J|A|C|S
COMMUNICATIONS

Published on Web 10/04/2008

Nickel-Catalyzed Enantioselective Alkylative Coupling of Alkynes and Aldehydes: Synthesis of Chiral Allylic Alcohols with Tetrasubstituted Olefins

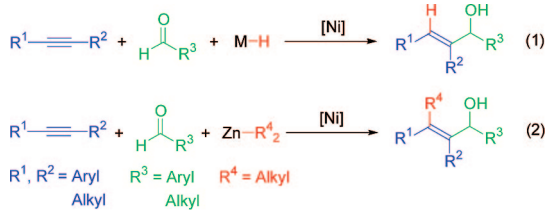
Yun Yang, Shou-Fei Zhu, Chang-Yue Zhou, and Qi-Lin Zhou*

State Key Laboratory and Institute of Elemento-organic Chemistry, Nankai University, Tianjin 300071, China

Received July 9, 2008; E-mail: qlzhou@nankai.edu.cn

Transition metal-catalyzed asymmetric carbon−carbon bond formation is the essence of organic synthesis. Nickel-catalyzed coupling reactions of alkynes and carbonyl compounds[1] provide a direct access to stereochemically defined allylic alcohols, valuable intermediates in organic synthesis that commonly occur as building blocks in natural products.[2] The nickel-catalyzed asymmetric reductive coupling between alkynes and aldehydes or ketones in the presence of reducing reagents such as organometallics or silanes (Scheme 1, eq 1) has been well developed by Jamison and by other

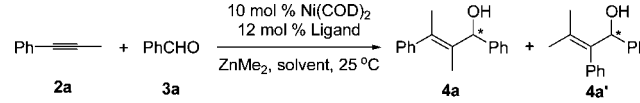
Scheme 1

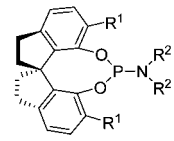


groups.[3] Chiral allylic alcohols with a di- or trisubstituted olefin have been prepared in good to excellent enantioselectivities. Besides the reductive coupling reactions, the nickel-catalyzed alkylative coupling reaction of alkynes with aldehydes developed by Montgomery and co-workers is another important coupling reaction.[4] The alkylative coupling reaction includes a transfer of an alkyl group instead of a hydrogen atom from organometallic reagents to the alkyne (Scheme 1, eq 2), and is therefore a more atom-efficient process compared to its reductive counterpart and commonly produces allylic alcohols with a tetrasubstituted olefin. Because the chiral allylic alcohols with a tetrasubstituted olefin are useful building blocks for bioactive compounds[5] and because they are difficult to synthesize by other methods, the nickel-catalyzed asymmetric alkylative coupling of alkyne and aldehydes holds great potential in organic synthesis. However, the asymmetric version of this important transformation is, to our best knowledge, still unexplored.[6] In this Communication, we report the first highly enantioselective alkylative coupling of alkynes and aldehydes catalyzed by nickel complexes of chiral spiro phosphoramidite ligands, which provides a convenient approach to the preparation of chiral allylic alcohols bearing a tetrasubstituted olefin.

We initially examined the alkylative coupling of 1-phenyl-1-propyne (1.0 equiv), benzaldehyde (2.0 equiv) and dimethylzinc (3.0 equiv) in the presence of nickel catalysts prepared in situ from $Ni(COD)_2$ and chiral spiro phosphoramidite ligands in 1:1.2 molar ratio. With the ligand (*R*)-SIPHOS, both yield and enantioselectivity of the reaction were low (Table 1, entry 1). To improve the activity and enantioselectivity of the catalyst, a variety of chiral spiro phosphoramidite ligands (**1**) with different substituents at the 6,6′-positions of the spirobiindane backbone and the *N*-atom were examined. Introduction of phenyl groups on the 6,6′-positions of

Table 1. Ni-Catalyzed Asymmetric Alkylative Coupling of 1-Phenyl-1-propyne and Benzaldehyde: Optimization of Conditions[a]





(*R*)-**1a**: R^1 = H, R^2 = Me (SIPHOS)
(*R*)-**1b**: R^1 = Me, R^2 = Me
(*R*)-**1c**: R^1 = Ph, R^2 = Me
(*R*)-**1d**: R^1 = Xyl, R^2 = Me
(*R*)-**1e**: R^1 = Ph, R^2 = Et
(*R*)-**1f**: R^1 = Ph, R^2 = Morpholine

entry	ligand	solvent	yield (%)[b]	ee (%)[c]
1	**1a**	dioxane	10	12
2	**1b**	dioxane	38	28
3	**1c**	dioxane	87	94
4	**1d**	dioxane	84	90
5	**1e**	dioxane	63	84
6	**1f**	dioxane	61	91
7	**1c**	THF	71	92
8	**1c**	Et_2O	84	90
9	**1c**	CH_2Cl_2	80	85
10	**1c**	toluene	88	95
11[d]	**1c**	toluene	70	90
12[e]	**1c**	toluene	71	88

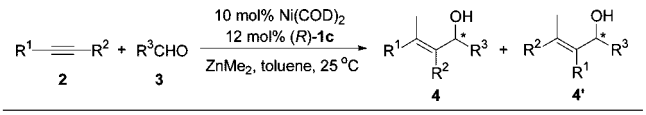
[a] Reaction conditions: $Ni(COD)_2$/Ligand/$ZnMe_2$/**2a**/**3a** = 0.015/0.018/0.45/0.15/0.30 (mmol), toluene, 25 °C for 20 h. [b] Isolated yield. Regioselectivity (**4a**/**4a′**) was >95% in all cases. [c] Determined by HPLC using a Chiralcel OD column. [d] With 5 mol % catalyst. [e] With 1 mol % catalyst.

the spirobiindane backbone of ligand (**1c**) significantly increased the yield (87%) and the enantioselectivity (94% ee) (entry 3). The amine moiety of the phosphoramidite ligand was also important in the alkylative coupling reaction. Replacement of the Me_2N group in the ligand **1c** by either a Et_2N group (**1e**) or a morpholine (**1f**) diminished both yield and enantioselectivity of the reaction (entries 5 and 6). Other monodentate chiral phosphorus ligands including Monophos and Mop with a binaphthyl backbone gave either low yield or low enantioselectivity (see Supporting Information). The reactions with bidentate ligands such as BINAP, SDP, and Phox provided a racemic product, indicating that only monodentate ligands induce enantioselectivity in the Ni-catalyzed alkylative coupling reactions.[7] Toluene was the most suitable solvent for high yield as well as for enantioselectivity (entry 10). Efforts to optimize other reaction parameters including the nickel precursors and reaction temperatures, however, had no positive effects (data not shown). The reaction was also performed with a reducing catalyst loading of 5 mol % or even as low as 1 mol %, although the yield and enantioselectivity were slightly lower (entries 11 and 12).

Once the optimal conditions were established, the scope of substrates was explored. The alkylative couplings of 1-phenyl-1-propyne with benzaldehyde and its derivatives were smoothly

10.1021/ja805296k CCC: $40.75

Table 2. Ni-Catalyzed Asymmetric Alkylative Couplings of Alkynes with Aldehydes[a]



2 3 4 4′

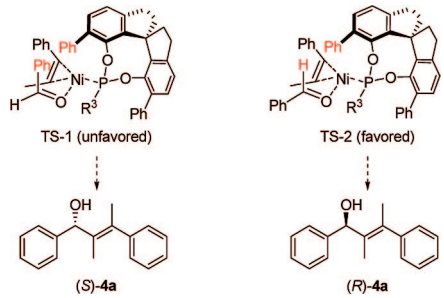
entry	R^1	R^2	R^3	yield of **4** (%)	**4**/**4′**	ee (%)
1	Ph	Me	Ph	88 (**4a**)	>95/5	95 (*R*)
2	Ph	Me	*m*-$MeOC_6H_4$	92 (**4b**)	>95/5	95
3	Ph	Me	*p*-MeC_6H_4	95 (**4c**)	>95/5	94
4	Ph	Me	*p*-$MeOC_6H_4$	94 (**4d**)	93/7	93
5	Ph	Me	*p*-FC_6H_4	89 (**4e**)	>95/5	96
6	Ph	Me	*p*-$CF_3C_6H_4$	89 (**4f**)	85/15	95
7	Ph	Me	2-naphthyl	70 (**4g**)	>95/5	86
8	Ph	Me	2-thiophene	82 (**4h**)	>95/5	92
9	Ph	Me	*n*-butyl	88 (**4i**)	>95/5	88
10	Et	Et	*p*-FC_6H_4	90 (**4j**)		98
11	*n*-Pr	*n*-Pr	*p*-FC_6H_4	92 (**4k**)		99
12	Ph	Ph	*p*-FC_6H_4	92 (**4l**)		98
13	Ph	Et	*p*-FC_6H_4	92 (**4m**)	6/1	98
14	Ph	*n*-Bu	*p*-FC_6H_4	91 (**4n**)	6/1	99

[a] Reaction conditions were the same as those in Table 1, entry 10. For analysis of products see Supporting Information.

accomplished to provide the corresponding allylic alcohols containing tetrasubstituted olefins in good yields and excellent enantioselectivities (Table 2, entries 2−6). The nature and the position of the substituent on the phenyl ring of benzaldehydes have little influence on the reaction with the exception of the CF_3 group at the *para* position, which resulted in a slightly lower regioselectivity (**4**/**4′**) (entry 6). In addition to benzaldehyde and its derivatives, naphthaldehyde, thiophene-2-carbaldehyde, as well as aliphatic *n*-butylaldehyde can also be coupled with 1-phenyl-1-propyne to produce the corresponding allylic alcohols in good enantioselectivities (entries 7−9). To extend the scope of the reaction, various disubstituted alkynes were investigated in the coupling reactions with *p*-fluorobenzaldehyde and the desired allylic alcohols with the tetrasubstituted olefin functionality were obtained in high yields and excellent enantioselectivities (98−99% ee, entries 10−14). However, lower regioselectivities (**4**/**4′** = 6:1) were obtained in the reactions with 1-phenyl-1-butyne and 1-phenyl-1-hexyne (entries 13 and 14). The decreased regioselectivity may be attributed to the fact that as the difference between the sizes of the two substituents of the alkyne became smaller, distinguishing the two ends of the alkyne became more difficult. Different dialkylzinc reagents were investigated in the alkylative coupling of 1-phenyl-1-propyne and benzaldehyde. When Et_2Zn, which contained β-H atoms, was used, a mixture of the reductive coupling product (33%, 57% ee) and the alkylative coupling product (50%, 71% ee) was obtained, while Ph_2Zn gave no reaction under the standard reaction conditions.

A reaction model was proposed for rationalizing the steric determination based on the absolute configuration of the alkylative coupling products and the literature work.[8] Two transition states (TS) of enantioselectivity-determined step were proposed (Scheme 2). In the model TS-1, there is an obvious repulsion between the two phenyl groups, one at the 6,6′-position of ligand and the other located on the aldehyde. Conversely, no repulsion occurs in the model TS-2 since the phenyl group of the aldehyde is oriented away from the phenyl group on the 6,6′-position of the ligand. According to the model TS-2, the nickel-activated alkyne approaches the

Scheme 2



aldehyde from its *Si* face, leading to the formation of allylic alcohols with *R* configuration, which is consistent with our experiment results.

In summary, we have developed a nickel-catalyzed highly enantioselective alkylative coupling reaction between alkynes and aldehydes in the presence of Me_2Zn by using 6,6′-disubstituted spiro phosphoramidite ligands. The asymmetric alkylative coupling reaction provides an efficient approach to varieties of chiral allylic alcohols with tetrasubstituted olefin functionality in high yields, high regioselectivities, and enantioselectivities.

Acknowledgment. We thank the National Natural Science Foundation of China (Grants 20532010, 20721062), the Major Basic Research Development Program (Grant 2006CB806106), and the "111" project (B06005) for financial support.

Supporting Information Available: Experimental procedures, the characterizations and the analysis of ee values of products. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) For reviews, see: (a) *Modern Organo Nickel Chemistry*; Tamaru, Y., Ed.; Willey-VCH: Weinheim, Germany, 2005. (b) Ikeda, S. *Angew. Chem., Int. Ed.* **2003**, *42*, 5120. (c) Montgomery, J. *Angew. Chem., Int. Ed.* **2004**, *43*, 3890. (d) Moslin, R. M.; Miller-Moslin, K.; Jamison, T. F. *Chem. Commun.* **2007**, 4441.

(2) For reviews, see: (a) *Comprehensive Organic Synthesis*, Trost, B. M., Ed.; Pergamon Press: Oxford, 1991. (b) Hoveyda, A. H.; Evans, D. A.; Fu, G. C. *Chem. Rev.* **1993**, *93*, 1307.

(3) (a) Miller, K. M.; Huang, W.-S.; Jamison, T. F. *J. Am. Chem. Soc.* **2003**, *125*, 3442. (b) Miller, K. M.; Jamison, T. F. *Org. Lett.* **2005**, *7*, 3077 For non-asymmetric examples, see: (c) Tang, X.-Q.; Montgomery, J. *J. Am. Chem. Soc.* **1999**, *121*, 6098. (d) Huang, W.-S.; Chan, J.; Jamison, T. F. *Org. Lett.* **2000**, *2*, 4221. (e) Takai, K.; Sakamoto, S.; Isshiki, T. *Org. Lett.* **2003**, *5*, 653. (f) Mahandru, G. M.; Liu, G.; Montgomery, J. *J. Am. Chem. Soc.* **2004**, *126*, 3698. (g) Miller, K. M.; Luanphaisarnnont, T.; Molinaro, C.; Jamison, T. F. *J. Am. Chem. Soc.* **2004**, *126*, 4130. (h) Miller, K. M.; Jamison, T. F. *J. Am. Chem. Soc.* **2004**, *126*, 15342 For asymmetric reductive coupling with chiral Rh and Ir catalysts and H_2 as reducing reagent, see: (i) Skucas, E.; Ngai, M.-Y.; Komanduri, V.; Krische, M. J. *Acc. Chem. Res.* **2007**, *40*, 1394 For nickel-catalyzed asymmetric reductive coupling of diene and aldehydes, see: (j) Sato, Y.; Saito, N.; Mori, M. *J. Am. Chem. Soc.* **2000**, *122*, 2371. (k) Sato, Y.; Saito, N.; Mori, M. *J. Org. Chem.* **2002**, *67*, 9310. (l) Yang, Y.; Zhu, S.-F.; Duan, H.-F.; Zhou, C.-Y.; Wang, L.-X.; Zhou, Q.-L. *J. Am. Chem. Soc.* **2007**, *129*, 2248.

(4) (a) Oblinger, E.; Montgomery, J. *J. Am. Chem. Soc.* **1997**, *119*, 9065. (b) Lozanov, M.; Montgomery, J. *J. Am. Chem. Soc.* **2002**, *124*, 2106. (c) Ni, Y.; Amarasinghe, K. K. D.; Montgomery, J. *Org. Lett.* **2002**, *4*, 1743.

(5) (a) Barboni, L.; Giarlo, G.; Ricciutelli, M.; Ballini, R.; Georg, G. I.; VanderVelde, D. G.; Himes, R. H.; Wang, M.; Lakdawala, A.; Snyder, J. P. *Org. Lett.* **2004**, *6*, 461–464. (b) Mehta, G.; Roy, S. *Org. Lett.* **2004**, *6*, 2389.

(6) For Ni-catalyzed asymmetric alkylative coupling reactions of alkynes and imines, see: (a) Patel, S. J.; Jamison, T. F. *Angew. Chem., Int. Ed.* **2003**, *42*, 1364. (b) Patel, S. J.; Jamison, T. F. *Angew. Chem., Int. Ed.* **2004**, *43*, 3941 For Rh-catalyzed enantioselective arylative cyclization of alkynals, see: (c) Shintani, R.; Okamoto, K.; Otomaru, Y.; Ueyama, K.; Hayashi, T. *J. Am. Chem. Soc.* **2005**, *127*, 54.

(7) See Supporting Information and refs 3a, b, j, and 3l.

(8) Ogoshi, S.; Arai, T.; Ohashi, M.; Kunosawa, H. *Chem. Commun.* **2008**, 1347.

JA805296K