J|A|C|S COMMUNICATIONS

Published on Web 03/24/2009

anti-Aminoallylation of Aldehydes via Ruthenium-Catalyzed Transfer Hydrogenative Coupling of Sulfonamido Allenes: 1,2-Aminoalcohols

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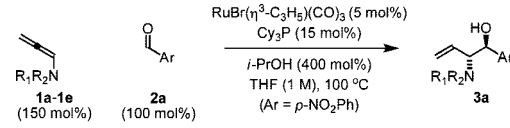
Classical protocols for the addition of nonstabilized carbanions to carbonyl compounds and imines rely upon the use of preformed organometallic reagents. Recent studies from our laboratory demonstrate that simple unsaturates (alkenes, alkynes, and allenes) serve as nonstabilized carbanion equivalents 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 are 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-aminoalcohols.[8−12] This process represents a new functional group interconversion and an alternative to the use of amino-substituted allylborane reagents in carbonyl aminoallylation.[12]

Initial studies focused on the reductive coupling of sulfonamido allenes **1a**−**e** to *p*-nitrobenzaldehyde (**2a**). Several 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. However, 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 ^{1}H 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**−**l** (Table 2). Aromatic aldehydes **2a**−**f** were transformed to adducts **3a**−**f** as single diastereomers, α,β-unsaturated aldehydes **2g**−**i** to adducts **3g**−**i** as single diastereomers, and aliphatic aldehydes **2j** and **2k** bearing α-heteroatoms to the corresponding *anti*-aminoallylation products **3j** and **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 %) were 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** (Scheme 1). Notably, the *p*-nitrobenzenesulfonyl and 2,4-dimethoxybenzyl protecting groups were subject to removal under mild conditions.

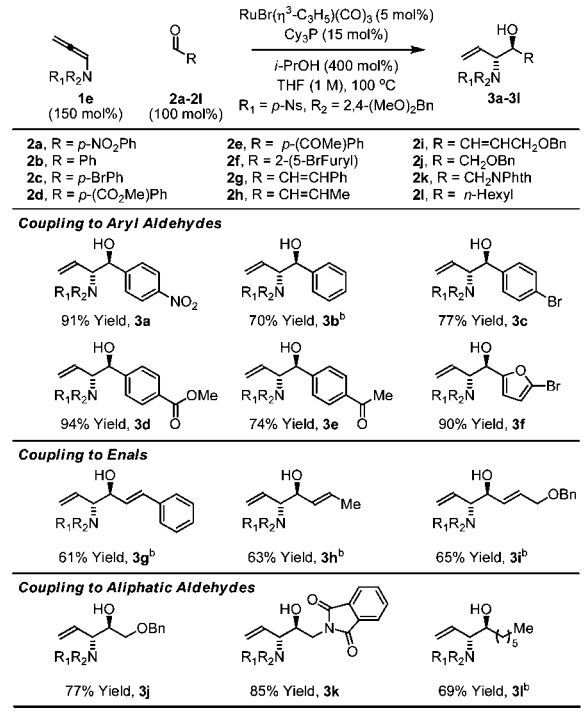
Table 1. Diastereoselective *anti*-Aminoallylation of Aldehydes via Ruthenium-Catalyzed Transfer Hydrogenative Coupling of N-Substituted Allenes **1a**−**e**[a]



entry	allene	R_1	R_2	**3a** % yield (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	50 (≥20:1)
5	**1e**	*p*-nitrobenzenesulfonyl	2,4-dimethoxybenzyl	91 (≥20:1)

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

Table 2. Ruthenium-Catalyzed Transfer Hydrogenative Coupling of Sulfonamido Allene **1e** to Aldehydes **2a**−**l**[a]

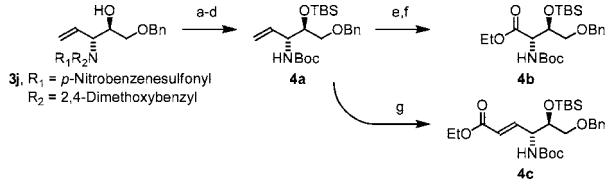


[a] In all cases, cited yields are of isolated material and represent the average of two runs. In each case, >20:1 *anti*-diastereoselectivity was observed, as determined by ^{1}H NMR analysis. See the Supporting Information for detailed experimental procedures. [b] Using 2 equiv of allene **1e**.

One possible model to account for the observed branch regioselectivity and *anti*-diastereoselectivity involves regio- and stereoselective allene hydrometalation at the π-face distal and opposite to the

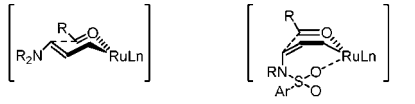
10.1021/ja900827p CCC: $40.75

Scheme 1. Elaboration of Aminoallylation Product **3j** to Nonproteinogenic Amino Acid Esters **4b** and **4c**[a]



[a] Reagents and conditions: (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*. In all cases, cited yields are of isolated material. See the Supporting Information for detailed experimental procedures.

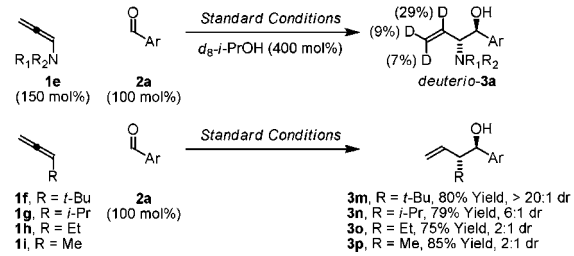
sulfonamido moiety to provide the primary (*Z*)-σ-allylruthenium intermediate. Internal chelation to the sulfonamido oxygen[13] may stabilize the kinetic (*Z*)-σ-allyl haptomer, which must then engage the aldehyde through a boatlike transition structure. Alternatively, the kinetic (*Z*)-σ-allyl haptomer 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 2-propanol-d_8 as a 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 hydrometalation with incomplete regioselectivity in advance of carbonyl addition.[14] Finally, a series of alkyl-substituted allenes **1f**−**i** were coupled to aldehyde **2a** under standard conditions to deliver adducts **3m**−**p**. Notably, high levels of *anti*-diastereoselectivity were observed only when *tert*-butyl allene **1f** was used, 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, corroborating the intervention of the (*E*)-σ-allyl haptomer and a chairlike 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 process are currently under investigation.

Acknowledgment. The Robert A. Welch Foundation and the NIH−NIGMS (RO1-GM069445) are acknowledged for partial support of this research. E.S. thanks the Livingston Endowment for a graduate fellowship.

Supporting Information Available: Experimental procedures, spectral data for new compounds, and single-crystal X-ray diffraction data for compounds **3a** and **3m** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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JA900827P