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Mechanistic Implications of Nickel-Catalyzed Reductive Coupling of Aldehydes and Chiral 1,6-Enynes

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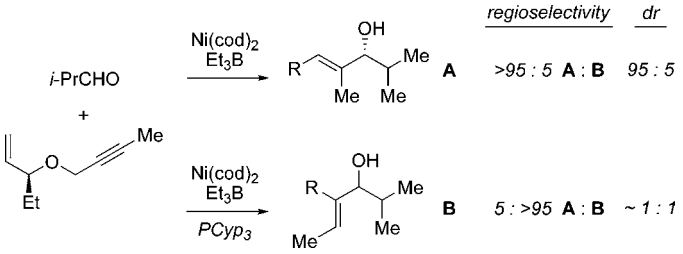
ABSTRACT

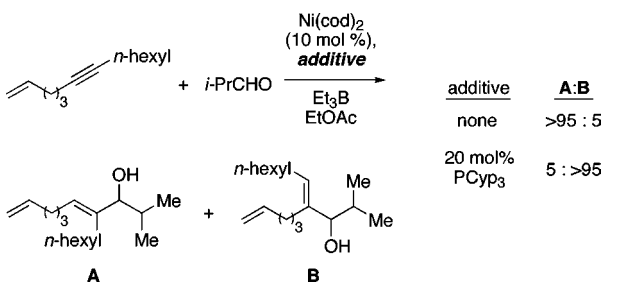


A study of nickel-catalyzed reductive coupling reactions of aldehydes and chiral 1,6-enynes has provided evidence for three distinct mechanistic pathways that govern regioselectivity in this transformation. In the absence of a phosphine additive, high regioselectivity and high diastereoselectivity are obtained as a direct result of coordination of both the alkyne and the olefin to the metal center during the C–C bond-forming step.

Nickel-catalyzed reductive coupling of alkynes and aldehydes has emerged as an efficient and selective method for the synthesis of allylic alcohols.[1] Enantioselective coupling reactions have been achieved through the use of chiral monodentate phosphines,[2] and several different classes of alkynes afford coupling products in excellent regioselectivity.[3]

Recently, we reported a highly regioselective reductive coupling of 1,6-enynes and aldehydes (Scheme 1) in which the sense of regioselectivity was completely reversed upon the addition of catalytic amounts of tricyclopentylphosphine ($PCyp_3$).[3e] We proposed that this remarkable inversion was the result of two distinct mechanistic pathways: one involving an oxametallacycle and one involving alkyne hydrometalation.

Scheme 1



Herein we report that further investigation of coupling reactions involving chiral 1,6-enynes has afforded evidence to support an alternate theory, one in which *both* pathways proceed via a common oxametallacycle, but regioselectivity

(1) Review: Montgomery, J. *Angew. Chem., Int. Ed.* **2004**, *43*, 3890−3908.

(2) (a) Miller, K. M.; Huang, W.-S.; Jamison, T. F. *J. Am. Chem. Soc.* **2003**, *125*, 3442−3443. (b) Colby, E. A.; Jamison, T. F. *J. Org. Chem.* **2003**, *68*, 156−166.

(3) (a) Oblinger, E.; Montgomery, J. *J. Am. Chem. Soc.* **1997**, *119*, 9065−9066. (b) Huang, W.-S.; Chan, J.; Jamison, T. F. *Org. Lett.* **2000**, *2*, 4221−4223. (c) Mahandru, G. M.; Liu, G.; Montgomery, J. *J. Am. Chem. Soc.* **2004**, *126*, 3698−3699. (d) Miller, K. M.; Luanphaisarnnont, T.; Molinaro, C.; Jamison, T. F. *J. Am. Chem. Soc.* **2004**, *126*, 4130−4131. (e) Miller, K. M.; Jamison, T. F. *J. Am. Chem. Soc.* **2004**, *126*, 15342−15343.

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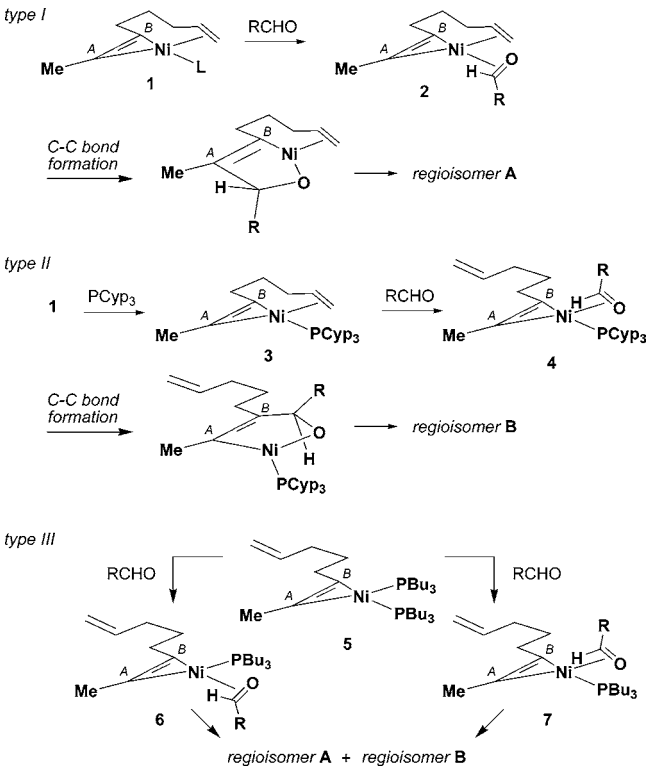
is determined by stereospecific ligand substitution at the nickel center.

The three proposed mechanistic pathways for the reductive coupling of 1,6-enynes and aldehydes under varying conditions are illustrated in Scheme 2.

Scheme 2



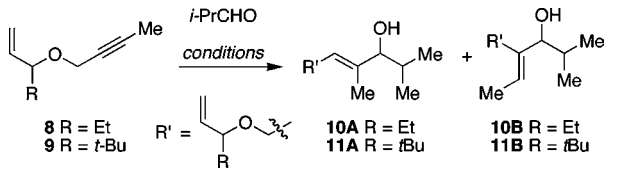
All pathways involve an approximately planar, three-coordinate, d^8 nickel complex (**1**) that would be expected to undergo ligand substitution with retention of stereochemistry through an associative pathway.[4] In all cases, C−C bond formation is believed to occur through an oxanickellacyclopentene.[2,3] Also, in all cases, the third ligand (L) is assumed to be an olefin[5] and, as it is not part of a bidentate chelate, is considered to be the most weakly bound ligand. Therefore, in all cases L is the ligand that is displaced from the metal center in substitution reactions of **1**.

In the absence of a phosphine ligand (Scheme 2, type I), ligand substitution places the aldehyde *cis* to the carbon distal to the alkene, C(*A*), and *cis* to the bound olefin, giving **2**. C−C bond formation occurs at C(*A*) while the olefin tether is coordinated to the nickel, resulting in exclusive formation of regioisomer **A**. In type II reactions, tricyclopentylphosphine ($PCyp_3$) substitutes for L to give **3**. $PCyp_3$ is coordinated more strongly to the metal center than the tethered alkene, which is thus displaced stereospecifically by the aldehyde, ultimately leading to regioisomer **B** by way of **4**. Thus, despite not being bound during the C−C bond formation, the olefin nevertheless determines regioselectivity. Finally, we propose that when a smaller ligand such as tri-*n*-butylphosphine (PBu_3) is employed (type III), two equivalents of phosphine are bound to the metal center displacing both the olefin tether and L to give **5**. In this case, regioselectivity would not be determined by the olefin, and a nonselective displacement of either phosphine leads to a mixture of **6** and **7**, which in turn affords a mixture of regioisomers **A** and **B**.

To test these mechanistic hypotheses and the overriding assumption of a planar, three-coordinate nickel complex, we evaluated the effect of a stereogenic center in the olefin tether. We hypothesized that in the absence of a phosphine (type I), coordination of the olefin to the metal center should enhance diastereoselection, while conditions employing achiral phosphines (types II and III) should lead to lower diastereoselectivity since the olefin would be dissociated during the C−C bond-forming step.

Thus, chiral 1,6-enynes **8** and **9** were synthesized and coupled with isobutyraldehyde under three distinct sets of catalytic conditions: (I) $Ni(cod)_2$ with no additives; (II) $Ni(cod)_2$ + $PCyp_3$; and (III) $Ni(cod)_2$ + PBu_3 (Table 1).

Table 1. Coupling Reactions of Chiral 1,6-Enynes



entry	enyne[a]	reaction conditions[b]	products	A/B[c]	dr A[d]	dr B[d]
1	**8**	I	**10A, B**	>95:5	95:5	
2	(R = Et)	II		<5:95		45:55
3		III		55:45	50:50	45:55
4	**9**	I	**11A, B**	>95:5	>95:5	
5	(R = *t*-Bu)	II		<5:95		42:58
6		III		51:49	45:55	42:58

[a] Racemic **8** and **9** were employed in this series of reactions. [b] I: $Ni(cod)_2$ (10 mol %), Et_3B (200 mol %). II: reaction conditions I + $PCyp_3$ (20 mol %). III: reaction conditions I + PBu_3 (20 mol %). [c] Based on isolated yields. [d] Determined by ^1H NMR.

As predicted, under type I reaction conditions (no phosphine) both enynes gave exclusively regioisomer **A** (Table 1, entries 1 and 4). In addition, both allylic alcohols were formed in excellent diastereoselectivity, indicating a strong influence of the stereogenic center in the tether, despite being separated from the site of C−C bond formation by five atoms (1,6-induction).

Conversely, under type II reaction conditions, regioisomer **B** is formed exclusively, but diastereoselection is negligible (entries 2 and 5). Type III reaction conditions are neither regioselective nor diastereoselective (entries 3 and 6).

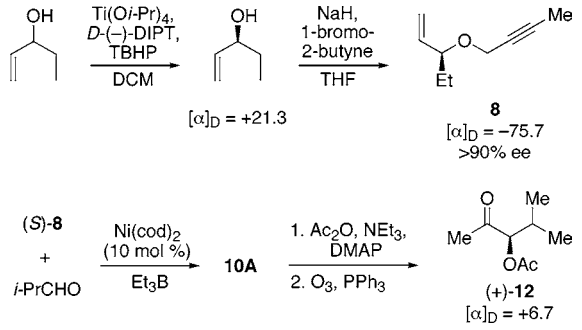
(4) Collman, J. P.; Hegedus, L. S.; Norton, J. R.; Finke, R. G. *Principles and Applications of Organotransition Metal Chemistry*; University Science Books: Mill Valley, CA, 1987; pp 241−244.

(5) Ethylene, 1,5-cyclooctadiene, or another equivalent of **8** or **9** are all possible.

Taken together, these experiments strongly support the notion that, in the absence of phosphine (type I), the alkene is coordinated to Ni during the C−C bond-forming step and that, in the presence of phosphine (type II or III), the alkene is *not* coordinated to Ni during the C−C bond-forming step.

The high levels of diastereoselectivity afforded by enynes **8** and **9** in the absence of phosphine (Table 1, entries 1 and 4) prompted us to investigate coupling reactions of these chiral enynes further. To determine the sense of induction in the formation of regioisomer **A**, enantiomerically enriched enyne **8** was prepared (Scheme 3). 1-Penten-3-ol was

Scheme 3



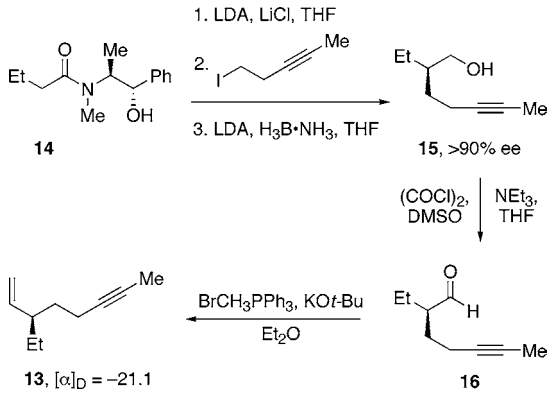
resolved using a Sharpless asymmetric epoxidation,[6,7] and Williamson ether synthesis using the (*S*) enantiomer afforded enyne **8**.

Nickel-catalyzed coupling of (*S*)-**8** and *i*-PrCHO in the absence of a phosphine (type I reaction conditions) afforded **10A** in >95:5 regioselectivity and 95:5 diastereoselectivity. Conversion to the corresponding acetate followed by ozonolysis afforded ketone (+)-**12**. The sign of the specific rotation of this compound was opposite that of (−)-**12** prepared from commercially available (*S*)-2-hydroxy-3-methylbutyric acid,[8] thus establishing the allylic alcohol configuration in **10A** as *R*.

To test the possibility that the oxygen atom in the tether plays a key role in the mode of diastereoinduction (e.g., chelation of this oxygen and that of the aldehyde by an organoboron species), we synthesized a 1,6-enyne (**13**) in which the oxygen was replaced with a methylene group (Scheme 4).[9] A highly diastereoselective Myers alkylation, Swern oxidation, and Wittig olefination afforded **13** in a straightforward manner.

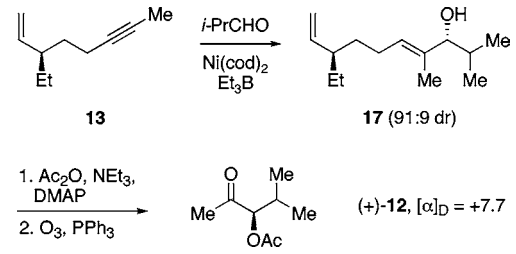
Under type I coupling conditions, enyne **13** gave results similar to those obtained with the enynes possessing an ethereal tether between the alkene and the alkyne. Nickel-catalyzed reductive coupling of **13** and *i*-PrCHO afforded allylic alcohol **17** in very high regioselectivity and in slightly

Scheme 4



reduced but nevertheless high diastereoselectivity (Scheme 5). The sense of induction, determined to be *R* using the

Scheme 5



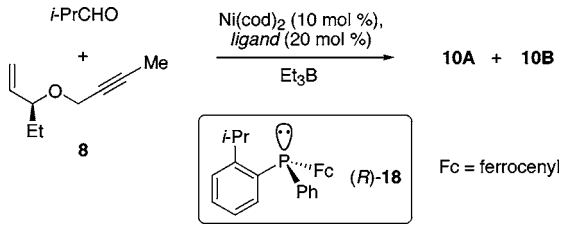
same sequence of operations shown in Scheme 3, was also the same as that observed with enynes **8** and **9**. Thus, an oxygen atom and a CH_2 group at this position in the tether have similar (but measurably different) effects in type I coupling reactions.

At this stage, we wanted to test a critical aspect of the type II and III mechanisms, that the *phosphine* is bound to Ni during the C−C bond-forming step. We reasoned that since the influence of the chiral center in the tether in these cases is minimal, any diastereoselectivity induced by a *chiral* phosphine could be attributed to the phosphine alone, a result that would be consistent with phosphine being bound to Ni as the C−C bond is formed.

To this end, we subjected enyne **8** and isobutyraldehyde to reductive coupling conditions in the presence of an achiral or chiral ferrocenyl-containing phosphine (Table 2).[2b,10] Nearly equimolar amounts of regioisomers **A** and **B** were obtained in all cases, suggesting that the reaction occurs via a type III mechanistic pathway (cf. Scheme 2). Both the *R* and *S* phosphine ligands afforded modest diastereoinduction. These results demonstrate that the enyne stereocenter exerts little to no influence on the diastereoselectivity and clearly indicate that phosphine is bound to nickel during the C−C bond-forming step.

(6) Hill, M. L.; Raphael, R. A. *Tetrahedron* **1990**, *46*, 4487−4594.
(7) Kagan, H. B, *Stereochemistry*; George Thieme: Stuttgart, 1977; Vol. 4, p 224.
(8) Bach, J.; Berenguer, R.; Farràs, J.; Garcia, J.; Meseguer, J.; Vilarrasa, J. *Tetrahedron: Asymmetry* **1995**, *6*, 2683−2686.
(9) Myers, A. G.; Yang, B. H.; Chen, H.; McKinstry, L.; Kopecky, D. J.; Gleason, J. L. *J. Am. Chem. Soc.* **1997**, *119*, 6496−6511.
(10) Miller, K. M.; Jamison, T. F. *Org. Lett.* **2005**, *7*, 3077−3080.

Table 2. Coupling Reactions of Chiral, Enantiomerically Enriched 1,6-Enynes with Ferrocenyl-Containing Phosphines



ligand	**A/B**[a]	dr **10A** (*R*/*S*)[b]	dr **10B**[b,c]
(*R*)-**18**	48:52	30:70	28:72
(*S*)-**18**	55:45	66:34	68:32
$FcPPh_2$	54:46	56:44	48:52

[a] Based on isolated yields. [b] Configuration of allylic alcohol stereogenic center. [c] Relative stereochemistry not determined.

The exact mode of diastereoinduction is unknown. However, one possibility is that one of the conformations of **1** is highly favored and reacts with the aldehyde in a highly stereoselective manner.

In summary, subtle changes to the reaction conditions of reductive coupling reactions of aldehydes and chiral 1,6-enynes have a significant impact on both regioselectivity and diastereoselectivity. At least three distinct mechanistic pathways are possible in these reactions, and selectivity is influenced not only by the presence or absence of a phosphine additive, but also by the nature of the phosphine chosen. These results support the hypothesis that nickel-catalyzed reductive coupling reactions of alkynes and aldehydes proceed through an approximately planar, three-coordinate d^8 nickel complex. Finally, the chelation-controlled, highly diastereoselective transformations in the absence of phosphine suggest synthetic applications, and the mechanistic insight gained through this investigation should facilitate the development of other selective, nickel-catalyzed transformations.

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

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