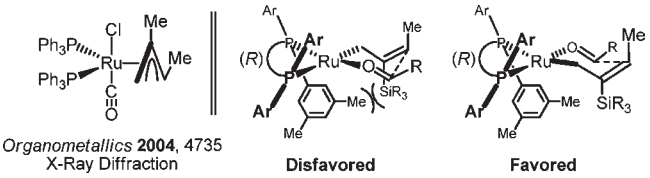
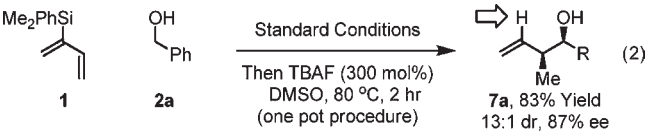


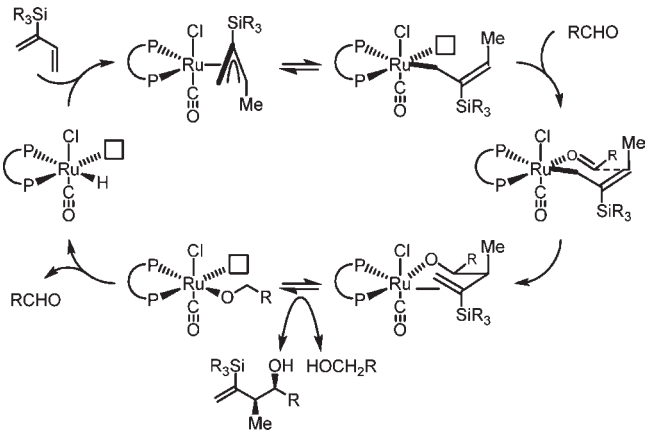
Figure 2. Stereochemical model for 2-silyl-butadiene-mediated *syn*-crotylation employing a (*R*)-DM-SEGPHOS modified ruthenium catalyst.

To illustrate the utility of the coupling products, compound **4a** was converted to the silyl ether and subjected to diastereoselective hydroboration−Suzuki cross-coupling with aryl halides and vinyl halides to furnish adducts **5a** and **5b**, respectively.[16] Protection of the hydroxyl moiety of **4a** as the TBS is required to enforce high levels of diastereoselectivity (10:1 dr) in the hydroboration event. The benzyl ether derived from **4a** displays low levels of diastereoselectivity (2:1 dr) upon hydroboration under identical conditions. Fleming−Tamao oxidation of the C−Si bond was especially challenging. However, upon exposure of the Suzuki coupling products **5a** and **5b** to Woerpel's modified conditions for oxidative C−Si bond cleavage,[17] the diols **6a** and **6b**, which possess *anti,syn*-stereotriads found in numerous polyketide natural products, could be isolated in good yield (Scheme 1). Finally, if products of conventional *syn*-crotylation are desired, direct addition of TBAF to the reaction mixture enables protodesilylation in a convenient one-pot procedure, as demonstrated by the formation of **7a** (eq 2).



With regard to mechanism, the stoichiometric reaction of $RuHCl(CO)(PPh_3)_3$ with 1,2- and 1,3-dienes to form π-allyl complexes that have been characterized by single crystal X-ray diffraction and NMR, respectively, is known (Figure 2).[18] Carbonyl addition by way of the σ-bound allylruthenium haptomer through a closed transition structure delivers the homoallylic ruthenium alkoxide, which upon substitution with a reactant alcohol provides a pentacoordinate ruthenium alkoxide. The vacant coordination site at this stage enables dehydrogenation to form

Scheme 2. Proposed Catalytic Mechanism for Ruthenium-Catalyzed Diene Hydrohydroxymethylation As Supported by Established Stoichiometric Transformations



an aldehyde and regenerate the ruthenium hydride to close the catalytic cycle (Scheme 2). The stereochemical outcome of the reaction may be predicted on the basis of the indicated model (Figure 2). Absolute and relative stereochemistry of adducts **4a**−**4j** was assigned in analogy to **7a**, which was compared to an authentic sample.[7c]

CONCLUSION

In summary, exposure of alcohols **2a**−**2j** to 2-silyl-butadiene **1** in the presence of the ruthenium catalyst obtained upon the combination of $RuHCl(CO)(PPh_3)_3$ and (*R*)-SEGPHOS or (*R*)-DM-SEGPHOS provides products of hydrohydroxyalkylation **4a**−**4j** with complete regioselectivity and with good to excellent levels of diastereo- and enantioselectivity. In the presence of isopropanol, but under otherwise identical conditions, an equivalent set of adducts **4a**−**4j** are generated in an equally selective fashion from aldehydes **3a**−**3j**. In this way, catalytic *syn*-diastereo- and enantioselective carbonyl crotylation is achieved from the alcohol or aldehyde oxidation level. This carbonyl crotylation protocol circumvents stoichiometric byproducts and cryogenic conditions and does not require glovebox techniques, thus representing an important step toward the development of scalable methods for the construction of polyketide natural products and related compounds. However, many unmet challenges remain, including the development of second generation catalysts that promote efficient, stereoselective couplings to α-chiral alcohols and aldehydes, and that enable related imine additions from the amine oxidation level. Future studies will address these goals.

ASSOCIATED CONTENT

Supporting Information. Experimental procedures and spectral data for all new compounds (^{1}H NMR, ^{13}C NMR, IR, HRMS). This material is available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

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