EurJOC European Journal of Organic Chemistry

SHORT COMMUNICATION

DOI: 10.1002/ejoc.201201008

Nickel-Catalyzed Indium(I)-Mediated *syn*-Selective Propargylation of Aldehydes

Tsunehisa Hirashita,*[a] Yuuki Suzuki,[a] Hiromitsu Tsuji,[a] Yoshiki Sato,[a] Kojiro Naito,[a] and Shuki Araki[a]

Keywords: Indium / Nickel / Diastereoselectivity / C-C coupling / Alkynes

Low-valent indium(I)-mediated nickel-catalyzed propargylation of aldehydes is described. The nickel/indium(I)-mediated reaction of propargylic carbonates possessing different substitution patterns afforded *syn*-homopropargylic alcohols in high yields upon coupling with a variety of carbonyl compounds. Both the nickel catalyst and the phosphane ligands were found to play a crucial role in this transformation. The diastereoselectivity is strongly dependent on the ligand employed. A mechanism involving umpolung of the propargylnickel intermediates under the influence of low-valent indium is proposed to account for the dependence of the stereochemical characteristics of the phosphane ligands.

Introduction

Over the last decade, protocols involving the use of low-valent indium with a catalytic amount of a transition metal have been developed for organic synthesis.[1] After the formation of π-allylpalladium complexes by oxidative addition of Pd^0 to allylic alcohol derivatives[2] or by insertion of allenes to arylpalladium(II) compounds, transmetalation with In^I or In^0 yields allylic indium reagents that react with carbonyl compounds to give the corresponding homoallylic alcohols in high yields.[3] Although the addition of allenyl/propargylic metals with carbonyl compounds is an extremely powerful method to prepare homopropargylic alcohols,[4] regioselective and stereoselective propargylation mediated by indium has received less attention than In-mediated allylation.[5] Propargylic indium reagents are prepared from propargylic halides by oxidative addition in a manner similar to that of allylic indium reagents or reductive transmetalation from propargylic palladium compounds with InI or In^0. Marshall and co-workers studied the InI-mediated propargylation of carbonyl compounds extensively eventually to produce *anti*-homopropargylic alcohols with high selectivity.[6] We explored a new method for the InI-mediated allylation of carbonyl compounds by using π-allylnickel complexes, where allylic alcohols[7] and dienes[8] serve as good precursors to the allylic reagents. We describe herein that the Ni-catalyzed InI-mediated reaction of propargyl alcohol derivatives with aldehydes gives the corresponding homopropargylic alcohols with high *syn* selectivity, which is opposite to Marshall propargylation promoted by palladium catalysts.

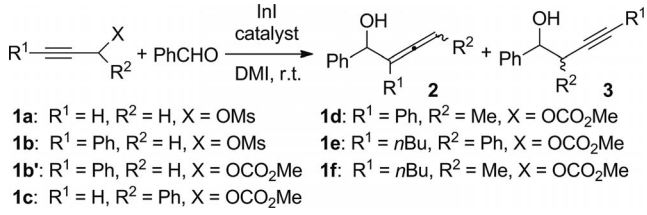
Results and Discussion

Propargylic mesylates and carbonates **1a**–**f** were initially tested in the propargylation reaction (Scheme 1 and Table 1). When propargyl mesylate (**1a**) and benzaldehyde were treated with InI in the presence of $Ni(acac)_2$ (20 mol-%) and PPh_3 (80 mol-%) in 1,3-dimethyl-2-imidazolidinone (DMI), a mixture of homoallenyl alcohol **2a** and homopropargyl alcohol **3a** was obtained in moderate yield (Table 1, entry 1). A similar reaction catalyzed by $Pd(PPh_3)_4$ selectively afforded **3a** (Table 1, entry 2). The Pd-catalyzed reaction of mesylate **1b** gave homoallenyl alcohol **2b** in 82% yield, although carbonate **1b′** gave no product (Table 1, entry 4). However, the Ni-catalyzed reaction of **1b′** proceeded rapidly to furnish **2b** (61%) together with **3b** (30%; Table 1, entry 5). Substituents at the propargylic position were found to have a crucial effect on this reaction: benzyl carbonates **1c** and **1e** underwent propargylation by both nickel and palladium catalysts to afford **3c** and **3e** (Table 1, entries 6, 7, 10, and 11). In contrast, propargylation with carbonates **1d** and **1f** bearing a methyl group at the propargylic carbon atom proceeded only in the presence of the nickel catalyst to give **3d** and **3f** in high yields (Table 1, entries 8, 12 vs. 9, 13).

The stereochemical outcome of this propargylation was confirmed by the reaction of **1d** with cyclohexanecarbaldehyde, which gave homopropargylic alcohol **3g** selectively with a 93:7 ratio of diastereomers. The configuration of the major diastereomer was determined to be *syn* by comparison with an authentic sample.[9] A similar reaction per-

[a] Graduate School of Engineering, Nagoya Institute of Technology,
Gokiso-cho, Showa-ku, Nagoya 466-8555, Japan
Fax: +81-52-735-5206
E-mail: hirasita@nitech.ac.jp
Homepage: http://www.nitech.ac.jp/

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.201201008.



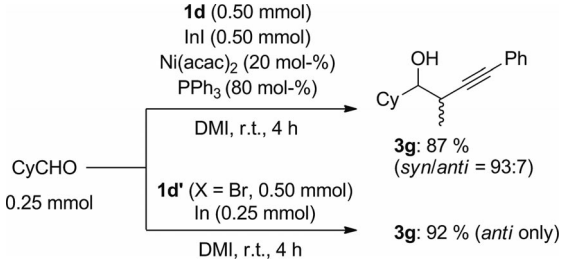
Scheme 1. Propargylic mesylates and carbonates for propargylation.

Table 1. Reaction of derivatives of propargylic alcohol with benzaldehyde.[a]

Entry	1	Catalyst[b]	Time [h]	Yield [%][c] 2	3
1	**1a**	Ni	1	**2a**: 9	**3a**: 46
2	**1a**	Pd	8	0	**3a**: 22
3[d]	**1b**	Pd	3	**2b**: 82	0
4	**1b′**	Pd	24	0	0
5	**1b′**	Ni	2	**2b**: 61	**3b**: 30
6	**1c**	Ni	3	0	**3c**: 69 (62:38)[c]
7	**1c**	Pd	4	0	**3c**: 100 (56:44)[c]
8	**1d**	Ni	4	0	**3d**: 90 (82:18)[e]
9	**1d**	Pd	22	0	0
10	**1e**	Ni	3	0	**3e**: 91 (100:0)[c]
11	**1e**	Pd	3	0	**3e**: 92 (63:37)[c]
12	**1f**	Ni	2	0	**3f**: 98 (96:4)[e]
13	**1f**	Pd	23	0	0

[a] All reactions were conducted with **1** (0.50 mmol), benzaldehyde (0.25 mmol), Ni or Pd catalyst, and InI (0.50 mmol) in DMI at r.t. [b] Pd: $Pd(PPh_3)_4$ (10 mol-%); Ni: $Ni(acac)_2$ (20 mol-%) and PPh_3 (80 mol-%). [c] Determined by ^1H NMR spectroscopy. [d] The reaction was performed on 0.30-mmol scale. [e] Determined by GC analysis of the corresponding acetates.

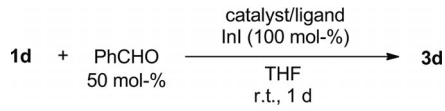
formed with propargylic bromide **1d′** and metallic indium afforded the *anti* adduct selectively (Scheme 2).



Scheme 2. Divergent diastereoselective propargylation.

The results showed that the limitations of the Pd-catalyzed reaction were simply overcome by changing the solvent. In THF, even non-benzylic propargylic carbonates were useful in the reaction. Therefore, we next examined the effects of ligands on the stereoselectivity of the reaction of **1d** with benzaldehyde (Table 2).

Table 2. Reaction of propargylic carbonate **1d** with benzaldehyde.[a]



Entry	Ligand	Yield [%] (*syn*/*anti*)[b] Pd	Ni
1	PPh_3	82 (64:36)	96 (87:13)[c]
2	PPh_3	>99 (62:38)[d]	
3	PPh_2Cy	25 (67:33)	76 (95:5)
4	$PPhCy_2$	NR	39 (64:36)
5	PCy_3	NR	33 (71:29)
6	$P(p\text{-MePh})_3$	96 (74:26)	97 (72:28)
7	$P(p\text{-MeOPh})_3$	89 (78:22)	>99 (58:42)
8	$P(p\text{-CF}_3\text{Ph})_3$	NR	trace
9	$P(o\text{-MePh})_3$	NR	NR
10	dppf	94 (77:23)	100 (37:63)
11			>99 (80:20)[e]
12	dpe-phos	89 (89:11)	93 (52:48)
13			>99 (87:13)[e]
14	P(2-furyl)$_3$	trace	NR
15	IPr	NR	NR
16	none	NR[d]	NR

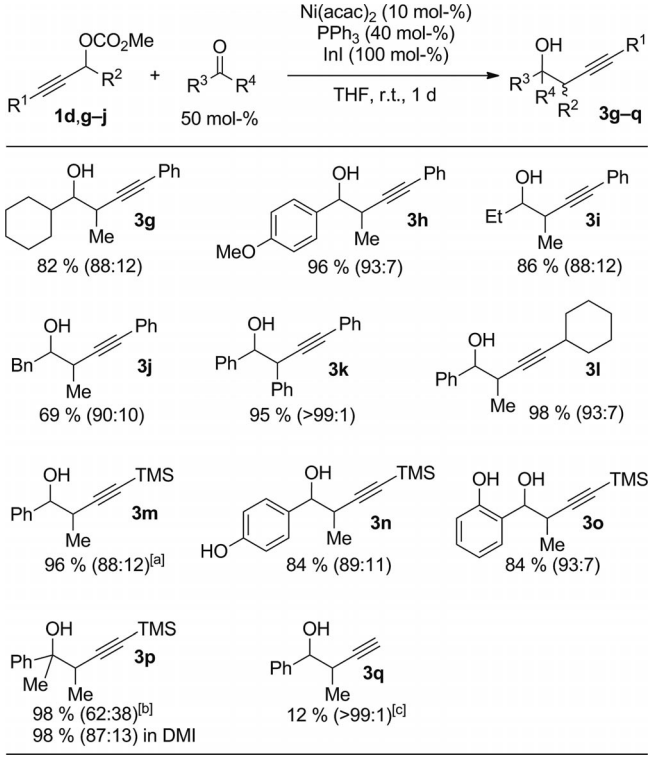
[a] Pd: $Pd(OAc)_2$ (5 mol-%), monodentate ligand (20 mol-%) or bidentate ligand (10 mol-%); Ni: $Ni(acac)_2$ (10 mol-%), monodentate ligand (40 mol-%) or bidentate ligand (20 mol-%). [b] Yield and *dr* values were determined by ^1H NMR spectroscopy with 1,4-dimethoxybenzene as a standard. [c] Isolated yield. [d] $Pd(acac)_2$ was used as the catalyst. [e] In DMI.

When PPh_3 was used as a ligand in the Pd-catalyzed reaction, **3d** was obtained with moderate selectivity, whereas the Ni-catalyzed reaction gave **3d** with high *syn* selectivity (Table 2). This *syn* selection is not attributable to the acetylacetonate ligand because $Pd(acac)_2$ showed no effect on the diastereoselectivity (Table 2, entry 2). Aromatic substituents on the phosphane atom are crucial for promoting the reaction; replacing the phenyl groups by cyclohexyl groups led to erosion of the yields and the selectivities (Table 2, entries 3–5). Introducing a methyl or a methoxy group at the *para* position affected both the Pd-catalyzed and Ni-catalyzed reactions in an opposite manner (Table 2, entries 6 and 7). An increase in the *syn* selectivity was found in the former and a large decrease in the diastereoselectivity was observed in the latter, in particular for $P(o\text{-MeOC}_6H_4)_3$. The introduction of a CF_3 group at the *para* position or a methyl group at the *ortho* position suppressed the propargylation completely (Table 2, entries 8 and 9). A bidentate ligand exerted markedly different effects on the two reactions (Table 2, entries 10–13). The use of diphenylphosphanylferrocene (dppf) and dpe-phos (bis[2-(diphenylphosphanyl)phenyl] ether) improved the selectivity of the Pd-catalyzed reaction. However, when dppf was used in the Ni-catalyzed reaction, the *anti* isomer prevailed slightly (Table 2, entry 10), and the Ni-catalyzed reaction with dpe-phos showed almost no diastereomeric selectivity (Table 2, entry 12). The reactions performed in DMI (Table 2, entries 11 and 13) caused recovery of the *syn* selectivity similar to that of entry 8 in Table 1. 2-Furylphosphane and a *N*-heterocyclic carbene ligand were not operative under the

conditions for this reaction (Table 2, entries 14 and 15). Both $Pd(acac)_2$ and $Ni(acac)_2$ without phosphane ligands were found to be inactive (Table 2, entry 16).

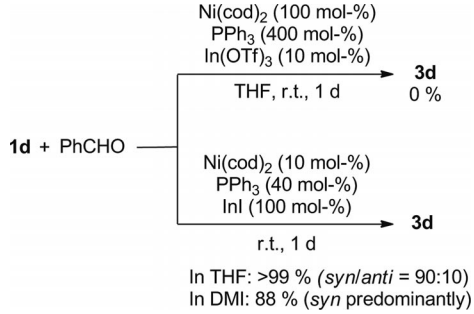
Because the highest *syn* selectivity was observed in the case with PPh_3, a series of Ni-catalyzed reactions of propargylic carbonates with carbonyl compounds was next examined in the presence of PPh_3 (Table 3). The reactions of **1d** with cyclohexanecarbaldehyde afforded **3g** in good yield with a ratio similar to that of benzaldehyde. The reactions of **1d** with *p*-anisaldehyde or aliphatic aldehydes gave the corresponding homopropargylic alcohols **3h**–**j** in good yields with high *syn* selectivity. When α-phenyl-substituted carbonate **1g** was subjected to coupling with benzaldehyde, **3k** was obtained with *syn* selectivity. Substituents at the acetylenic terminus did not affect this tendency: carbonates **1h** and **1i** afforded **3l** and **3m** in good yields while maintaining high levels of *syn* selectivity. The reaction of **1i** with *ortho*- and *para*-hydroxybenzaldehydes gave **3n** and **3o**, indicating that the phenolic hydroxy group neither deterred the reaction nor affected the selectivity. Upon coupling of **1i** with acetophenone, the predominant formation of *syn*-**3p** and an increase in the *syn* selectivity in DMI were also observed. When carbonate **1j** with a free acetylenic hydrogen atom was subjected to the conditions, the corresponding homopropargylic alcohol **3q** was obtained accompanying its hydrogenated product.

Table 3. Propargylation of aldehydes with **1d** and **1g**–**j**.



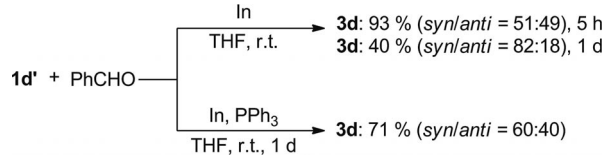
[a] Figures in parentheses show a *syn*/*anti* ratio determined by ^1H NMR spectroscopy. [b] Yield determined by NMR spectroscopy. [c] *syn*-2-Methyl-1-phenylbut-3-en-1-ol was obtained (12%).

The strong effect of the ligand on the diastereoselectivity shown in Table 2 might imply that the allenyl/propargyl nickel reagents react directly with benzaldehyde and InI simply acts as a reducing agent for the Ni^{II} catalyst. To elucidate this possibility, reaction with a stoichiometric amount of $Ni(cod)_2$ was conducted in the absence of InI (Scheme 3). The reaction did not proceed in the presence of an indium(III) salt, which is thought to be formed in situ during the oxidative process of In^{I}. In contrast, reaction with a catalytic amount of $Ni(cod)_2$ (10 mol-%) and InI (100 mol-%) gave the corresponding alcohol **3d** in good yield.



Scheme 3. Propargylation with stoichiometric and catalytic amounts of Ni catalyst.

Recently, allylindium reagents having a square pyramidal geometry with apical phosphane ligands were isolated and fully characterized by X-ray analysis.[10] These isolable allylindium compounds were prepared by the addition of the phosphane ligands to the allylic indium compounds. We next examined the possibility that a similar coordination of the phosphanes to the allenylindium reagents is responsible for the capricious characteristics of these propargylations. Consequently, the allenyl/propargylindium reagent, prepared from **1d**′ and metallic indium, was allowed to react with benzaldehyde in the presence or absence of PPh_3 (Scheme 4). The In-mediated propargylation gave **3d** in good yield with almost 1:1 diastereomeric ratio after 5 h, although a lowered yield with bias to the *syn* isomer was observed after 1 d, indicating that selective decomposition of the *anti* isomer occurred, as found in crotylation reactions.[11] This decay was suppressed by PPh_3: **3d** was obtained in 71% yield with a slight bias to the *syn* isomer. These observations were informative but insufficient to account for the *syn* selectivity.



Scheme 4. Effects of PPh_3 on the allenyl/propargylindium reagent.

Considering the results described previously, we raise an important question: why did the phosphane ligands affect

the stereochemical outcome of the propargylation? The phosphane ligands might no longer be able to exist on the allenyl/propargyl indium reagents provided that the transmetalation is completed. In connection with our study, the mechanism of the palladium-catalyzed umpolung allylation[12] and propargylation[13] using Et_2Zn or Et_3B might be helpful for understanding the present reaction. Recently, η^1-allylpalladium species are proposed as intermediates for the enantioselective allylations that cannot be reconciled with the initially proposed mechanism involving allylic zinc or allylic boron reagents through transmetalation.[14,15] Dimetallic Pd–Zn complexes have also been proposed for propargylation by a computational study.[16] A similar mechanism based on the umpolung of the propargylnickel intermediates under the influence of low-valent indium is apparently a plausible explanation for the present reaction.

The preferred stereochemical mode of propargylation with allenyl/propargyl metals depends on the intrinsic properties of the counter metal and the circumstances.[17,18] Although a general approach to *anti*-homopropargylic alcohols, including the Pd-catalyzed InI-mediated propargylation, has been well established, little is known about accessing *syn* isomers. The present propargylation provides a facile and efficient route to these compounds by using only nickel catalysts instead of palladium catalysts, which give the *anti* isomers predominantly.

Conclusions

In summary, we have developed the InI-mediated *syn*-selective propargylation of carbonyl compounds with propargyl carbonates in the presence of Ni catalysts. The present Ni-catalyzed propargylation proved to have a different nature than either the In^0-mediated or the Pd-catalyzed InI-mediated reactions. Further applications of this propargylation reaction are currently under study.

Experimental Section

Typical Experimental Procedure: To a mixture of $Ni(acac)_2$, prepared by heating $Ni(acac)_2{\cdot}2H_2O$ (15 mg, 0.05 mmol) under reduced pressure, was added PPh_3 (53 mg, 0.2 mmol), indium(I) iodide (121 mg, 0.50 mmol) in THF (1.0 mL), methyl 4-phenylbut-3-yn-2-yl carbonate (**1d**; 90 μL, 0.50 mmol), and benzaldehyde (26 μL, 0.25 mmol). The reaction mixture was stirred at room temperature under an atmosphere of argon for 1 d and then quenched with dilute hydrochloric acid (1 M). The product was extracted with diethyl ether and washed with aqueous saturated sodium hydrogen carbonate, water, and brine. The organic layer was dried with anhydrous sodium sulfate, and the solvent was removed under reduced pressure. The residue was purified by chromatography on silica gel (EtOAc/hexane = 1:5) to give 2-methyl-1,4-diphenylbut-3-yn-1-ol (**3d**; 58 mg, 96%, *syn*/*anti* = 87:13).

Supporting Information (see footnote on the first page of this article): General methods, assignment of *syn*/*anti* isomers, experimental procedures, spectroscopic data of the products, and copies of the ^1H NMR spectra.

Acknowledgments

This work was partially supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Science, Sports and Culture, Japan (No. 14340195).

[1] a) S. Araki, T. Hirashita in *Main Group Metals in Organic Synthesis Vol. 1* (Eds.: H. Yamamoto, K. Oshima), Wiley, New York, **2004**, pp. 323–386; b) S. Araki, T. Hirashita in *Comprehensive Organometallic Chemistry III* (Eds.: R. Crabtree, M. Mingos), Elsevier, Oxford, **2007**, pp. 649–751.
[2] a) J. A. Marshall, L. M. McNulty, D. Zou, *J. Org. Chem.* **1999**, *64*, 5193–5200; b) S. Araki, T. Kamei, T. Hirashita, H. Yamamura, M. Kawai, *Org. Lett.* **2000**, *2*, 847–849.
[3] a) U. Anwar, R. Grigg, M. Rasprini, V. Savic, V. Sridharan, *Chem. Commun.* **2000**, 645–646; b) U. Anwar, R. Grigg, V. Sridharan, *Chem. Commun.* **2000**, 933–934; c) I. R. Cooper, R. Grigg, W. S. MacLachlan, M. Thornton-Petta, V. Sridharana, *Chem. Commun.* **2002**, 1372–1373; d) L. a. T. Cleghorn, I. R. Cooper, R. Grigg, W. S. MacLachlan, V. Sridharan, *J. Organomet. Chem.* **2003**, *687*, 483–493; e) L. a. T. Cleghorn, I. R. Cooper, R. Grigg, W. S. MacLachlan, V. Sridharan, *Tetrahedron Lett.* **2003**, *44*, 7969–7973; f) I. R. Cooper, R. Grigg, M. J. Hardie, W. S. MacLachlan, V. Sridharan, W. A. Thomas, *Tetrahedron Lett.* **2003**, *44*, 2283–2285; g) I. R. Cooper, R. Grigg, W. S. MacLachlan, V. Sridharana, M. Thornton-Petta, *Tetrahedron Lett.* **2003**, *44*, 403–405; h) L. a. T. Cleghorn, R. Grigg, C. Kilner, W. S. MacLachlan, V. Sridharan, *Chem. Commun.* **2005**, 3071–3073; i) R. Grigg, S. McCaffrey, V. Sridharan, C. W. G. Fishwick, C. Kilner, S. Korn, K. Bailey, J. Blacker, *Tetrahedron* **2006**, *62*, 12159–12171; j) L. a. T. Cleghorn, R. Grigg, V. Savic, M. Simic, *Tetrahedron* **2008**, *64*, 8731–8737; k) R. Grigg, J. Blacker, C. Kilner, S. McCaffrey, V. Savic, V. Sridharan, *Tetrahedron* **2008**, *64*, 8177–8181.
[4] C. H. Ding, X. L. Hou, *Chem. Rev.* **2011**, *111*, 1914–1937.
[5] a) T. P. Loh, M. J. Lin, K. L. Tan, *Tetrahedron Lett.* **2003**, *44*, 507–509; b) M.-J. Lin, T.-P. Loh, *J. Am. Chem. Soc.* **2003**, *125*, 13042–13043; c) W. Miao, L. W. Chung, W. Yun-Dong, T. H. Chan, *J. Am. Chem. Soc.* **2004**, *126*, 13326–13334; d) D. Seomoon, J. A, P. H. Lee, *Org. Lett.* **2009**, *11*, 2401–2404.
[6] a) J. A. Marshall, C. M. Grant, *J. Org. Chem.* **1999**, *64*, 696–697; b) J. A. Marshall, C. M. Grant, *J. Org. Chem.* **1999**, *64*, 8214–8219; c) J. A. Marshall, H. R. Chobanian, *J. Org. Chem.* **2000**, *65*, 8357–8360; d) J. A. Marshall, B. A. Johns, *J. Org. Chem.* **2000**, *65*, 1501–1510; e) J. A. Marshall, P. Eidam, H. S. Eidam, *J. Org. Chem.* **2006**, *71*, 4840–4844; f) J. A. Marshall, *J. Org. Chem.* **2007**, *72*, 8153–8166.
[7] T. Hirashita, S. Kambe, H. Tsuji, H. Omori, S. Araki, *J. Org. Chem.* **2004**, *69*, 5054–5059.
[8] T. Hirashita, S. Kambe, H. Tsuji, S. Araki, *Chem. Commun.* **2006**, 2595–2597.
[9] K. Furuta, M. Ishiguro, R. Haruta, N. Ikeda, H. Yamamoto, *Bull. Chem. Soc. Jpn.* **1984**, *57*, 2768–2776.
[10] a) M. Yasuda, M. Haga, A. Baba, *Eur. J. Org. Chem.* **2009**, 5513–5517; b) M. Yasuda, M. Haga, A. Baba, *Organometallics* **2009**, *28*, 1998–2000.
[11] G. C. Lloyd-Jones, T. Russell, *Synlett* **1998**, 903–905.
[12] Y. Tamaru, A. Tanaka, K. Yasui, S. Goto, S. Tanaka, *Angew. Chem.* **1995**, *107*, 862; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 787–789.
[13] Y. Tamaru, S. Goto, A. Tanaka, M. Shimizu, M. Kimura, *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 879–880.
[14] G. P. Howell, A. J. Minnaard, B. L. Feringa, *Org. Biomol. Chem.* **2006**, *4*, 1278–1283.
[15] S.-F. Zhu, X.-C. Qiao, Y.-Z. Zhang, L.-X. Wang, Q.-L. Zhou, *Chem. Sci.* **2011**, *2*, 1135.
[16] R. Álvarez, A. R. D. Lera, J. M. Aurrecoechea, A. Durana, *Organometallics* **2007**, *26*, 2799–2802.

[17] a) E. Vrancken, H. Gérard, D. Linder, S. Ouizem, N. Alouane, E. Roubineau, K. Bentayeb, J. Marrot, P. Mangeney, *J. Am. Chem. Soc.* **2011**, *133*, 10790–10802 and references cited therein b) M. Chen, W. R. Roush, *J. Am. Chem. Soc.* **2012**, *134*, 10947–10952; c) Y. Sasaki, M. Sawamura, H. Ito, *Chem. Lett.* **2011**, *40*, 1044–1046; d) L. N. Guo, H. Gao, P. Mayer, P. Knochel, *Chem. Eur. J.* **2010**, *16*, 9829–9834.

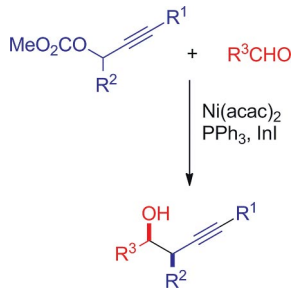
[18] Marshall propargylation normally gives *anti*-homopropargylic alcohols upon coupling of a broad range of aldehydes; however, reaction of benzaldehyde afforded a nearly 1:1 mixture of *anti* and *syn* adducts in agreement with the results shown in Table 1. See ref.[6a]

Received: July 27, 2012
Published Online: ■

SHORT COMMUNICATION

Propargylation

The Ni-catalyzed InI-mediated propargylation of carbonyl compounds gave the corresponding homopropargylic alcohols in high yields with *syn* selectivity. Aromatic phosphane ligands were found to play a crucial role in this transformation.



Keywords: Indium / Nickel / Diastereoselectivity / C-C coupling / Alkynes

