Communication

Highly Enantioselective and Regioselective Nickel-Catalyzed Coupling of Allenes, Aldehydes, and Silanes

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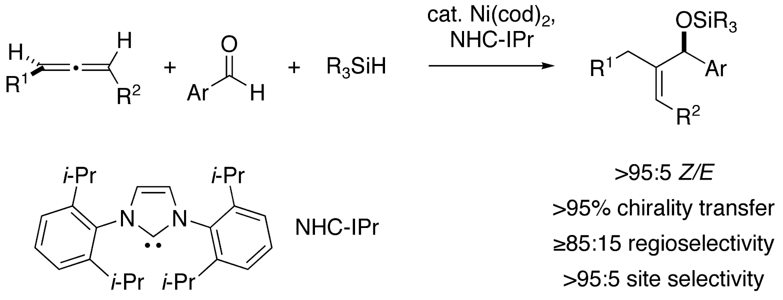
J. Am. Chem. Soc., **2005**, 127 (20), 7320-7321• DOI: 10.1021/ja0521831 • Publication Date (Web): 29 April 2005



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Highly Enantioselective and Regioselective Nickel-Catalyzed Coupling of Allenes, Aldehydes, and Silanes

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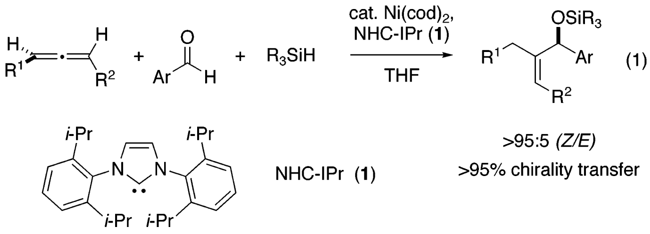
Received April 5, 2005; E-mail: tfj@mit.edu

Catalytic, stereoselective multicomponent coupling reactions assemble highly functionalized molecules in a single operation from very simple precursors.[1] We and others have developed several such reactions that involve catalytic reductive coupling of alkynes with common functional groups, such as aldehydes,[2] epoxides,[3] and imines.[4] Allenes,[5] however, have received far less attention in this context.[6] Moreover, nearly all existing classes of intermolecular reactions between allenes and aldehydes involve the coupling of an sp^2-hybridized carbon with the carbonyl group, affording either homoallylic alcohols (multicomponent coupling reactions)[6] or homopropargylic alcohols (allenylmetal additions).[7] We report here a rare example of the alternative, that is, the intermolecular addition of an electrophile to the central, sp-hybridized,[8] and ostensibly *least* nucleophilic carbon of an unactivated allene (eq 1).[9] Among intermolecular transition-metal-catalyzed multicomponent coupling reactions involving allenes and aldehydes, these are the first that give allylic (as opposed to homoallylic[6]) alcohol derivatives, the first that are reductive (instead of alkylative[6]), and finally, the first that are highly enantioselective.[10]



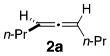
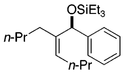
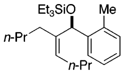
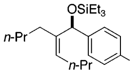
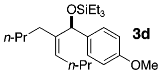
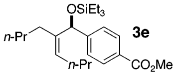
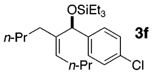
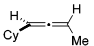
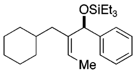
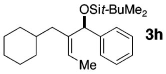
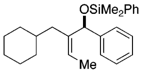
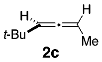
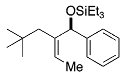
(1)

In examining combinations of allenes, aldehydes, and reducing agents, we found that a species derived from Ni(cod)$_2$ and tricyclopentylphosphine (Cyp$_3$P) catalyzed a novel, efficient, and selective three-component coupling process[11] when Et$_3$SiH was used (Table 1, entry 1). The ratio of allylic and homoallylic products (i.e., coupling at the sp vs an sp^2 carbon) was >95:5, and only the *Z* allylic alcohol was detected,[12] but there was significant erosion of enantiomeric purity, from 95 to 62% ee.

The use of the imidazolinyl carbene ligand NHC−IPr[13,14] (**1**, entry 2) completely eliminated this limitation, a case of a dependence of enantioselectivity upon the nature of an *achiral* ligand. Chirality transfer is commonly observed in intramolecular reactions of enantiomerically enriched allenes,[15] but the vast majority of intermolecular examples[16] involve allenylmetal additions.[5,7c] Moreover, only achiral, racemic, or 1:1 mixtures of diastereomeric allenes were used in all previous multicomponent coupling reactions.[6] Thus, the transfer of allene axial chirality in such processes is now documented for the first time.

Other noteworthy features include the compatibility of these carbon−carbon bond-forming reactions with Lewis basic ethers, esters, and aryl chlorides (entries 5−7) and, in the case of differentially substituted 1,3-allenes, the complete site selectivity (which double bond reacts) in the formation of the allylic product (entries 8−11). Other organosilanes can also be employed, giving the user flexibility with respect to which silyl "protective group" is incorporated (entries 9 and 10).

Table 1. Nickel-Catalyzed, Enantioselective Three-Component Coupling of Allenes, Aldehydes, and Organosilanes[a]

entry	allene	product	allylic: homoallylic [b,c]	yield (allylic),[d] *Z* / *E* [c]	site selectivity [c]	ee (%) [e]
1 [f]	 **2a** (95% ee)	 **3a**	>97:3	77%, >95:5	n.a.	62
2	**2a**	**3a**	94:6	80%, >95:5	n.a.	95
3	**2a**	 **3b**	90:10	70%, >95:5	n.a.	95
4	**2a**	 **3c**	95:5	74%, >95:5	n.a.	95
5	**2a**	 **3d**	93:7	75%, >95:5	n.a.	95
6	**2a**	 **3e**	90:10	56%, >95:5	n.a.	95
7 [g]	**2a**	 **3f**	90:10	66%, >95:5	n.a.	95
8	 **2b** (98% ee)	 **3g**	93:7	76%, >95:5	>95:5	98
9	**2b**	 **3h**	90:10	68%, >95:5	>95:5	98
10	**2b**	 **3i**	93:7	65%, >95:5	>95:5	98
11	 **2c** (98% ee)	 **3j**	85:15	40%, >95:5	>95:5	98

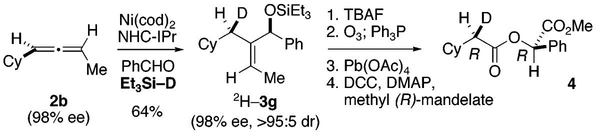
[a] See eq 1. Standard conditions: to a solution of Ni(cod)$_2$ (20 mol %) and **1** (40 mol %) in THF at −78 °C were added the allene (100 mol %), aldehyde (300 mol %), and silane (300 mol %). The mixture was warmed to ambient room temperature over 6 h, stirred 12 h, and purified by chromatography (SiO$_2$). Absolute configuration determined by Mosher ester analysis. See Supporting Information. [b] Ratio of allylic to the sum of all homoallylic products. [c] Determined by ^{1}H NMR of unpurified reaction mixtures. [d] Isolated yield of allylic alcohol shown. [e] Determined by chiral HPLC. [f] Cyp$_3$P (20 mol %) was used in place of **1**. [g] ^{1}H NMR of crude reaction mixture indicated a 94:6 ratio of **3f**:**3a** (reductive dechlorination).

Two aspects of the complete preference for the *Z* alkene geometry deserve further comment. In related reductive coupling reactions involving alkynes, *E* allylic alcohols are formed exclusively (cis addition of H and RCHO across the triple bond).[2] Allenes and alkynes are thus complementary to one another in this regard. Second, the *Z* geometry corresponds to attachment of the aldehyde to the *more hindered* face of the allene. In a similar vein, the site

10.1021/ja0521831 CCC: $30.25 © 2005 American Chemical Society

selectivity observed with allenes **2b** and **2c** (entries 8−11) suggests addition across the *more hindered* double bond.

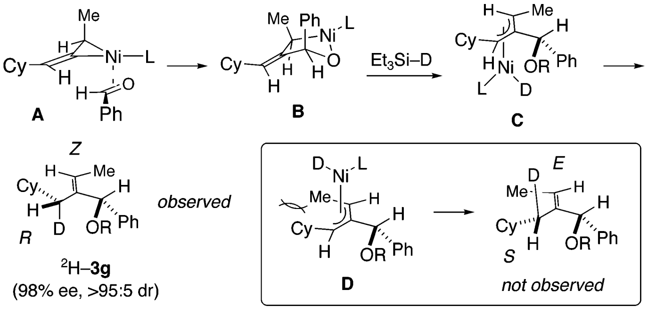
The results of a deuterium labeling experiment provided information critical to the development of an explanation for these surprising results. We repeated a previous experiment (entry 8), using Et_3SiD (97% D) in place of Et_3SiH (eq 2). Slightly lower allylic:homoallylic selectivity (89:11) was observed, but ^{2}H-**3g** had the same enantiomeric excess, *Z*/*E* ratio, and site selectivity as that of **3g**. Deuterium incorporation occurred at a single site and with >95:5 diastereoselectivity. The configuration was assigned as *R* by converting ^{2}H-**3g** to the known 2-^{2}H-cyclohexylacetic acid, esterifying with methyl (*R*)-mandelate, and comparing ^{1}H NMR spectra of the product (**4**) and the corresponding unlabeled ester.[17]



(2)

The results of this experiment can be accounted for by the sequence of events shown in Scheme 1. Back-bonding likely induces significant deformation from linearity of the allene, and of the four isomeric 1:1:1 complexes of Ni, NHC−IPr (L), and allene **2b**, only **A** places the large Ni−L complex on the less hindered allene face *and* less substituted double bond. The sense of induction may be explained by benzaldehyde coordination away from the methyl group with the Ph group placed between L and (cyclohexyl)-methylidene, reorganization to allow overlap between a C−Ni bond and π^*, and oxidative addition to give metallacycle **B**.

Scheme 1



We believe that there is a direct link between the selectivity for the *Z* alkene geometry and the sense of induction of deuterium labeling. σ-Bond metathesis between **B** and Et_3SiD could afford η^3-allyl−Ni complex **C**. Reductive elimination with retention leads to the observed *Z* alkene and *R* configuration at the labeled carbon. Conversely, the alternative complex (**D**) gives the opposite sense of selectivity in *both* cases (*E* and *S*, respectively). Our explanation for the absence of this product is the severe 1,3-interaction between the Me and Cy groups present in **D**.

Finally, the overall site selectivity avoids formation of the more congested alkene (Cy vs Me), and this bias appears to be operative in the transition state of reductive elimination from **C**.

In summary, this enantioselective, three-component coupling occurs by way of a previously unobserved process in allene−aldehyde reactions and is promoted by a Ni−NHC complex that transfers the axial chirality of the allene to the product with very high fidelity. This catalyst also possesses the qualities necessary to induce a surprising sense and degree of *Z*/*E* and site selectivity. The implementation of this single-step formation of synthetically useful, silyl-protected *Z* allylic alcohols in the synthesis of complex molecules is currently under investigation.

Acknowledgment. Support for this work was provided by the National Institute of General Medical Sciences (GM-063755). We also thank the NIGMS (GM-072566), NSF (CAREER CHE-0134704), Amgen, Boehringer Ingelheim, Bristol Myers-Squibb, GlaxoSmithKline, Johnson & Johnson, Merck Research Laboratories, Pfizer, the Sloan Foundation, Wyeth, and the Deshpande Center (MIT) for generous financial support. We are grateful to Dr. Li Li for obtaining mass spectrometric data for all compounds (MIT Department of Chemistry Instrumentation Facility, which is supported in part by the NSF (CHE-9809061 and DBI-9729592) and the NIH (1S10RR13886-01)).

Supporting Information Available: Experimental procedures and data for all new compounds (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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JA0521831