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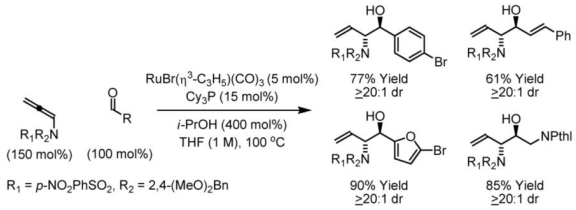
anti-Aminoallylation of Aldehydes *via* Ruthenium Catalyzed Transfer Hydrogenative Coupling of Sulfonamido-Allenes:

1,2-Aminoalcohols

Eduardas Skucas, **Jason R. Zbieg**, and **Michael J. Krische**
University of Texas at Austin, Department of Chemistry and Biochemistry, Austin, TX 78712

Abstract



Ruthenium catalyzed transfer hydrogenation of *N*-sulfonamido allene **1e** in the presence of aromatic aldehydes **2a-2f**, α,β-unsaturated aldehydes **2g-2i** and aliphatic aldehydes **2j-2l** results in reductive coupling to furnish *anti*-aminoallylation products **3a-3l**. Reductive coupling of allenamide **1e** to aldehyde **2a** conducted using d_8-isopropanol as terminal reductant delivers *deuterio*-**3a**. The observed pattern of deuterium incorporation suggests reversible allene hydrometallation with incomplete regioselectivity in advance of carbonyl addition. A survey of mono-substituted allenes **1f-1i** was conducted. High levels of *anti*-diastereoselectivity only are observed using *tert*-butyl allene **1f**. This protocol represents an alternative to the use of amino-substituted allylborane reagents in carbonyl amino-allylation and avoids the use of stoichiometric metallic reagents.

Classical protocols for the addition of non-stabilized carbanions to carbonyl compounds and imines rely upon the use of preformed organometallic reagents. Recent studies from our laboratory demonstrate that simple unsaturates (alkenes, alkynes and allenes) serve as non-stabilized carbanion equivalents under the conditions of hydrogenation and transfer hydrogenation.[1] This concept has evoked a diverse set of methods for catalytic carbonyl vinylation,[2,3] allylation,[4,5] propargylation[6] and aldol addition.[7] Unlike their classical counterparts, such hydrogenative carbonyl additions occur under essentially neutral conditions, avoid generation of stoichiometric metallic byproducts and, in certain cases, may be conducted directly from the alcohol oxidation level.[1c,2f,4b-f,5a,b,6]

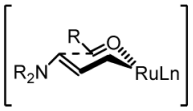
Whereas diastereo- and enantioselective carbonyl allylation and crotylation is achieved under the conditions of iridium catalyzed transfer hydrogenation,[4b-f] related ruthenium catalyzed allylations lack stereocontrol.[1c,5] Here, we report that sulfonamido-allenes engage aldehydes in highly *anti*-diastereoselective reductive addition to deliver vinyl-substituted 1,2-amino alcohols.[8-12] This process represents a new functional group interconversion and an alternative to the use of amino-substituted allylborane reagents in carbonyl amino-allylation.[12]

E-mail: mkrische@mail.utexas.edu.

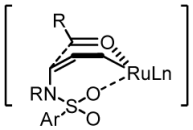
Initial studies focused on the reductive coupling of sulfonamido allenes **1a**-**1e**, to *p*-nitrobenzaldehyde **2a**. A range of ruthenium catalysts were assayed: $Ru(O_2CCF_3)_2(CO)(PPh_3)_2$, $RuHCl(CO)(PPh_3)_3$, $RuH_2(CO)(PPh_3)_2$, $RuCl_2(CO)_2(PPh_3)_2$ and $RuBr(\eta^3\text{-}C^3H_5)(CO)_3$. In accord with earlier studies on the reductive coupling of 1,1-disubstituted allenes to aldehydes,[5c] $RuBr(\eta^3\text{-}C_3H_5)(CO)_3$ was unique in its ability to catalyze C-C bond formation. Yet in stark contrast to earlier observations, substantial levels of *anti*-diastereocontrol were observed (Table 1 entries 1-5). Indeed, using allenamide **1e**, which incorporates *p*-nitrobenzenesulfonyl and 2,4-dimethoxybenzyl protecting groups, aldehyde **2a** is converted to the 2-sulfonamido-homoallyl alcohol **3a** in 91% isolated yield with complete regio- and *anti*-diastereoselectivity, as determined by ^1H NMR and single crystal X-ray diffraction analysis (Table 1 entry 5).

To explore the scope of this process, allenamide **1e** was coupled to structurally diverse aldehydes **2a**-**2l**. Aromatic aldehydes **2a**-**2f** are transformed to adducts **2a**-**2f** as single diastereomers, α,β-unsaturated aldehydes **2g**-**2i** are transformed to adducts **3g**-**3i** as single diastereomers, and aliphatic aldehydes bearing α-heteroatoms **2j**-**2k** are converted to *anti*-aminoallylation products **3j**-**3k** in good yield and with complete *anti*-diastereocontrol. Finally, as demonstrated by the conversion of **2l** to **3l**, simple unactivated aliphatic aldehydes engage in highly *anti*-diastereoselective reductive coupling (Table 2). In general, it was found that conversion improves upon use of more electrophilic aldehydes. For less activated aldehydes, higher loadings of allene **1e** (200 mol%) are required to enforce high conversion. To explore the utility of the aminoallylation products, adduct **3j** was converted to the fully protected nonproteinogenic amino acids **4b** and **4c.** Notably, the *p*-nitrobenzenesulfonyl and 2,4-dimethoxybenzyl protecting groups are subject to removal under mild conditions (Scheme 1).

One possible model to account for the observed branch-regioselectivity and *anti*-diastereoselectivity involves regio- and stereoselective allene hydrometallation at the π-face distal and opposite to the sulfonamido moiety to provide the primary (*Z*)-σ-allylruthenium intermediate. Internal chelation to the sulfonamido oxygen[13] may stabilize the kinetic (*Z*)-σ-allyl haptomer, which must then engage the aldehyde through a boat-like transition structure. Alternatively, the kinetic (*Z*)-σ-allyl haptomer may isomerize to the (*E*)-σ-allyl haptomer, which must then engage the aldehyde through a chair-like transition structure.

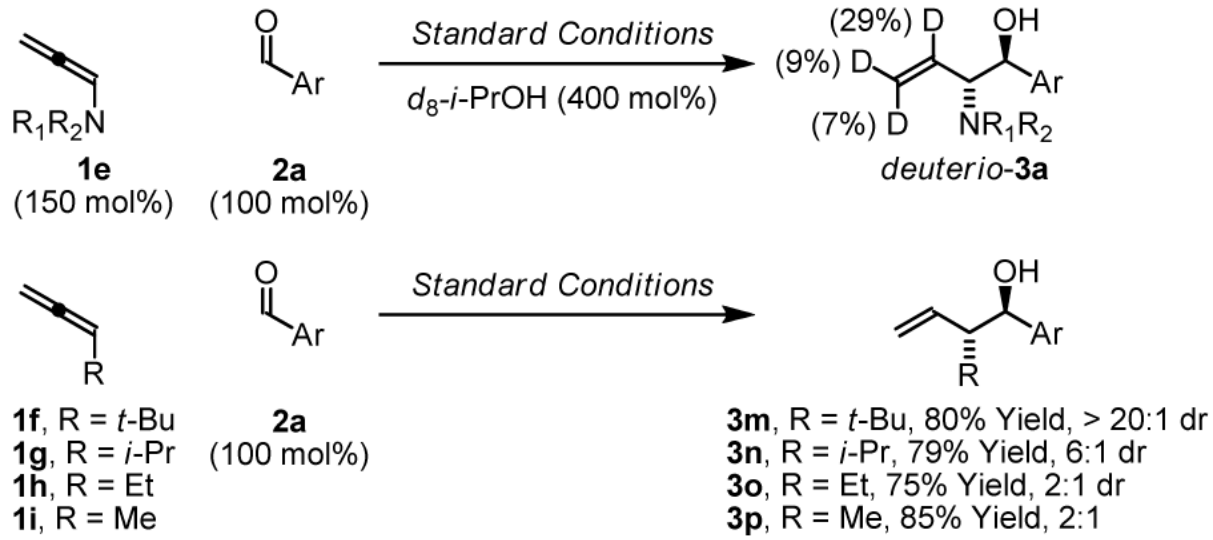


E-Allylruthenium
Chair-Like Transition Structure



Z-Allylruthenium
Boat-Like Transition Structure

To gain further mechanistic insight, and potentially discriminate between the aforementioned reaction pathways, the coupling of allenamide **1e** to aldehyde **2a** was conducted using d_8-isopropanol as terminal reductant. The product, *deuterio*-**3a**, incorporates deuterium at the internal vinylic position (29%) and terminal vinylic positions (9% and 7%). These data suggest reversible allene hydrometallation with incomplete regioselectivity in advance of carbonyl addition.[14] Finally, a series of alkyl-substituted allenes **1f**-**1i** were coupled to aldehyde **2a** under standard conditions to deliver adducts **3m**-**3p**. Notably, high levels of *anti*-diastereoselectivity only are observed using *tert*-butyl allene **1f**, as corroborated by single crystal X-ray diffraction analysis of **3m**. These data reveal that internal chelation to the sulfonamido oxygen[13] is not required for high levels of *anti*-diastereoselectivity, corroborate intervention of the (*E*)-σ-allyl haptomer and a chair-like transition structure.



In summary, we report an *anti*-diastereoselective reductive coupling of sulfonamido-allenes and aldehydes under the conditions of ruthenium catalyzed transfer hydrogenation. This protocol circumvents the use of stoichiometric metallic reagents in carbonyl aminoallylation and represents the first stereocontrolled C-C bond forming hydrogenation based on a ruthenium catalyst. Enantioselective variants of this processes are currently under investigation.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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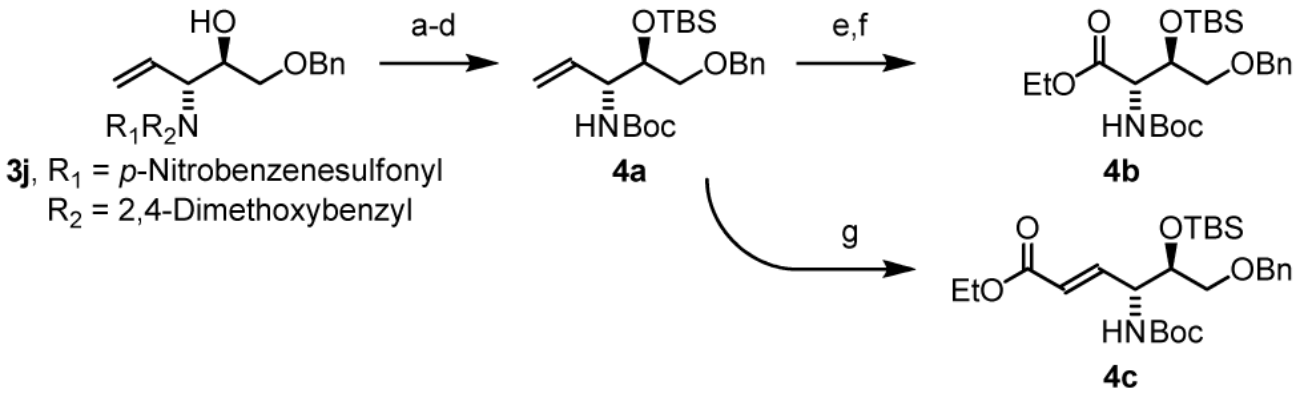


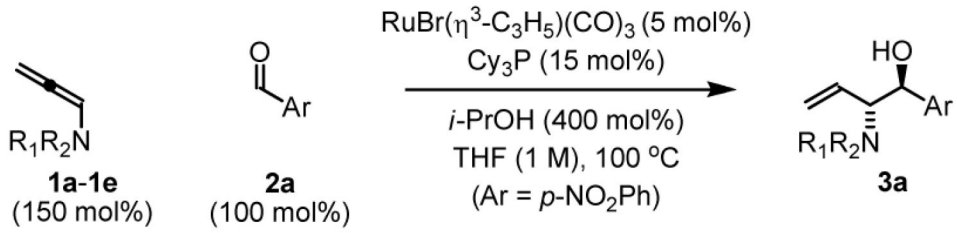
Scheme 1.

Elaboration of aminoallylation product **3j** to nonproteinogenic amino acid esters **4b** and **4c**.[a] **Reagents**: (a) TFA, PhMe-PhOMe, 25 °C, 89% Yield. (b) TBSOTf, 2,6-Lutidine, DCM, 25 °C, 88% Yield. (c) PhSH, Cs_2CO_3, MeCN, 50 °C. (d) Boc_2O, MeCN, 25 °C, 79% Yield Over 2 Steps. (e) $NaIO_4$, $RuCl_3(H_2O)$ (5 mol%), MeCN-CCl_4-H_2O, 25 °C. (f) $TMSCHN_2$, $CHCl_3$-MeOH, 25 °C, 67% Yield Over 2 Steps. (g) $MeO_2CCH{=}CH_2$, Hoveyda-Grubbs-II (5 mol%), DCM, 40 °C, 91% Yield, 20:1 Z:E.

[a]In all cases, cited yields are of isolated material. See Supporting Information for detailed experimental procedures.

Table 1

anti-Diastereoselective aminoallylation of aldehydes *via* ruthenium catalyzed transfer hydrogenative coupling of *N*-substituted allenes **1a**-**1e**[a]



Entry	Allene	R_1	R_2	Yield 3a (dr)
1	**1a**	*p*-Toluenesulfonyl	Benzyl	92% (5:1)
2	**1b**	Phthalimido	---	37% (3:1)
3	**1c**	Boc	Benzyl	71% (8:1)
4	**1d**	*o*-Nitrobenzenesulfonyl	Benzyl	59% (≥ 20:1)
5	**1e**	*p*-Nitrobenzenesulfonyl	2,4-Dimethoxybenzyl	91% (≥ 20:1)

[a] In all cases, cited yields are of isolated material. See Supporting Information for detailed experimental procedures.

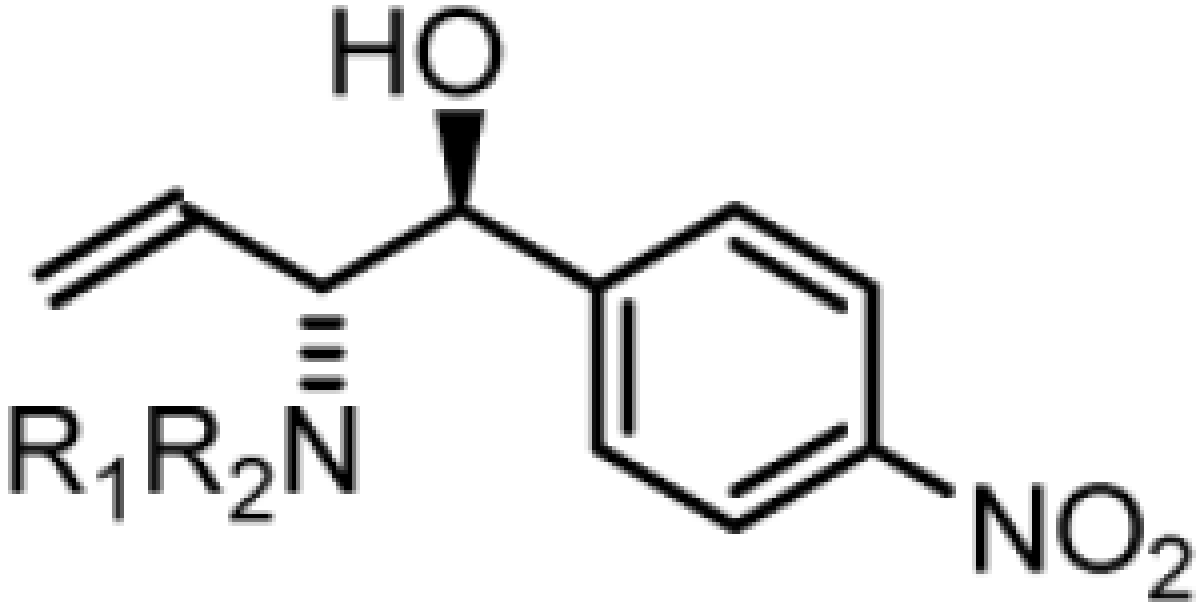
Table 2

Ruthenium catalyzed transfer hydrogenative coupling sulfonamido-allene **1e** to aldehydes **2a**-**2l**[a]

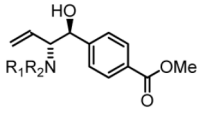
1e
(150 m

2a, R = *p*-
2b, R = P
2c, R = *p*-
2d, R = *p*-

Coupling to Aryl Aldehydes

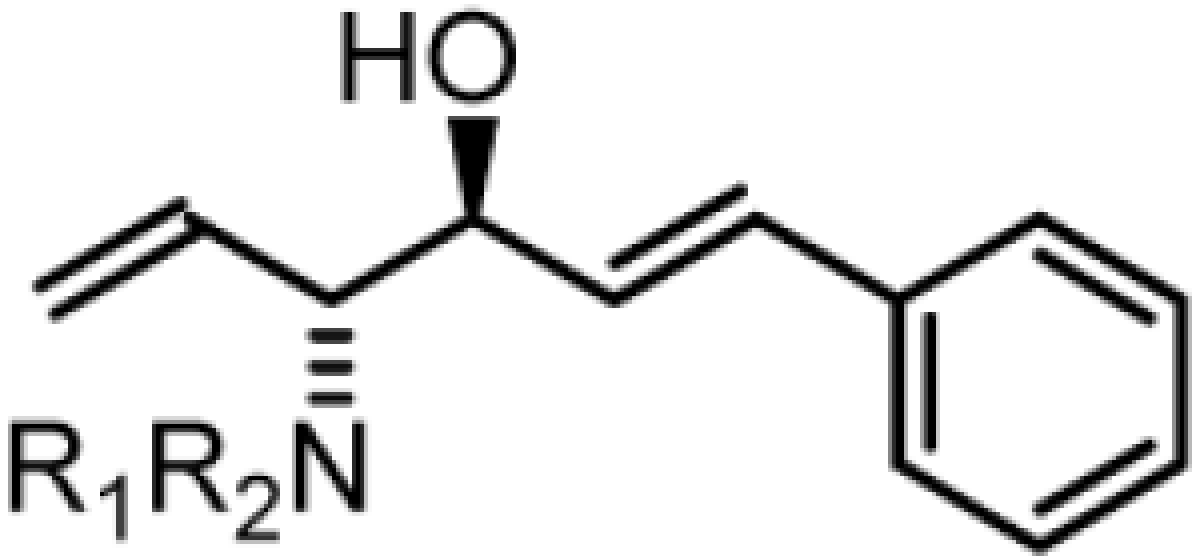


91% Yield, **3a**



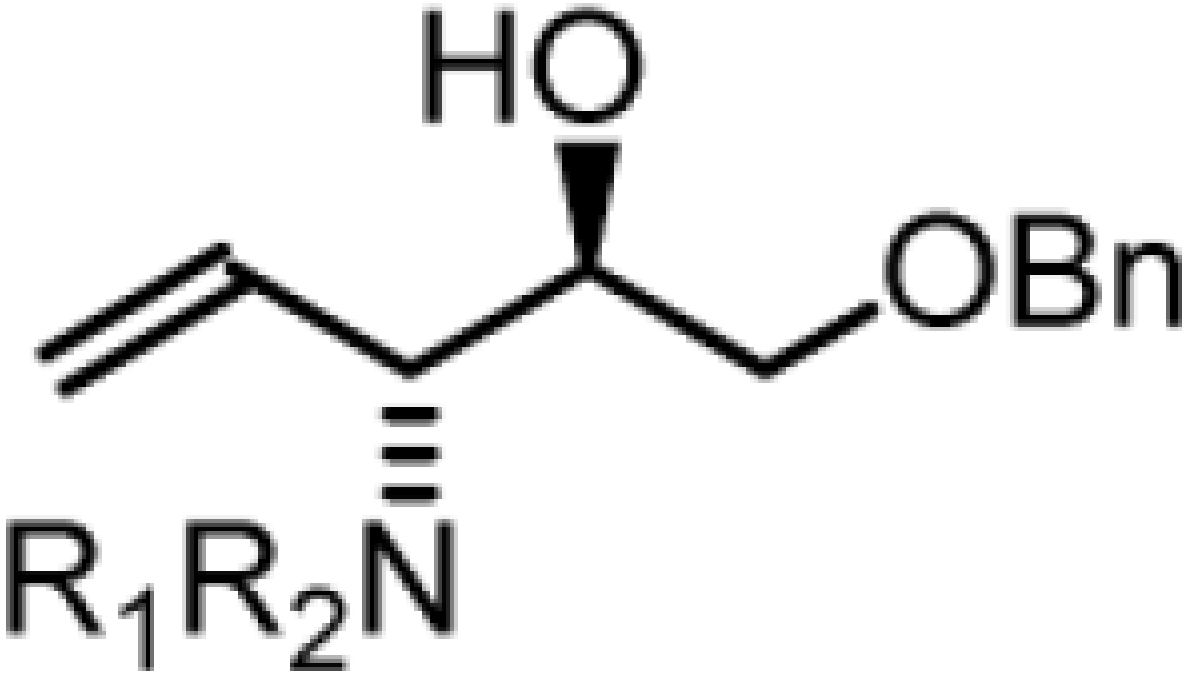
94% yield, **3d**

Coupling to Enals



61% Yield, **3g**[b]

Coupling to Aliphatic Aldehydes



77% Yied, **3j**

[a] In all cases, cited yields are of isolated material and represent the average of two runs. In each case, >20:1 anti-diastereoselectivity is observed, as determined by ^{1}H NMR analysis. See Supporting Information for detailed experimental procedures.

[b] Two equivalents of allene **1e** were used.