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Nickel-Catalyzed Reductive Coupling of Alkynes and Epoxides

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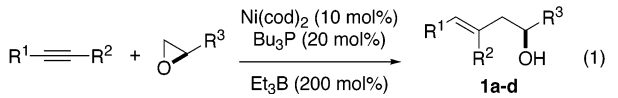
The development of catalytic reactions that effect carbon−carbon bond formation by uniting readily available functional groups is a major research area. We and others have recently reported several examples of such methods that are catalyzed by nickel(0)−ligand complexes,[1] and all of these involve the union of two π-electron systems (e.g., alkyne−aldehyde,[2] alkyne−imine,[3] 1,3-diene−aldehyde,[4] alkyne−α,β-unsaturated carbonyl,[1a,e] and allene−aldehyde[5]).[6] Herein, we describe the first member of this family that deviates from this requirement, wherein the π-system of one molecule (alkyne) combines with a functional group that has no multiple bonds (epoxide), affording synthetically useful, chiral homoallylic alcohols (eqs 1 and 2). Other metal salts catalyze an intramolecular form of this reaction by way of a single-electron-transfer mechanism,[7] but catalytic intermolecular alkyne−epoxide reductive coupling is without precedent. To our knowledge, there are no examples of nickel-catalyzed carbon−carbon bond-forming reactions of epoxides.[8]

In our initial investigations, we discovered that this process is quite sensitive to the nature of the phosphine and that the use of Bu_3P and Et_3B as reducing agent is the optimum combination for intermolecular reductive coupling (Table 1).[9] Only $(n\text{-Oct})_3P$ (entry 3) is of comparable efficacy, whereas Et_3P (or any of 15 other phosphines evaluated) provides less than 5% yield of the desired homoallylic alcohol (entry 1). While there is little dependence of yield upon solvent choice (entries 2, 4, 5), maximum yield is obtained without an added solvent (entries 6−9). Stereospecific cis addition[10] to the alkyne is observed in every case, and most notable is the complete (>95:5) regioselectivity with respect to *both* the alkyne and the epoxide in all cases except for styrene oxide (entry 9).[11,12]

Intramolecular cases display an especially noteworthy sense and degree of regioselectivity (eq 2, Table 2). The exo mode of epoxide ring-opening is typically favored in the absence of a significant electronic bias,[13] and the existing catalytic alkyne−epoxide reductive cyclizations follow this trend.[7] However, we observe complete (>95:5) endo opening in every case we have examined, regardless of the nature of the linking group or ring size.[10] The tolerance of heteroatoms allows for rapid transformation of glycidol into important tetrahydropyranyl and piperidinyl heterocycles possessing a stereogenic center and an exocyclic, trisubstituted olefin of defined geometry (entries 2 and 3).

The very high "endo" epoxide-opening regioselectivity in these cyclizations suggests a mechanistic framework very different from those we and others have proposed for Ni-catalyzed alkyne/π-electrophile couplings.[1−6] As shown in Scheme 1, a possible explanation involves the intermediacy of **A**, a metallaoxetane (oxametallacyclobutane) corresponding to a regioselective oxidative addition of a phosphine−nickel(0) complex into the less hindered C−O bond of the epoxide,[8c,d,14,15] followed by exo-dig cyclization onto the alkyne. Installation of the vinylic hydrogen atom could arise from transfer of Et to Ni from Et_3B, β-H elimination, and finally reductive elimination. This mechanism requires formation of cyclopentyl product **3e** to occur by way of a 3-nickella-4-oxabicyclo[3.2.1]oct-1-ene that would be classified as an "anti-Bredt" alkene if Ni were replaced with CR_2. However, the longer

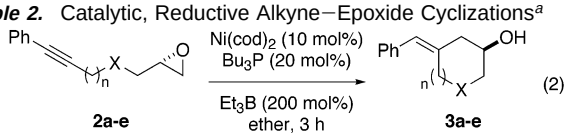
Table 1. Intermolecular Reductive Coupling of Alkynes and Epoxides[a]



entry	R^1	R^2	R^3	additive	product	yield (%)	regioselectivity alkyne	regioselectivity epoxide
1[b]	Ph	Me	Me	Et_3P	**1a**	0	>95:5	>95:5
2[b]	Ph	Me	Me	Bu_3P	**1a**	36	>95:5	>95:5
3[b]	Ph	Me	Me	$(n\text{-Oct})_3P$	**1a**	35	>95:5	>95:5
4[c]	Ph	Me	Me	Bu_3P	**1a**	25	>95:5	>95:5
5[d]	Ph	Me	Me	Bu_3P	**1a**	34	>95:5	>95:5
6	Ph	Me	Me	Bu_3P	**1a**	71	>95:5	>95:5
7	Ph	Me	*n*-Hex	Bu_3P	**1b**	68	>95:5	>95:5
8	Ph	Me	Ph	Bu_3P	**1c**	50[e]	88:12	83:17
9	*n*-Pr	*n*-Pr	Et	Bu_3P	**1d**	35[e]	na	>95:5

[a] See eq 1, ref 9, and Supporting Information. [b] Ether used as solvent. [c] Toluene used as solvent. [d] Ethyl acetate used as solvent. [e] Overall yield after conversion to TBDPS ether.

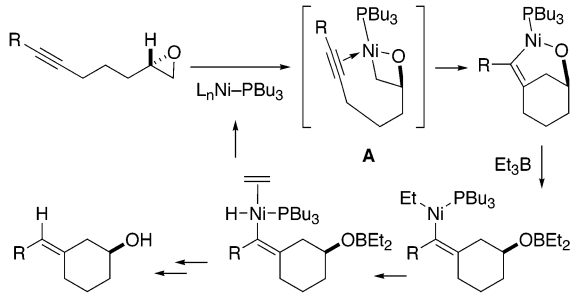
Table 2. Catalytic, Reductive Alkyne−Epoxide Cyclizations[a]



entry	X	*n*	product	yield (%)	regioselectivity (endo:exo)
1[b]	CH_2	1	**3a**	45	>95:5
2	O	1	**3b**	50	>95:5
3	NBn	1	**3c**	65	>95:5
4	$C(CO_2Me)_2$	1	**3d**	88[c]	>95:5
5	CH_2	0	**3e**	54	>95:5

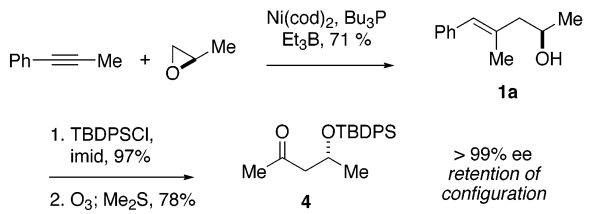
[a] See eq 2 and Supporting Information. [b] Toluene used as solvent. [c] Isolated as a 3:1 mixture of homoallylic alcohol and lactone (loss of MeOH).

Scheme 1. Reductive Cyclization via a Proposed Nickella(II)oxetane



10.1021/ja0361401 CCC: $25.00

Scheme 2



Ni−C and Ni−O bonds might be expected to accommodate the bridgehead olefin.[16]

Further support for **A** and the mechanistic proposal in Scheme 1 is the isolation of products of epoxide isomerization such as acetophenone and 2-octanone (Table 1, entries 7 and 8, respectively), which can be attributed to collapse of the metallaoxetane to a nickel(II) enolate[14c,16] and subsequent reductive elimination.

The experiment shown in Scheme 2 confirms that optical purity is preserved in the Ni-catalyzed alkyne−epoxide reductive coupling and is a further demonstration of the utility of this method. Using only commercially available reagents and catalysts, this procedure is an alternative to enantioselective addition of allylmetal reagents to aldehydes[17] and, after further elaboration, affords in >99% ee[18] a β-silyloxyketone (**4**) that corresponds to an asymmetric acetone−acetaldehyde aldol addition reaction.

The catalytic reaction described here represents the first use of a non-π-based electrophile in a growing class of nickel-catalyzed, multicomponent coupling reactions. It is also the first catalytic method of reductive coupling of alkynes and epoxides that is effective for both intermolecular and intramolecular cases and may also be mechanistically unique among these (nickella(II)oxetane). Another feature that is unprecedented in existing methods is the complete selectivity for the usually disfavored endo epoxide-opening product in alkyne−epoxide reductive cyclizations. Finally, the utility and ease of implementation of this method are direct results of the availability of terminal epoxides in >99% ee.[19] We continue to investigate the mechanistic details and potential applications of this method to the synthesis of carbocyclic and heterocyclic natural products.

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Supporting Information Available: Experimental procedures and data for **1a**−**d**, **2a**−**e**, **3a**−**e**, and **4** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) Alkene geometry confirmed by NOE experiments. See Supporting Information.

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