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Chiral-Anion-Dependent Inversion of Diastereo- and Enantioselectivity in Carbonyl Crotylation via Ruthenium-Catalyzed Butadiene Hydrohydroxyalkylation

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Supporting Information

ABSTRACT: The ruthenium catalyst generated in situ from $H_2Ru(CO)(PPh_3)_3$, (*S*)-SEGPHOS, and a TADDOL-derived phosphoric acid promotes butadiene hydrohydroxyalkylation to form enantiomerically enriched products. Notably, the observed diastereo- and enantioselectivity is the opposite of that observed using BINOL-derived phosphate counterions in combination with (*S*)-SEGPHOS, the same enantiomer of the chiral ligand. Match/mismatch effects between the chiral ligand and the chiral TADDOL-phosphate counterion are described. For the first time, single-crystal X-ray diffraction data for a ruthenium complex modified by a chiral phosphate counterion are reported.

In the course of developing C−C bond-forming hydrogenations beyond hydroformylation, we have found that hydrogen transfer between primary alcohols and π-unsaturated reactants generates organometal−aldehyde pairs that combine to form products of carbonyl addition, enabling a departure from stoichiometric organometallic reagents.[1] During this work, iridium catalysts for enantioselective carbonyl crotylation from the alcohol oxidation level employing α-methyl allyl acetate as a crotyl donor were developed.[2,3] Butadiene hydrohydroxyalkylation is an alternate strategy for carbonyl crotylation. In initial studies from our laboratory, iridium and ruthenium catalysts that displayed the essential reactivity and regioselectivity were identified, but poor stereoselectivity was observed.[4a,b] While stereoselectivity can be enforced through the use of 2-silylbutadienes,[4c] direct regio- and stereoselective hydrohydroxyalkylations of butadiene itself remained elusive until ruthenium catalysts modified by chiral phosphate counterions were explored.[4d,5−7] With the indicated H_8-BINOL-derived phosphate counterion, ruthenium-catalyzed butadiene hydrohydroxyalkylation with primary benzylic alcohols delivered products of crotylation with good levels of *anti*-diastereoselectivity and enantioselectivity. To achieve stereoselectivity in the corresponding reactions of primary aliphatic alcohols, chiral phosphate counterions were assayed in combination with the chiral phosphine ligands (*R*)- and (*S*)-SEGPHOS.[8] Here we disclose that ruthenium catalysts modified with H_8-BINOL and TADDOL-derived phosphate counterions enforce *opposite* diastereo- and enantioselectivities even when the same enantiomer of the chiral phosphine ligand is employed. On the basis of these findings, a protocol for *syn*-diastereo- and enantioselective carbonyl crotylation via butadiene hydrohydroxyalkylation was achieved (Figure 1).

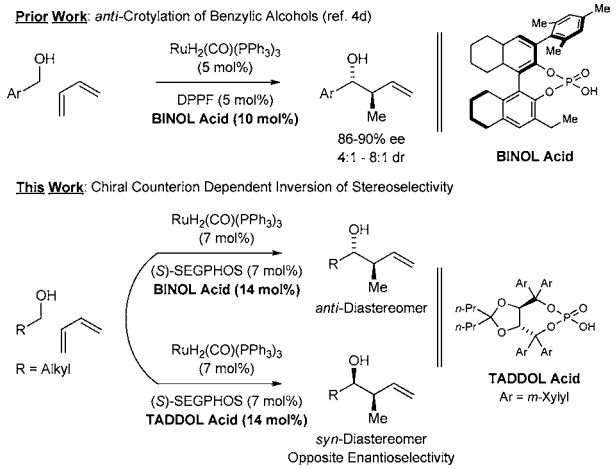

Figure 1. Ruthenium-catalyzed diastereo- and enantioselective crotylation via butadiene hydrohydroxyalkylation.

To develop stereoselective ruthenium-catalyzed butadiene hydrohydroxyalkylations applicable to primary aliphatic alcohols, structural classes of phosphate counterions beyond BINOL-derived systems were explored. As demonstrated previously,[4d,9] the acid−base reaction of $H_2Ru(CO)(PPh_3)_3$ with the chiral phosphoric acid HX conveniently attaches the chiral anion to the metal center. Remarkably, upon initial evaluation of TADDOL-derived phosphoric acids $\mathbf{A_1}$−$\mathbf{A_5}$ in the coupling of butadiene with heptanol (**1a**) using the achiral phosphine ligand 1,1′-bis(diphenylphosphino)ferrocene (DPPF), a modest preference for the *syn*-diastereomer **2a** was observed (Table 1, entries 1−5). The enantioselectivity increased with increasing size of the TADDOL aryl substituent, and when the 3,5-xylyl-substituted acid $\mathbf{A_5}$ was used, 78% enantiomeric excess (ee) was observed for the *syn*-diastereomer **2a** (entry 5). These data suggested the feasibility of developing a protocol for carbonyl *syn*-crotylation via butadiene hydrohydroxyalkylation. Toward this end, match/mismatch effects between the chiral phosphate counterion derived from $\mathbf{A_5}$ and the chiral phosphine ligands (*R*)- and (*S*)-SEGPHOS[8] were explored (entries 6 and 7). For the matched case involving the combination of acid $\mathbf{A_5}$ and (*S*)-SEGPHOS, 89% ee was

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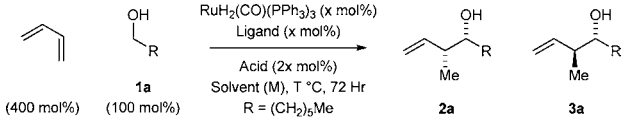
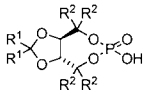
Table 1. Selected Optimization Experiments in the Ruthenium-Catalyzed *syn*-Diastereo- and Enantioselective Hydrohydroxyalkylation of Butadiene with Heptanol (1a)[a]



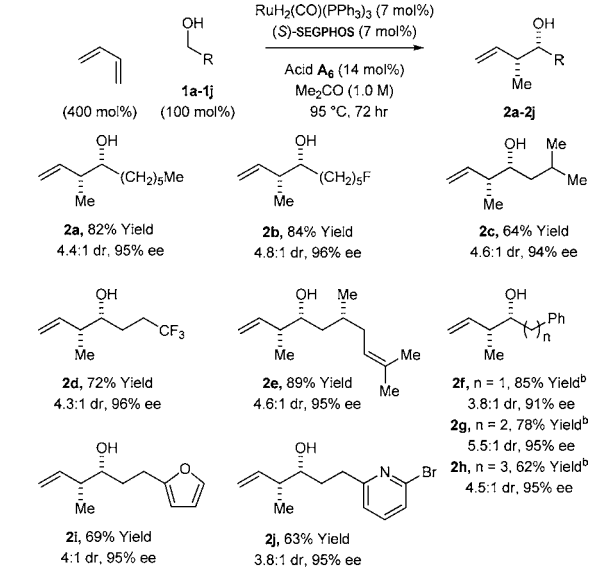
Entry	Acid	Ligand	Ru (mol%)	T (°C)	Solvent (M)	Yield (%)	ee (%)	2a:3a
1	A_1	DPPF	5	105	THF (2.0)	64	1	1:1
2	A_2	DPPF	5	105	THF (2.0)	82	18	1.6:1
3	A_3	DPPF	5	105	THF (2.0)	50	29	1.4:1
4	A_4	DPPF	5	105	THF (2.0)	58	63	1.8:1
5	A_5	DPPF	5	105	THF (2.0)	85	78	1.4:1
6	A_5	(*R*)-SEGPHOS	5	105	THF (2.0)	48	31	1.1:1
7	A_5	(*S*)-SEGPHOS	5	105	THF (2.0)	57	89	1.7:1
8	A_5	(*S*)-SEGPHOS	5	95	*t*-BuOH (2.0)	23	90	2.7:1
9	A_5	(*S*)-SEGPHOS	5	95	Me_2CO (2.0)	46	90	3.0:1
10	A_6	(*S*)-SEGPHOS	5	95	Me_2CO (2.0)	55	94	4.1:1
11	A_6	(*S*)-SEGPHOS	5	95	Me_2CO (1.0)	57	94	4.6:1
⇨ 12	A_6	(*S*)-SEGPHOS	7	95	Me_2CO (1.0)	82	95	4.4:1



A_1: R^1 = Me, R^2 = Me
A_2: R^1 = Me, R^2 = Ph
A_3: R^1 = Me, R^2 = 3-Ph-C_6H_4
A_4: R^1 = Me, R^2 = 3-Me-C_6H_4
A_5: R^1 = Me, R^2 = 3,5-Me-C_6H_4
A_6: R^1 = *n*-Pr, R^2 = 3,5-Me-C_6H_4

[a]Yields are of materials isolated by silica gel chromatography. DPPF = 1,1′-bis(diphenylphosphino)ferrocene; SEGPHOS = 5,5′-bis-(diphenylphosphino)-4,4′-bi-1,3-benzodioxole. See the Supporting Information for further details.

Table 2. Ruthenium-Catalyzed Crotylation via Butadiene Hydrohydroxyalkylation Using Aliphatic Alcohols 1a–j[a]

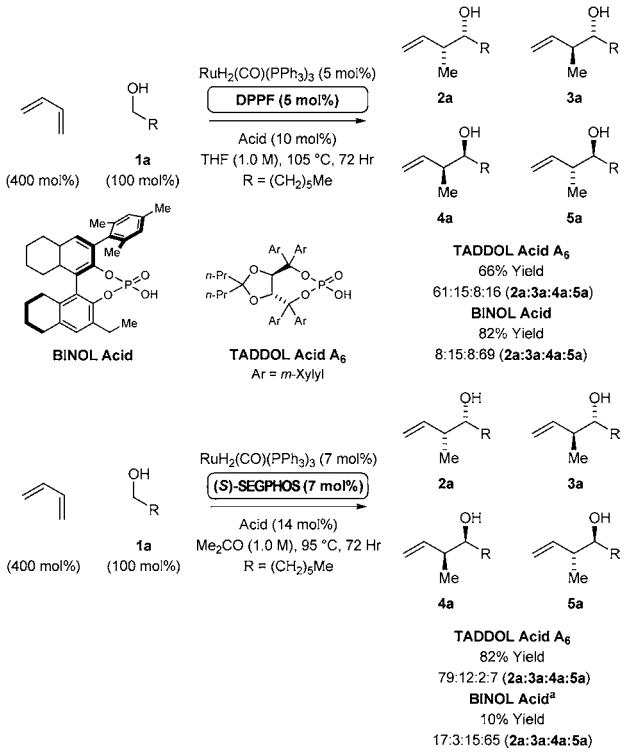


[a]Yields are of materials isolated by silica gel chromatography. See the Supporting Information for further details. [b]5 mol % catalyst, 5 mol % ligand, and 10 mol % acid were used.

observed for the *syn*-diastereomer **2a**, although *syn*-diastereoselectivity remained modest (entry 7). However, upon use of phosphoric acids $\mathbf{A_6}$ accompanied by further variation of the solvent, concentration, and temperature (entries 8–12), **2a** was generated in 82% yield with 95% ee and 4.4:1 *syn*-diastereoselectivity (entry 12).

To evaluate the reaction scope, the optimal conditions identified for the *syn*-crotylation of **1a** were applied to primary alcohols **1b–j**. The desired *syn*-crotylation products **2b–j** were obtained in good yield with *syn*-diastereoselectivities ranging between 4:1 and 5:1 and uniformly high levels of

Scheme 1. Chiral-Phosphate-Counterion-Dependent Inversion of Diastereo- and Enantioselectivity Using the Chiral Catalyst Modified by DPPF and (*S*)-SEGPHOS



[a]Reaction performed at 105 °C.

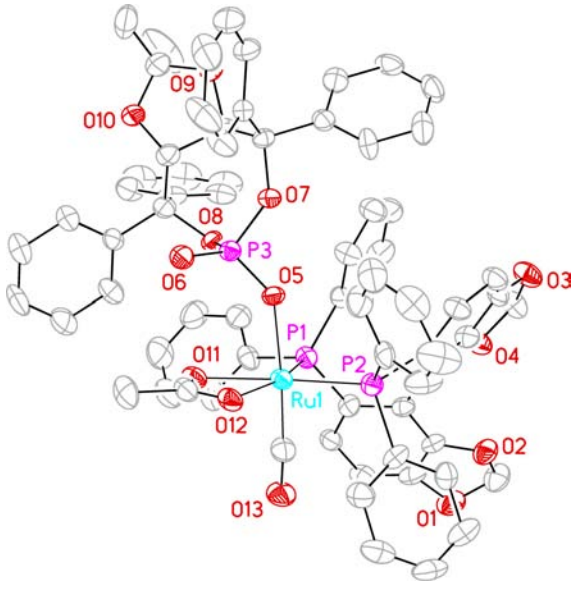


Figure 2. Structure of Ru(CO)(OAc)($\mathbf{A_2}$-phosphate)[(*S*)-SEGPHOS)] as determined by single-crystal XRD analysis. Displacement ellipsoids are scaled to the 50% probability level.

enantioselectivity (Table 2). Interestingly, the observed diastereo- and enantioselectivity is opposite to that observed using BINOL-derived phosphate counterions in combination with DPPF or even (*S*)-SEGPHOS (Scheme 1). To gain insight into the origins of the stereoselectivity, a crystal of the ruthenium complex modified with (*S*)-SEGPHOS and the phosphate counterion derived from acid $\mathbf{A_2}$ was subjected to X-

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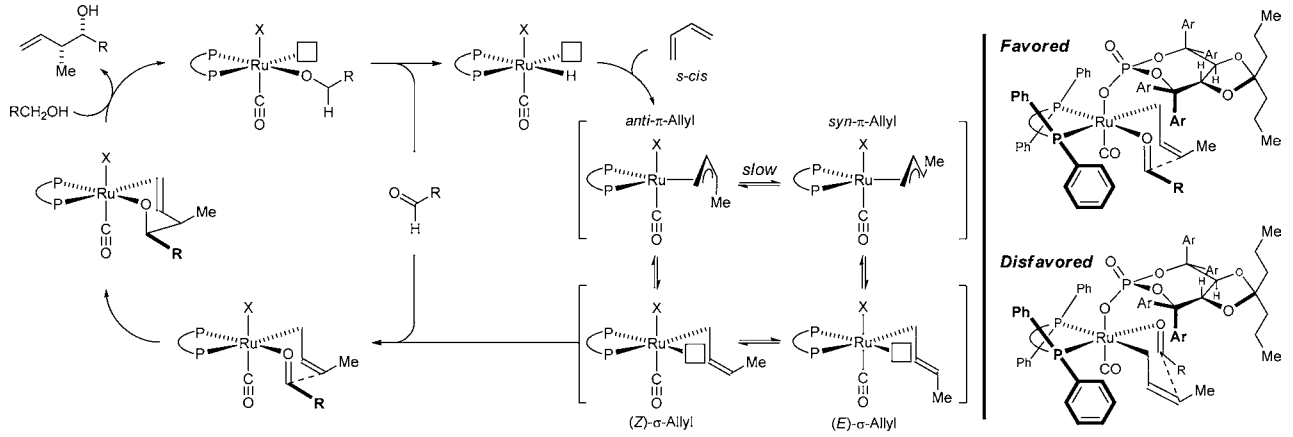
Scheme 2. Catalytic Mechanism for Ruthenium-Catalyzed Crotylation via Butadiene Hydrohydroxyalkylation



ray diffraction analysis (Figure 2). As anticipated, the phosphate counterion exists in a *trans*-relationship with respect to the carbonyl ligand.[10] On the basis of the connectivity revealed in the crystal structure and the observed stereoselectivities, a preliminary stereochemical model was formulated and reconciled with the indicated catalytic mechanism (Scheme 2). The unusual *syn*-diastereoselectivity may arise as a consequence of kinetically preferred hydrometalation of the s-cis conformer of butadiene to furnish the *anti*-π-crotylruthenium isomer.[11] It is postulated that the steric demand of the TADDOL-based phosphate counterion retards the rate of isomerization to the *syn*-π-crotylruthenium isomer, which would mandate the intervention of an even more sterically congested secondary σ-crotylruthenium species. In this way, the kinetic stereoselectivity of the hydrometalation event is preserved, and carbonyl addition occurs by way of the (*Z*)-σ-crotylruthenium haptomer via a closed Zimmerman–Traxler-type transition structure[12] to furnish the syn diastereomer.

In summary, we have reported the chiral-anion-dependent inversion of diastereo- and enantioselectivity in butadiene hydrohydroxyalkylation to form products of carbonyl *syn*-crotylation as well as the first X-ray crystal structure of a ruthenium complex modified by a chiral phosphate counterion. These studies have provided important insight into the structural and interactional features of the catalyst, which should accelerate the design of improved second-generation protocols. More broadly, the merged redox-construction events described herein minimize the degree of separation between reagent and feedstock and represent a departure from premetalated reagents in carbonyl addition, a cornerstone of synthetic organic chemistry.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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