ORGANIC LETTERS

2007
Vol. 9, No. 26
5597−5599

Nickel-Catalyzed Enantio- and Diastereoselective Three-Component Coupling of 1,3-Dienes, Aldehydes, and Silanes Using Chiral N-Heterocyclic Carbenes as Ligands

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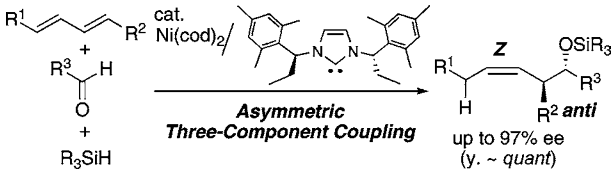
Received October 19, 2007

ABSTRACT

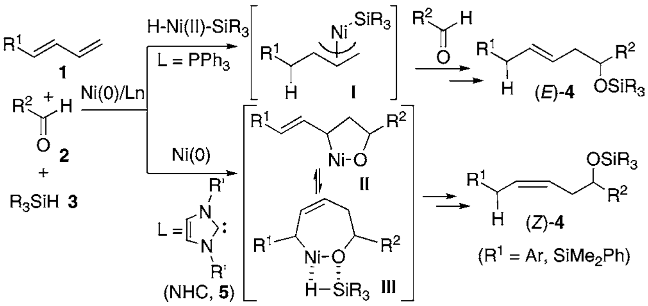


Nickel(0)-catalyzed asymmetric three-component coupling of 1,3-dienes, aldehydes, and silanes has been realized utilizing a chiral N-heterocyclic carbene as a ligand. On the basis of the screening of various NHC precursors, an imidazolium salt having 1-(2,4,6-trimethylphenyl)propyl groups on the nitrogen was designed and synthesized. In this reaction, various coupling products were produced in good yields with high regio-, diastereo- (anti selective in the case of the internal 1,3-diene), and enantioselectivities (up to 97% ee).

Multicomponent reactions that produce complex molecules from more than three parts of a simple compound in one operation are quite useful in organic synthesis.[1] We have recently developed nickel(0)-catalyzed stereoselective three-component coupling of 1,3-diene **1**, aldehyde **2**, and silane (R_3SiH) **3**, in which the stereoselectivity and the reaction pathway are controlled by the properties of the phosphorus ligand and N-heterocyclic carbene (NHC) (Scheme 1).[2,3] Thus, the use of PPh_3 as a ligand gave the coupling product (*E*)-**4** via π-allylnickel intermediate **I**, generated by the reaction of 1,3-diene **1** and H−Ni(II)-SiR_3.[2a]

On the other hand, it is interesting that the reaction using NHC **5** instead of PPh_3 proceeds via σ-bond metathesis between nickelacycle **III** and R_3SiH **3**, exclusively giving (*Z*)-**4**.[2b,c] The unique property of NHC prompted us to expand the latter reaction to an asymmetric one using a chiral NHC. NHCs have attracted much attention as ligands of various transition metals;[4] however, there are only a few examples of asymmetric reactions using a chiral NHC as a ligand.[5] Herein we report a nickel(0)-catalyzed asymmetric three-component coupling of 1,3-diene, aldehyde, and silanes using a chiral NHC.[6]

Scheme 1



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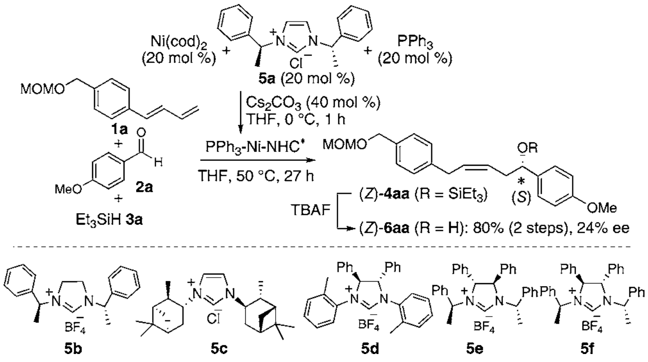
[1] (a) Zhu, J., Bienaymé, H., Eds. In *Multicomponent Reactions*; Wiley-VCH Verlag Gmbh and Co. KGaA: Weinhein, Germany, 2005. (b) Ramón, D. J.; Yus, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 1602.

[2] (a) Takimoto, M.; Hiraga, Y.; Sato, Y.; Mori, M. *Tetrahedron Lett.* **1998**, *39*, 4543. (b) Sato, Y.; Sawaki, R.; Mori, M. *Organometallics* **2001**, *20*, 5510. (c) Sawaki, R.; Sato, Y.; Mori, M. *Org. Lett.* **2004**, *6*, 1131.

10.1021/ol702543m CCC: \$37.00

First, we examined the coupling reaction of 1,3-diene **1a**, anisaldehyde (**2a**), and Et_3SiH (**3a**) using Ni(cod)$_2$ (20 mol %), PPh_3 (20 mol %), and chiral imidazolium salt **5a**[7a] (20 mol %) as an NHC precursor in the presence of Cs_2CO_3 (40 mol %) according to the previously reported optimal procedure (Scheme 2).[2c] As a result, the coupling product (*Z*)-**4aa** was obtained in a stereoselective manner, and its enantiomeric excess was determined to be 24% by HPLC analysis of alcohol (*Z*)-**6aa** obtained by desilylation of (*Z*)-**4aa** (80% yield, two steps). Asymmetric coupling utilizing **5b**,[7b] **5c**,[7c] **5d**,[7d] **5e**,[7b] or **5f**[7b] as an NHC precursor was investigated under the same conditions, but the ee was low in each case (**5b**, 79%, 4% ee (*S*); **5c**, 92%, 8% ee (*R*); **5d**, 76%, 28% ee (*S*); **5e**, 72%, 12% ee (*S*); **5f**, 78%, 20% ee (*R*)).

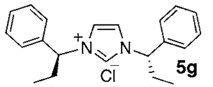
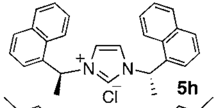
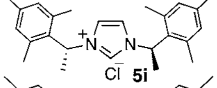
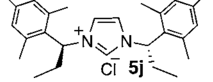
Scheme 2



Next, we tried to modify the structure of **5a** to improve the enantioselectivity (Table 1). The use of **5g** having 1-phenylpropyl groups slightly increased the ee of (*Z*)-**4aa** up to 31% (run 1).

Table 1. Reaction Using Various NHC Precursors[a]

$$\mathbf{1a} + \mathbf{2a} + \mathbf{3a} \xrightarrow[\text{THF, 50 °C}]{\text{PPh}_3\text{-Ni-NHC}^*} (Z)\text{-}\mathbf{4aa}$$

run	NHC precursor	time (h)	yield (%)	ee (%)
1	 **5g**	21	91	31 (*S*)
2	 **5h**	112	92	46 (*S*)
3	 **5i**	18	82	61 (*R*)
4[b]		18	91	68 (*R*)
5[b]	 **5j**	10	83	71 (*S*)

[a] All reactions (except for runs 4 and 5) were carried out using 20 mol % PPh_3−Ni−NHC* catalyst generated in situ from Ni(cod)$_2$ (20 mol %), PPh_3 (20 mol %), and imidazolium salt (20 mol %) in the presence of Cs_2CO_3 (40 mol %). [b] The reaction was carried out in the absence of PPh_3.

In the reaction using **5h**[7a] having naphthyl groups, (*Z*)-**4aa** was obtained in 92% yield with 46% ee (run 2), suggesting that the bulkiness of the aromatic ring is important for obtaining good enantioselectivity. The reaction was carried out using **5i**, in which mesityl groups had been introduced instead of phenyl groups in **5a**, and the ee of (*Z*)-**4aa** was improved to 61% (run 3). The reaction using Ni−NHC* catalyst prepared from Ni(cod)$_2$, **5i**, and Cs_2CO_3 in the absence of PPh_3 gave a better result (run 4). Finally, we designed and synthesized imidazolium salt **5j**, in which both methyl and phenyl groups in **5a** were changed into ethyl and mesityl groups, respectively. As expected, the ee of (*Z*)-**4aa** was improved to 71% (run 5).

Having tuned up the structure of the NHC precursor, we turned our attention to asymmetric coupling of various 1,3-dienes, aldehydes, and Et_3SiH using **5j** as the NHC precursor (Table 2). The reaction of **1a** and aldehyde **2b**, **2c**, or **2d** in the presence of Et_3SiH using Ni−NHC* catalyst prepared from Ni(cod)$_2$, **5j**, and Cs_2CO_3 afforded the product (*Z*)-**4ab**, **4ac**, or **4ad** in good yield with enantioselectivity comparable to that of (*Z*)-**4aa** (runs 1−3). The reaction of sila-diene **1b**, **2a**, and Et_3SiH (**3a**) gave **6ba** having a (*Z*)-allylsilane moiety in 60% yield (two steps) and 70% ee (run 4). It is interesting that the coupling of unsymmetrical internal 1,3-diene **1c**, **2a**,

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(3) Reviews on Ni(0)-catalyzed multicomponent coupling, see: (a) Ikeda, S.-i. *Acc. Chem. Res.* **2000**, *33*, 511. (b) Montgomery, J. *Acc. Chem. Res.* **2000**, *33*, 467. (c) Montgomery, J. *Angew. Chem., Int. Ed.* **2004**, *43*, 3890. For recent examples of Ni(0)-catalyzed multicomponent coupling: (d) Mahandru, G. M.; Liu, G.; Montgomery, J. *J. Am. Chem. Soc.* **2004**, *126*, 3698. (e) Chrovian, C. C.; Montgomery, J. *Org. Lett.* **2007**, *9*, 537. (f) Terao, J.; Nii, S.; Chowdhury, F. A.; Nakamura, A.; Kambe, N. *Adv. Synth. Catal.* **2004**, *346*, 905. (g) Kimura, M.; Miyachi, A.; Kojima, K.; Tanaka, S.; Tamaru, Y. *J. Am. Chem. Soc.* **2004**, *126*, 14360. (h) Kimura, M.; Ezoe, A.; Mori, M.; Tamaru, Y. *J. Am. Chem. Soc.* **2005**, *127*, 201. (i) Kimura, M.; Kojima, K.; Tatsuyama, Y.; Tamaru, Y. *J. Am. Chem. Soc.* **2006**, *128*, 6332. (j) Cozzi, P. G.; Rivalta, E. *Angew. Chem., Int. Ed.* **2005**, *44*, 3600. (k) Ng, S.-S.; Ho, C.-Y.; Jamison, T. F. *J. Am. Chem. Soc.* **2006**, *128*, 11513. (l) Ho, C.-Y.; Jamison, T. F. *Angew. Chem., Int. Ed.* **2007**, *46*, 782.

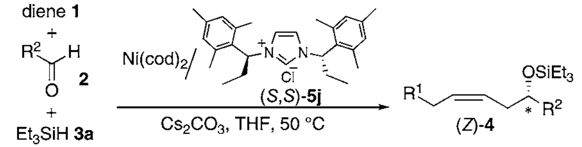
(4) Reviews of NHC ligands: (a) Herrmann, W. A. *Angew. Chem., Int. Ed.* **2002**, *41*, 1290. (b) Nolan, S. P., Ed. In *N-Heterocyclic Carbenes in Synthesis*; Wiley-VCH Verlag Gmbh and Co. KGaA: Weinhein, Germany, 2006. (c) For NHC ligands for Ni complex, see: Tekavec, T. N.; Louie, J. *Top. Organomet. Chem.* **2007**, *21*, 159.

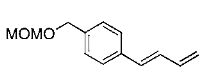
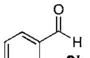
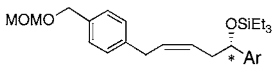
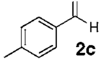
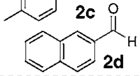
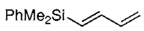
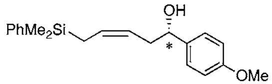
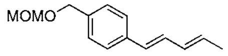
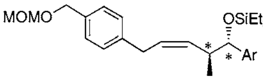
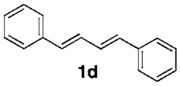
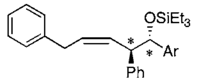
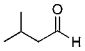
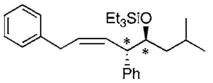
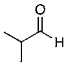
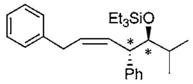
(5) Reviews of asymmetric reaction using chiral NHC ligands: (a) Gade, L. H.; Bellemin-Laponnaz, S. *Top. Organomet. Chem.* **2007**, *21*, 117. (b) Perry, M. C.; Burgess, K. *Tetrahedron: Asymmetry* **2003**, *14*, 951. For representative examples of asymmetric C−C bond forming reaction catalyzed by metal−NHC* complex, see: (c) Enders, D.; Gielen, H.; Raabe, G.; Runsink, J.; Teles, H. *Chem. Ber.* **1996**, *129*, 1483. (d) Lee, S.; Hartwig, J. F. *J. Org. Chem.* **2001**, *66*, 3402. (e) Funk, T. W.; Berlin, J. M.; Grubbs, R. H. *J. Am. Chem. Soc.* **2006**, *128*, 1840. (f) Bonnet, L. G.; Douthwaite, R. E.; Kariuki, B. M. *Organometallics* **2003**, *22*, 4187. (g) Ma, Y.; Song, C.; Ma, C.; Sun, Z.; Chai, Q.; Andrus, M. B. *Angew. Chem., Int. Ed.* **2003**, *42*, 5871. (h) Larsen, A. O.; Leu, W.; Oberhuber, C. N.; Campbell, J. E.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2004**, *126*, 11130. (i) Lee, Y.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2006**, *128*, 15604. (j) Martin, D.; Kehrli, S.; d'Augustin, M.; Clavier, H.; Mauduit, M.; Alexakis, A. *J. Am. Chem. Soc.* **2006**, *128*, 8416. Very recently, a Ni(0)-catalyzed asymmetric coupling using a chiral NHC ligand has been reported, see: (k) Chaulagain, M. R.; Sormunen, G. J.; Montgomery, J. *J. Am. Chem. Soc.* **2007**, *129*, 9568.

(6) For other examples of Ni(0)-catalyzed asymmetric coupling, see:(a) Ikeda, S.-i.; Cui, D.-M.; Sato, Y. *J. Am. Chem. Soc.* **1999**, *121*, 4712. (b) Miller, K. M.; Huang, W.-S.; Jamison, T. F. *J. Am. Chem. Soc.* **2003**, *125*, 3442.

(7) (a) Herrmann, W. A.; Goossen, L. J.; Köcher, C.; Artus, G. R. J. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2805. (b) Guillen, F.; Winn, C. L.; Alexakis, A. *Tetrahedron: Asymmetry* **2001**, *12*, 2083. (c) Huang, J.; Jafarpour, L.; Hillier, A. C.; Stevens, E. D.; Nolan, S. P. *Organometallics* **2001**, *20*, 2878. (d) Seiders, T. J.; William, W.; Grubbs, R. H. *Org. Lett.* **2001**, *3*, 3225.

Table 2. Reactions of Various 1,3-Dienes and Aldehydes[a]



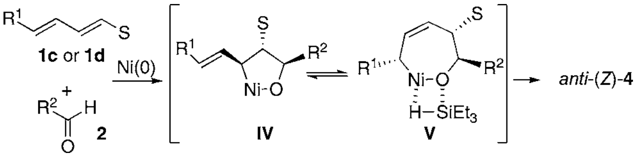
run	diene	R^2-CHO	coupling product
1	 **1a**	 **2b**	 **4ab**: 87% (12 h), 63% ee
2		 **2c**	**4ac**: 71% (20 h), 60% ee
3		 **2d**	**4ad**: 87% (41 h), 70% ee
4[b]	 **1b**	**2a**	 **6ba**: 60% (2 steps), 70% ee
5	 **1c**	**2a**	 **4ca**: 81% (18 h), 50% ee
6	 **1d**	**2a**	 **4da**: 87% (50 °C, 1.5 h), 90% ee
7		**2a**	**4da**: 90% (23 °C, 1.5 h), 93% ee
8		**2a**	**4da**: 93% (-20 °C, 48 h), 97% ee
9[c]		**2a**	**4da**: 100% (-20 °C, 93 h), 97% ee
10		**2d**	**4dd**: 81% (23 °C, 52 h), 95% ee
11[d]		 **2e**	 **4de**: 91% (50 °C, 17 h), 82% ee
12[d]		 **2f**	 **4df**: 85% (50 °C, 64 h), 93% ee

[a] Reaction run using 1,3-diene **1** (1.0 equiv), aldehyde **2** (1.0 equiv), Et_3SiH (5.0 equiv), and 20 mol % Ni−NHC* catalyst prepared from $Ni(cod)_2$ (20 mol %), (*S*,*S*)-**5j** (20 mol %) in the presence of Cs_2CO_3 (40 mol %), unless otherwise noted. [b] Reaction run using 1.5 equiv of aldehyde **2a** to 1,3-diene **1b**. [c] Reaction run using 10 mol % of Ni−NHC* catalyst. [d] Reaction run using 20 mol % of Ni−NHC* catalyst prepared from $Ni(cod)_2$ (20 mol %), (*R*,*R*)-**5j** (20 mol %) in the presence of Cs_2CO_3 (40 mol %).

and **3a** proceeded in a regio- and diastereoselective manner, giving (*Z*)-**4ca** in 81% yield as a sole product, although the ee was modest (50%) (run 5).[8] The reaction of (1*E*,3*E*)-1,4-diphenylbuta-1,3-diene (**1d**),[9] **2a**, and **3a** under the same conditions was completed within 1.5 h, and the *anti*-product (*Z*)-**4da** was again produced in 87% yield as a sole product (run 6).[8] We were very pleased that the ee of (*Z*)-**4da** increased up to 90%. The high reactivity of **1d** enabled us to conduct the coupling reaction at a lower temperature with a low catalyst loading. Thus, the coupling of **1d**, **2a**, and **3a** proceeded at 23 °C (run 7) and even at −20 °C (run 8), giving (*Z*)-**4da** in 90% yield (93% ee) and 93% yield (97% ee), respectively. The same reaction using 10 mol % Ni−NHC* catalyst also produced (*Z*)-**4da** in a quantitative yield with a high enantioselectivity (97% ee) (run 9). Similarly, the coupling of **1d**, **2d**, and **3a** also proceeded at 23 °C, giving (*Z*)-**4da** in 81% yield and 95% ee (run 10). Furthermore, aliphatic aldehydes are tolerated as a substrate in this coupling reaction, and the reaction of **1d** with **2e** or **2f** in the presence of **3a** proceeded at 50 °C in a regio- and diastereoselective manner, giving the corresponding *anti*-product (*Z*)-**4de** or (*Z*)-**4df** in 91% yield (82% ee) or 85% yield (93% ee), respectively.

The diastereoselectivity in the case of internal 1,3-dienes **1c** and **1d** can be explained as shown in Scheme 3. When the oxanickelacycle is formed from the internal 1,3-diene and aldehyde, it is thought that nickelacycle **IV** is most stable because all substituents are in a *trans*-orientation with respect to each other. Nickelacycle **IV** would be in equilibrium with **V**, and σ-bond metathesis between **V** with Et_3SiH occurs, giving the anti product (*Z*)-**4ca**, (*Z*)-**4da**, (*Z*)-**4dd**, (*Z*)-**4de**, or (*Z*)-**4df** in a diastereoselective manner.

Scheme 3



In summary, an asymmetric three-component coupling of 1,3-dienes, aldehydes, and silane has been realized using Ni−NHC* catalyst, and various coupling products were produced in good yields with high regio-, diastereo-, and enantioselectivities. Compared to the extensive and successful results of NHC as a ligand for transition metals, asymmetric reactions utilizing a chiral NHC in which a high enantioselectivity (>90% ee) has been achieved are still rare. The present results pave the way for extension of the utilization of NHCs as chiral ligands. Further studies along this line are in progress.

Acknowledgment. This work was supported by a Grant-in-Aid for Scientific Research on Priority Areas (No. 19028001, “Chemistry of Concerto Catalysis”) from the Ministry of Education, Culture, Sports, Science and Technology, Japan and by a Grant-in-Aid for Scientific Research (B) (No. 19390001) from the Japan Society for the Promotion of Science (JSPS).

Supporting Information Available: Experimental details and determination of the stereochemistry of the products. This material is available free of charge via the Internet at http://pubs.acs.org.

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[8] The reaction of **1c** or **1d** and **2c** in the presence of Et_3SiH using an achiral NHC, I^iPr as a ligand under similar conditions also gave **1cc** (95%, anti:syn = 11:1) or **1dc** (58%, anti only) in a diastereoselective manner: Sawaki, R.; Mori, M.; Sato, Y. Unpublished results.

[9] Very recently, an asymmetric reductive coupling of **1d** and aldehydes in the presence of $ZnEt_2$ using chiral phosphoramidite ligands has been reported. See: Yang, Y.; Zhu, S.-F.; Duan, H.-F.; Zhou, C.-Y.; Wang, L.-X.; Zhou, Q.-L. *J. Am. Chem. Soc.* **2007**, *129*, 2248.

[10] For determination of the absolute and relative configuration of the coupling products, see Supporting Information.