J|A|C|S
COMMUNICATIONS

Ligand-Dependent Scope and Divergent Mechanistic Behavior in Nickel-Catalyzed Reductive Couplings of Aldehydes and Alkynes

Gireesh M. Mahandru, Gang Liu, and John Montgomery*

Department of Chemistry, Wayne State University, Detroit, Michigan 48202

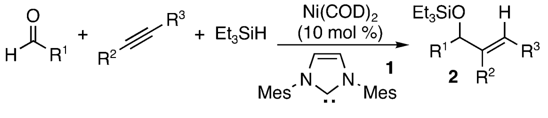
Received January 20, 2004; E-mail: jwm@chem.wayne.edu

Allylic alcohols are organic substructures that are exceptionally valuable in many synthetic applications. The most common method for their preparation involves coupling of alkenyl halides and aldehydes either by metalation/addition or Nozaki Hiyama Kishi coupling.[1] More recent advances from Wipf and Oppolzer include alkyne hydrozirconation or hydroboration followed by addition to aldehydes.[2] Our laboratory[3] and others[4] have recently focused on developing new methods for the catalytic reductive coupling of aldehydes and alkynes.[5] A broad range of reductive cyclizations of ynals has been demonstrated, but the corresponding intermolecular variants are often more challenging. Whereas efficient intermolecular couplings were developed by Jamison,[4a,b] alkyne trimerization can pose problems, particularly with terminal alkynes.

Given our continuing interest in the study of this general problem, we have expanded our original investigations of the process to include modification of $Ni(COD)_2$ with an imidazolium carbene ligand. This catalyst system, first prepared and characterized by Arduengo,[6] has been successfully used by several investigators in various reactions.[7] In keeping with those reports, we find that nickel carbene catalysts provide remarkably different reactivity from the $Ni(COD)_2/PBu_3$ catalyst formulation employed in our earlier investigations on alkyne/aldehyde reductive cyclizations. Using this catalyst formulation, we have now developed an improved procedure for the intermolecular reductive coupling of alkynes, aldehydes, and trialkylsilanes, which was not possible with $Ni(COD)_2/PBu_3$.[8] Initial studies to illustrate the broad scope of this procedure have been carried out, and mechanistic studies illustrate that the Ni(0) catalysts of PBu_3 and heterocyclic carbenes operate by different mechanisms. This finding requires that we modify our originally proposed mechanism for $Ni(COD)_2/PBu_3/Et_3SiH$-mediated reductive cyclizations of ynals.[3b]

We thus examined the three-component addition of aldehydes (1.0 equiv), alkynes (1.2 equiv), and triethylsilane (2.0 equiv) with the catalyst derived from $Ni(COD)_2$ and carbene **1** (1:1).[7,9] Optimized conditions involved syringe drive addition of the alkyne, typically over 15 min (see Supporting Information for details). The scope of this optimized procedure was broad, and good to excellent yields and regioselectivities were observed across a broad range of substrates (Table 1). Aromatic and aliphatic aldehydes were excellent participants in the procedure, including electron-rich aromatic aldehydes and sterically demanding aliphatic aldehydes with branching at the α-carbon. In the case of 2-methylbutanal, a 1.5:1 ratio of diastereomers was observed (entry 6). The alkyne may be internal or terminal, with aromatic or aliphatic substitution patterns being tolerated in both cases. Highly regioselective alkyne insertion was noted in all cases with the exception of an internal aliphatic alkyne (entry 5), which proceeded to afford a 1.3:1 ratio of isomers in favor of the one depicted. Conjugated enynes were efficient substrates in the preparation of dienyl alcohols (entries 8, 9). Unprotected alcohols were tolerated, with the unusual feature that the TES protecting group was selectively installed on the most hindered alcohol of the product diol (entry 10). Advantages of this procedure include the broad scope, the use of a stable, easily handled reducing agent, and the selective incorporation of a convenient hydroxyl protecting group during the coupling procedure.

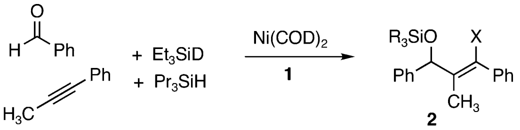
Table 1. Catalytic Intermolecular Couplings[a,b]



entry	R^1	R^2	R^3	yield (regioselectivity)
1	Ph	CH_3	Ph	84% (>98:2)
2	C_6H_{13}	CH_3	Ph	82% (>98:2)
3	Ph	H	C_6H_{13}	71% (>98:2)
4	Ph	H	Ph	72% (>98:2)
5	Ph	CH_3	C_4H_9	84% (1.3:1)
6	*s*-Bu	CH_3	Ph	81% (>98:2)[c]
7	$C_6H_4OCH_3$	CH_3	Ph	66% (>98:2)
8	Ph	Ph	$C(CH_3){=}CH_2$	84% (>98:2)
9	Ph	H	$CH{=}CHC_6H_{13}$	56% (>98:2)
10	Ph	H	$(CH_2)_4OH$	72% (>98:2)[d]

[a] Reactions were carried out in THF at 25−45 °C.[9] [b] Use of triethylborane or diethylzinc as a reducing agent or $NiCl_2$ as a precatalyst led to lower yields. [c] A 1.5:1 ratio of diastereomers was obtained. [d] Performed with 1.5 equiv of the alkyne.

Table 2. Intermolecular Crossover Experiment

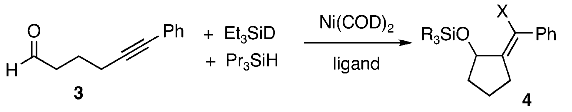


R	X	product	relative %
Et	H	**2a**	<1
Et	D	**2b**	48
Pr	H	**2c**	50
Pr	D	**2d**	<1

A particularly intriguing feature of these studies is the significant difference in scope of catalysts derived from PBu_3 and carbene **1**. Thus, we became very interested in developing a mechanistic probe, involving crossover experiments between Et_3SiD and Pr_3SiH, that would allow comparison of these two ligand classes.[10] We therefore examined the reductive coupling of benzaldehyde and 1-phenylpropyne in the presence of 1 equiv each of Et_3SiD and Pr_3SiH (Table 2). With the complex of $Ni(COD)_2$ and **1**, products **2b** and **2c** were cleanly produced in comparable amounts, and <1% of crossover products **2a** and **2d** were observed. In intramolecular couplings of ynal **3** using $Ni(COD)_2$ with **1**, results similar to intermolecular couplings were observed (Table 3). Products **4b** and **4c** were produced in 55 and 41% yields, respectively, and crossover products **4a** and **4d** were observed in <2% yield each. However, in cyclizations of **3** with the $Ni(COD)_2/PBu_3$ catalyst system,

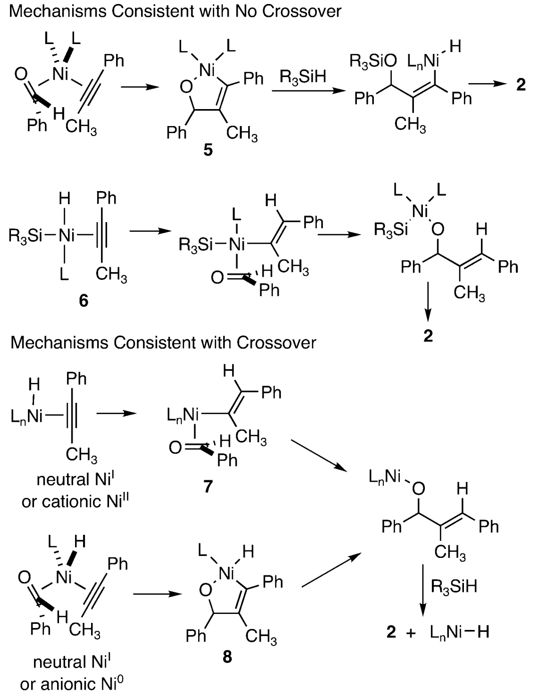
10.1021/ja049644n CCC: $27.50

Table 3. Intramolecular Crossover Experiments



R	X	product	relative % from **1**	relative % from PBu$_3$
Et	H	**4a**	<2	25
Et	D	**4b**	55	34
Pr	H	**4c**	41	23
Pr	D	**4d**	<2	18

Scheme 1. Possible Mechanisms



significant crossover was observed, with products **4a**, **4b**, **4c**, and **4d** being observed in a 25:34:23:18 ratio (Table 3). Recovered silanes in the latter experiment contained only 3% of the scrambled silanes Et_3SiH and Pr_3SiD. Thus, this combination of crossover experiments unambiguously demonstrates that the mechanisms of the two procedures fundamentally differ.[11]

We originally proposed a mechanism for the PBu$_3$-based procedure involving formation of metallacycle **5** followed by σ-bond metathesis (Scheme 1).[3b] Another reasonable alternative[12] involves nickel species **6** (Scheme 1). Either mechanism is consistent with the lack of crossover observed in couplings catalyzed by Ni(COD)$_2$/**1**, but the extensive crossover observed in cyclizations catalyzed by Ni(COD)$_2$/PBu$_3$ is clearly inconsistent with either of these mechanistic scenarios. Possibilities that are consistent with the observed crossover in experiments with PBu$_3$ likely involve a catalyst that possesses either a nickel hydride or nickel silyl species, but not both. For instance, formation of a nickel hydride species that undergoes sequential alkyne and aldehyde insertions via intermediate **7**, followed by σ-bond metathesis, would be consistent with crossover (Scheme 1).[13] Alternatively, participation of a nickel hydride species in the formation of metallacycle **8**, followed by C−H reductive elimination and σ-bond metathesis, would also lead to crossover (Scheme 1). As depicted, several options exist in terms of catalyst oxidation state and overall charge in both instances. Alternatively, similar mechanisms that are initiated by a silylnickel species that lacks the hydride ligand may also be envisioned.[14]

In summary, an efficient and selective new procedure for reductive couplings of aldehydes and alkynes has been developed. A novel crossover deuterium-labeling mechanistic probe has been utilized that demonstrates that catalyst formulations involving PBu$_3$ and carbene ligand **1** proceed largely by fundamentally different mechanisms, which helps to explain the different scope of these two procedures. This mechanistic probe should be useful in the study of other processes that involve metal-catalyzed hydrosilylation.

Acknowledgment. The authors wish to acknowledge receipt of NIH Grant GM-57014 and a Johnson and Johnson Focused Giving Award in support of this research. Andy Skauge is thanked for a preliminary experiment.

Supporting Information Available: Full experimental details and copies of NMR spectra and GCMS data (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) (a) Jin, H.; Uenishi, J.; Christ, W. J.; Kishi, Y. *J. Am. Chem. Soc.* **1986**, *108*, 5644. (b) Takai, K.; Tagashira, M.; Kuroda, T.; Oshima, K.; Utimoto, K.; Nozaki, H. *J. Am. Chem. Soc.* **1986**, *108*, 6048.
(2) (a) Wipf, P.; Xu, W. *Tetrahedron Lett.* **1994**, *35*, 5197. (b) Oppolzer, W.; Radinov, R. N. *J. Am. Chem. Soc.* **1993**, *115*, 1593.
(3) (a) Oblinger, E.; Montgomery, J. *J. Am. Chem. Soc.* **1997**, *119*, 9065. (b) Tang, X. Q.; Montgomery, J. *J. Am. Chem. Soc.* **1999**, *121*, 6098. (c) Lozanov, M.; Montgomery, J. *J. Am. Chem. Soc.* **2002**, *124*, 2106.
(4) (a) Huang, W.-S.; Chan, J.; Jamison, T. F. *Org. Lett.* **2000**, *2*, 4221. (b) Miller, K. M.; Huang, W.-S.; Jamison, T. F. *J. Am. Chem. Soc.* **2003**, *125*, 3442. (c) Crowe, W. E.; Rachita, M. J. *J. Am. Chem. Soc.* **1995**, *117*, 6787. (d) Takai, K.; Sakamoto, S.; Isshiki, T. *Org. Lett.* **2003**, *5*, 653. (e) Huddleston, R. R.; Jang, H.-Y.; Krische, M. J. *J. Am. Chem. Soc.* **2003**, *125*, 11488.
(5) For a review of the development of nickel-catalyzed methods, see: Montgomery, J. *Angew. Chem., Int. Ed.* In press.
(6) Arduengo, A. J.; Gamper, S. F.; Calabrese, J. C.; Davidson, F. *J. Am. Chem. Soc.* **1994**, *116*, 4391.
(7) (a) Louie, J.; Gibby, J. E.; Farnworth, M. V.; Tekavec, T. N. *J. Am. Chem. Soc.* **2002**, *124*, 15188. (b) Sato, Y.; Sawaki, R.; Mori, M. *Organometallics* **2001**, *20*, 5510. (c) Dible, B. R.; Sigman, M. S. *J. Am. Chem. Soc.* **2003**, *125*, 872. (d) See also: Jurkauskas, V.; Sadighi, J. P.; Buchwald, S. L. *Org. Lett.* **2003**, *5*, 2417. (e) For a review of earlier examples, see: Herrmann, W. A. *Angew. Chem. Int. Ed.* **2002**, *41*, 1290.
(8) Attempted intermolecular couplings with Et_3SiH, Ni(COD)$_2$, and PBu$_3$ were sluggish and afforded very poor yields of **2**.
(9) Carbene **1** was prepared *in situ* by treatment of the corresponding imidazolium salt with BuLi.
(10) In control experiments, these two silanes were found to undergo coupling at comparable rates. Furthermore, the PBu$_3$ and heterocyclic carbene complexes of Ni(COD)$_2$ catalyze the scrambling of deuterium in a mixture of Et_3SiD and Pr_3SiH too slowly to be important in reductive couplings, and the catalysts do not promote silyl exchange among the products of reductive coupling.
(11) Since **4b** and **4c** are produced in excess of **4a** and **4d** when PBu$_3$ is used, it appears likely that the major pathway proceeds with crossover and a minor pathway proceeds without crossover.
(12) Sato, Y.; Takimoto, M.; Mori, M. *J. Am. Chem. Soc.* **2000**, *122*, 1624.
(13) For nickel hydride-mediated reactions, see: (a) Wilke, G. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 185. (b) Nomura, N.; Jin, J.; Park, H.; RajanBabu, T. V. *J. Am. Chem. Soc.* **1998**, *120*, 459.
(14) (a) For an ynal silylcarbocyclization that proceeds with opposite chemoselectivity, see: Ojima, I.; Tzamarioudaki, M.; Tsai, C.-Y. *J. Am. Chem. Soc.* **1994**, *116*, 3643. (b) For discussion of silylmetalation processes, see: LaPointe, A. M.; Rix, F. C.; Brookhart, M. *J. Am. Chem. Soc.* **1997**, *119*, 906. (c) Widenhoefer, R. A. *Acc. Chem. Res.* **2002**, *35*, 905. (d) Park, K. H.; Kim, S. Y.; Son, S. U.; Chung, Y. K. *Eur. J. Org. Chem.* **2003**, 4341.

JA049644N