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Amplification of *anti*-Diastereoselectivity *via* Curtin-Hammett Effects in Ruthenium Catalyzed Hydrohydroxyalkylation of 1,1-Disubstituted Allenes: Diastereoselective Formation of All-Carbon Quaternary Centers

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Abstract

Under the conditions of ruthenium catalyzed transfer hydrogenation, 1,1-disubstituted allenes **1a–1c** and alcohols **2a–2g** engage in redox-triggered generation of allylruthenium-aldehyde pairs to form products of hydrohydroxyalkylation **3a–3g**, **4a–4g** and **5a–5g** with complete branched regioselectivity. By exploiting Curtin-Hammett effects, good to excellent levels of *anti*-diastereoselectivity (4:1 – >20:1) are obtained. Thus, all carbon quaternary centers are formed in a diastereoselective fashion upon carbonyl addition from the alcohol oxidation level in the absence of pre-metallated nucleophiles or stoichiometric byproducts. Exposure of allene **1b** to equimolar quantities of alcohol **2a** and aldehyde **6b** under standard reaction conditions delivers adducts **4a** and **4b** in a 1:1 ratio. Similarly, exposure of allene **1b** to equimolar quantities of aldehyde **6a** and alcohol **2b** provides adducts **4a** and **4b** in an identical equimolar ratio. Exposure of allene **1b** to *d*₂-*para*-nitrobenzyl alcohol, *deuterio-2a*, under standard reaction conditions delivers the product of hydrohydroxymethylation *deuterio-4a*, which incorporates deuterium at the carbinol position (>95% ²H) and the interior vinylic position (34% ²H). Competition experiments involving exposure of allene **1b** to equimolar quantities of benzylic alcohols **2a** and *deuterio-2a* reveal no significant kinetic effect. The collective data corroborate rapid, reversible alcohol dehydrogenation, allene hydrometallation and (*E*)-, (*Z*)-isomerization of the transient allylruthenium in advance of turn-over limiting carbonyl addition. Notably, analogous allene-aldehyde reductive C-C couplings employing isopropanol as the terminal reductant display poor levels of *anti*-diastereoselectivity, suggesting carbonyl addition is not turn-over limiting in reactions conducted from the aldehyde oxidation level.

Introduction

In the course of exploring C-C bond forming hydrogenations beyond hydroformylation,¹ it was found that ruthenium² and iridium³ based catalysts promote direct hydrohydroxyalkylation of π -unsaturated reactants.^{1,2,3} In such processes, primary alcohols engage π -unsaturated reactants as redox partners, where hydrogen exchange triggers generation of electrophile-nucleophile pairs en route to products of C-C coupling. In this way, carbonyl addition is achieved directly from the alcohol oxidation level in the absence of pre-metallated nucleophiles or stoichiometric byproducts. In nearly all systems studied, identical products of carbonyl addition may be formed from the aldehyde oxidation level

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

under transfer hydrogenation conditions employing isopropanol or formic acid as terminal reductant.^{1,2,3}

While control of relative and absolute stereochemistry has been achieved in iridium catalyzed hydrohydroxyalkylations,³ stereoselective ruthenium catalyzed processes have proven elusive. Indeed, under the conditions of ruthenium catalysis, high diastereoselectivities only have been observed in couplings of unsubstituted allenamides, where complete partitioning of (*Z*)- and (*E*)- σ -allylruthenium intermediates is achieved readily through steric differentiation of hydrogen and the sterically demanding NR_1R_2 moiety.^{2f,4} Exclusive carbonyl addition from the (*E*)- σ -allylruthenium through a chair-like transition structure accounts for the observed *anti*diastereoselectivity.

The energetic bias required for partitioning *trisubstituted* (*Z*)- and (*E*)- σ -allylruthenium intermediates derived upon hydrometallation of 1,1-disubstituted allenes is far more difficult to achieve. Studies on stoichiometric hydrometallation of 1,1-disubstituted allenes or dienes employing $\text{HXRu}(\text{CO})(\text{PR}_3)_3$ (X = Cl, Br) reveal the resulting π -allylruthenium complexes $\text{Ru}(\eta^3\text{-allyl})(\text{X})(\text{CO})(\text{PR}_3)_2$ are highly fluxional.^{5,6} Rapid interconversion of π -allyl- and σ -allylruthenium complexes precludes kinetically controlled partitioning of (*Z*)- and (*E*)- σ -allylruthenium isomers *via* stereoselective hydrometallation. Therefore, it was postulated that crowding at the ruthenium center might result in energetic differentiation of the transient (*Z*)- and (*E*)- σ -allylruthenium isomers, or perhaps manifest in a Curtin-Hammett scenario, wherein a given σ -allyl isomer preferentially participates in carbonyl addition. However, while the feasibility of enacting Curtin-Hammett effects by virtue of configurationally dynamic allylmetal intermediates is suggested by stereoconvergence observed in the addition of γ -monosubstituted allylchromium reagents,^{7a,b} γ,γ -disubstituted allylchromium reagents were found to act stereospecifically.^{7c} Here, we report that exceptional levels of *anti*-diastereoselectivity may be obtained in the hydrohydroxyalkylation of 1,1-disubstituted allenes through exploitation of Curtin-Hammett effects. This method, which combines oxidation-construction events, enables diastereoselective formation of all-carbon quaternary centers under catalytic conditions in the absence of pre-metallated nucleophiles or stoichiometric byproducts.^{8,9}

Results and Discussion

In an initial experiment, 1,1-disubstituted allene **1a** was exposed to *p*-nitrobenzyl alcohol **2a** in the presence of a ruthenium catalyst derived upon the combination of $\text{HClRu}(\text{CO})(\text{PPh}_3)_3$ and dippf [dippf = bis(diisopropylphosphino)ferrocene] in THF solvent at 50 °C. Although the desired hydrohydroxyalkylation product **3a** was isolated in excellent yield with complete branched regioselectivity, a modest 2:1 diastereoselectivity was observed. Based on the aforementioned line of reasoning, an assay of counterion was undertaken. Complexes $\text{HXRu}(\text{CO})(\text{dippf})(\text{PPh}_3)_n$ are conveniently prepared *in situ* through the acid base reaction of $\text{H}_2\text{Ru}(\text{CO})(\text{PPh}_3)_3$ and HX (eqn. 1).¹⁰

(1)

It was found for the specific combination of allene **1a** and *p*-nitrobenzyl alcohol **2a**, the ruthenium mesitylenesulfonate complex enforced complete levels of *anti*-diastereoselectivity. Encouraged by these results, the hydrohydroxyalkylation of 1,1-disubstituted allenes **1a–1c** employing alcohols **2a–2g** were explored. In many cases, the chloride counterion provided the highest levels of *anti*-diastereoselectivity. However, in other cases, for example allene **1b**, the BINOL-modified phosphate counterion was most effective in promoting *anti*-diastereoselectivity.¹¹ Finally, whereas dippf was the ligand of choice for allenes **1a** and **1b**, alternate ligands were required to achieved optimal levels of *anti*-diastereoselectivity for the phthalimido-substituted allene **1c**. The assignment of relative stereochemistry for adducts **3a–3g**, **4a–4g** and **5a–5g** is made in analogy to that determined for compound **5a**, which was established *via* single crystal X-ray diffraction analysis, and compound **3c**, which is reported in the literature (Table 1).^{8b}

Under identical reaction conditions, a given allene can display substantially different levels of diastereoselectivity in response to the structure of its transient aldehyde partner. This observation suggests the relative thermodynamic stabilities of the (*Z*)- and (*E*)- σ -allylruthenium intermediates do not alone determine diastereocontrol. Rather, it appears that a Curtin-Hammett scenario is operative, wherein the transient aldehyde influences energetic partitioning of the diastereomeric transition structures. Kinetically controlled diastereoselection is suggested by the fact that the diastereomeric ratio does not change over the course of the reaction. This observation is significant, as reversible carbonyl addition or product oxidation, could potentially occur. However, although secondary alcohol oxidation is in general thermodynamically more favorable than primary alcohol oxidation, further oxidation of the coupling product is not observed. Our collective studies² suggest that coordination of the homoallylic olefin to the catalyst provides a hexa-coordinate, 18-electron complex, suppressing β -hydride elimination through occupation of all available coordination sites. Indeed, in ruthenium catalyzed diene-carbonyl C-C couplings, coordinative saturation of the catalyst could be varied to partition formation of secondary alcohol and ketone products.^{2b} In the present case, resubjecting adduct **3a** to standard coupling conditions in the presence of allene **1a**, which may serve as a hydrogen acceptor, does not result in any oxidation or erosion diastereomeric purity of recovered **3a**, corroborating kinetically controlled carbonyl addition (eqn. 2).

(2)

Notably, when the allene coupling is conducted from the aldehyde oxidation level, diastereoselectivity is essentially absent. For example, whereas 10:1 and 8:1 *anti*-diastereoselectivities are observed in the coupling of allene **1c** to alcohols **2a** and **2c**, respectively, corresponding couplings of aldehydes **6a** and **6c** employing isopropanol as terminal reductant under otherwise identical conditions are not diastereoselective (Table 2). These data suggest that carbonyl addition is no longer turnover-limiting in couplings conducted from the aldehyde oxidation level. There are two probable explanations for this. In reactions conducted from the aldehyde oxidation level, aldehyde concentration is higher throughout the course of the reaction, which should accelerate carbonyl addition. Alternatively, for such sterically congested ruthenium complexes, dehydrogenation of isopropanol, a secondary alcohol, may be slower than primary alcohol dehydrogenation. In either case, Curtin-Hammett effects can no longer be exploited to amplify diastereoselectivity. Consistent with this interpretation, in reactions conducted from the alcohol oxidation level, diastereoselectivity is found to be highly concentration dependent. Presumably, at lower concentration, carbonyl addition is sufficiently slow that the (*E*)- σ -allylruthenium consumed upon addition may be replenished *via* isomerization of the remaining (*Z*)- σ -allylruthenium isomer (Table 3).

To assess whether primary alcohol dehydrogenation is indeed more rapid than carbonyl addition the following competition experiment was performed. Allene **1b** was exposed to equimolar quantities of alcohol **2a** and aldehyde **6b** under standard conditions employing the ruthenium catalyst generated *in situ* from $\text{H}_2\text{Ru}(\text{CO})(\text{PPh}_3)_3$, dppf and *rac*-BINOL- PO_2H at 75 °C in THF solvent (1.0 M). The C-C coupling products **4a** and **4b** were produced in a 1:1 ratio. Under identical conditions employing equimolar quantities of aldehyde **6a** and alcohol **2b**, a nearly identical product ratio of coupling products **4a** and **4b** is observed. These data are consistent with rapid, reversible primary alcohol dehydrogenation in advance of turnover-limiting carbonyl addition (Scheme 1).¹²

Further insight into the catalytic mechanism is provided by deuterium labeling and competition kinetics experiments (Scheme 2).¹³ Exposure of allene **1b** to *d*₂-*p*-nitrobenzyl alcohol under standard coupling conditions delivers *deuterio-4a*, which incorporates deuterium at the carbinol methine (>99% ²H) and at the interior vinylic position (34% ²H), as determined by ¹H and ²H NMR analyses. Complete retention of deuterium at the carbinol methine, along with kinetically controlled anti-diastereoselectivity (*vide supra*), corroborates resistance of the coupling products toward reversible dehydrogenation. Incomplete deuterium incorporation at the interior vinylic position suggests β -hydride elimination of the π -allylruthenium intermediate occurs to furnish diene byproducts. Such byproducts appear to be present in the crude reaction mixture and may account for the requirement of super-stoichiometric loadings of allene. Competition kinetic experiments involving exposure of allene **1b** to equimolar quantities of *p*-nitrobenzyl alcohol and *d*₂-*p*-nitrobenzyl alcohol reveal no significant kinetic effect ($k_{\text{H}}/k_{\text{D}} = 1.06$), within the error limits of the experiment, suggesting alcohol oxidation is not the turn-over limiting event. If carbonyl addition was the turn-over limiting event, an inverse secondary isotope effect

would be anticipated. Given the error limits of the experiment, the absence of such an effect is inconclusive.

Conclusion

In summary, by taking advantage of Curtin-Hammett effects in ruthenium catalyzed alcohol-allene C-C coupling, one bypasses the need to partition trisubstituted σ -allylmetal species in the ground state. Rather, from an equilibrating mixture of transient (*Z*)- and (*E*)- σ -allylruthenium isomers, preferential selection of the (*E*)- σ -allylruthenium species occurs upon energetic partitioning in the transition state for carbonyl addition. Such Curtin-Hammett effects provide a basis for diastereoselective carbonyl allylation to furnish secondary neopentyl homoallylic alcohols, which possess all carbon quaternary centers, thus setting the stage for development of related diastereo- and enantioselective processes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Scheme 1.

Competition experiments corroborating rapid, reversible dehydrogenation in advance of C-C coupling.^a

^aAs described in Table 1. Ar₁ = *p*-NO₂Ph, Ar₂ = *p*-CF₃Ph. Products **4a** and **4b** are obtained as 1:1.5 (*syn:anti*) diastereomeric mixtures.

Scheme 2. Deuterium labeling and competition kinetics experiments.^a^aAs described in Table 1. Ar = *p*-NO₂Ph,

Table 1

Oxidation level dependent *anti*-diastereoselectivity in ruthenium catalyzed couplings of allene **1c**.

Entry	X	Alcohol	R	Ligand, T (M)	Yield (dr)
1	OMes	2a	<i>p</i> -NO ₂ Ph	A, 50 °C (1 M)	3a , 84% (>20:1) ^d
2	Cl	2b	<i>p</i> -CF ₃ Ph	A, 40 °C (0.5 M)	3b , 85% (4:1)
3	Cl	2c	Ph	A, 60 °C (0.5 M)	3c , 99% (6:1)
4	Cl	2d	2-Furyl	A, 60 °C (0.5 M)	3d , 99% (10:1)
5	Cl	2e	HC=CHPh	A, 60 °C (0.2 M)	3e , 99% (5:1)
6	Cl	2f	<i>n</i> -Hexyl	A, 75 °C (1 M)	3f , 77% (>20:1) ^{c,d}
7	Cl	2g	(CH ₂) ₃ OBn	A, 75 °C (1 M)	3g , 67% (>20:1) ^{c,d}

Entry	X	Alcohol	R	Ligand, T (M)	Yield (dr)
8	O ₂ PBinol	2a	<i>p</i> -NO ₂ Ph	A, 75 °C (1 M)	4a , 97% (16:1)
9	O ₂ PBinol	2b	<i>p</i> -CF ₃ Ph	A, 75 °C (1 M)	4b , 93% (>20:1)
10	O ₂ PBinol	2c	Ph	A, 95 °C (1 M)	4c , 85% (17:1)
11	O ₂ PBinol	2d	2-Furyl	A, 95 °C (1 M)	4d , 71% (15:1)
12	O ₂ PBinol	2e	HC=CHPh	A, 95 °C (1 M)	4e , 94% (14:1)
13	Cl	2f	<i>n</i> -Hexyl	A, 95 °C (1 M)	4f , 86% (4:1) ^{c,d}
14	Cl	2g	(CH ₂) ₃ OBn	A, 95 °C (1 M)	4g , 69% (4:1) ^{c,d}

Entry	X	Alcohol	R	Ligand, T (M)	Yield (dr)
15	Cl	2a	<i>p</i> -NO ₂ Ph	C, 95 °C (0.5 M)	5a , 83% (10:1)
16	Cl	2b	<i>p</i> -CF ₃ Ph	C, 95 °C (0.5 M)	5b , 65% (14:1)
17	Cl	2c	Ph	B, 75 °C (0.5 M)	5c , 99% (8:1) ^d
18	O ₃ SCam.	2d	2-Furyl	A, 85°C (1 M)	5d , 84% (7:1)
19	Cl	2e	HC=CHPh	B, 85°C (0.1 M)	5e , 99% (5:1) ^d
20	Cl	2f	<i>n</i> -Hexyl	A, 95°C (1 M)	5f , 93% (>20:1) ^{c,d}
21	Cl	2g	(CH ₂) ₃ OBn	A, 85°C (1 M)	5g , 72% (>20:1) ^d

^aYields are of isolated material. Diastereoselectivity was determined via ¹H NMR analysis of crude reaction mixtures. See supporting information for further experimental details.

^bLigands: A = dipfpf (5 mol %); B = dCypf, (5 mol%); C = PPh₂Cy (15 mol %).

^cThree equivalents of allene.

^d48 hours.

Table 2Oxidation level dependent *anti*-diastereoselectivity in ruthenium catalyzed couplings of allene **1c**.^a

Reaction scheme showing the coupling of allene **1c** (200 mol %) with various alcohols or aldehydes (**2a, 2c** or **6a, 6c**, 100 mol %) using $\text{HClRu}(\text{CO})(\text{PPh}_3)_3$ (5 mol %) as the catalyst and ligand in THF (0.5 M). The reaction conditions are specified for different substrates and temperatures. The products are **5a, 5c**, showing *anti*-diastereoselectivity.

Entry	Oxidation Level	R	Ligand	Yield (dr)
1	Alcohol, 2a	<i>p</i> -NO ₂ Ph	CyPPh ₂ (15 mol%)	5a , 83% (10:1)
2	Aldehyde, 6a	<i>p</i> -NO ₂ Ph	CyPPh ₂ (15 mol%)	5a , 99% (1:1)
3	Alcohol, 2c	Ph	dCypf (5 mol%)	5c , 99% (8:1)
4	Aldehyde, 6c	Ph	dCypf (5 mol%)	5c , 72% (1:1)

^a As described in Table 1.

Table 3

Concentration dependent *anti*-diastereoselectivity in ruthenium catalyzed couplings of allene **1c**.

Entry	Alcohol	X	T °C	THF (conc.)	Yield (dr)
1	2a	Cl	95 °C	1.0 M	5a , 87% (6:1)
2	2a	Cl	95 °C	0.5 M	5a , 83% (10:1)
3	2a	Cl	95 °C	0.2 M	5a , 55% (> 20:1)
4	2d	O ₃ S-Camphor	85 °C	0.5 M	5d , 72% (2:1)
5	2d	O ₃ S-Camphor	85 °C	0.2 M	5d , 79% (4:1)
6	2d	O ₃ S-Camphor	85 °C	0.1 M	5d , 82% (5:1)

^a As described in Table 1.