Communications to the Editor

A Novel Asymmetric Cyclization of *ω*-Formyl-1,3-dienes Catalyzed by a Zerovalent Nickel Complex in the Presence of Silanes

Yoshihiro Sato, Nozomi Saito, and Miwako Mori*

Graduate School of Pharmaceutical Sciences
Hokkaido University, Sapporo 060-0812, Japan

Received November 19, 1999

The development of the methodology for synthesis of cyclic compounds (i.e., carbocycles or heterocycles) as an optically active form is quite important and indispensable in modern synthetic organic chemistry since there are many biologically active compounds having complicated cyclic structures. Transition metal-catalyzed cyclization of prochiral substrates utilizing chiral ligands should be one of the most useful and promising strategies for the construction of chiral carbon centers, which are attached to the ring or contained in the ring framework, in the cyclic compounds. However, there have only been a few excellent reports on transition metal-catalyzed asymmetric cyclization via a C−C bond forming reaction.[1,2] Here we report the first example of a nickel(0)-catalyzed asymmetric cyclization of 1,3-diene and a tethered aldehyde in the presence of silanes.

We recently reported a nickel-catalyzed cyclization of 1,3-dienes and tethered carbonyl groups to produce five- to seven-membered ring carbocycles,[3a−c] heterocycles,[3e] and bicyclic heterocycles (pyrrolizidine and indolizidine)[3d,e] in a stereoselective manner. To examine the feasibility of applying this cyclization to an asymmetric version, we tried the cyclization of prochiral substrate **1** using various ligands in the presence of Et_3SiH (Scheme 1). First of all, treatment of **1** with $Ni(cod)_2$ (20 mol %) and PPh_3 (40 mol %) in the presence of Et_3SiH (5 equiv) in degassed THF at room temperature for 12 h afforded the cyclized product **2a**[4] in 84% yield as a sole product.

Next, we tried asymmetric cyclization of **1** with $Ni(cod)_2$ (20 mol %) and various chiral ligands (20 mol % (bidentate ligand) or 40 mol % (monodentate ligand)) in the presence of Et_3SiH (5 equiv) in THF. Unfortunately, the use of various chiral ligands gave only a low conversion and enantiomeric excess of **2a** [e.g., (*S*)-BINAP:[5a] 2% yield, 0% ee (SM recovered in 38%); (*R*)-H-MOP:[5b] 2% yield, 16% ee (SM recovered in 50%); (*S*)-(*R*)-PPFA:[5c] 3% yield, 10% ee (SM recovered in 43%); (4*S*)-2-(2-diphenylphosphinophenyl)-4-isopropyl-1,3-oxazoline:[5d] 13% yield, 3% ee (SM recovered in 40%); NMDPP:[5e] 2% yield, ee not determined (SM recovered in 32%)]. However, it was surprising that the reaction of **1** using $Ni(cod)_2$ (10 mol %) and chiral phosphorane **4**[5f] (20 mol %) as a monodentate ligand in the presence of Et_3SiH (5 equiv) in THF smoothly proceeded at room temperature to afford the cyclized products **2a** and **3a**[4] in 84% yield (ratio of 4.3:1). The enantiomeric excesses of **2a** and **3a** were determined by HPLC analysis with a chiral stationary phase column to be 2% ee and 47% ee, respectively. Encouraged by this result, the effects of silane on the ratio and enantiomeric excess of the cyclized products were carefully examined, and the results are summarized in Table 1.[4]

Scheme 1

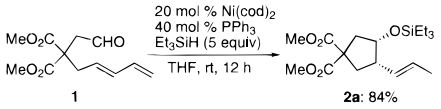
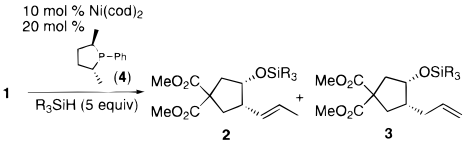


Table 1. Cyclization of **1** Using $Ni(cod)_2$ and Ligand **4** in the Presence of Various Silanes



run	R_3SiH	time (h)	yield (%) (**2**+**3**)	ratio[a] **2**/**3**	ee (%) **2**/**3**
1[b]	Et_3SiH (**a**)	5	84	4.3/1	2/47
2[b]	$^tBuMe_2SiH$ (**b**)	8	83	>50/1	16/−
3[c]	$(EtO)_3SiH$ (**c**)	5	60	12/1	46/33
4[c]	Ph_3SiH (**d**)	2	80	1.7/1	47/53
5[c]	Ph_2MeSiH (**e**)	2	83	1.2/1	27/78
6[c]	$PhMe_2SiH$ (**f**)	7	82	1.9/1	21/72

[a] The ratio was determined by ^1H NMR. [b] The reaction was carried out in THF at room temperature. [c] The reaction was carried out in THF at 0 °C.

The cyclization of **1** using $^tBuMe_2SiH$ produced **2b** in 83% yield exclusively, and the ee was increased to 16% ee (run 2). The use of $(EtO)_3SiH$ improved the enantiomeric excess of **2c** up to 46% ee, while the ratio of **2c** to **3c** was still kept high (run 3). It was interesting that the reaction using Ph_2MeSiH afforded **3e** with good enantioselectivity (78% ee), although the ratio of **3e** to **2e** was low (run 5). Thus, we focused on the solvent effects in the reaction using $(EtO)_3SiH$ and Ph_2MeSiH (Table 2). It was found that the use of a polar solvent (e.g., DMF, CH_3CN) gave a high ratio and enantioselectivity of **2c** in the reaction using $(EtO)_3SiH$. Namely, the reaction of **1** with $Ni(cod)_2$ (10 mol %)

* Correspondence author. E-mail: mori@pharm.hokudai.ac.jp.

(1) For reviews, see: (a) Ojima, I.; Tzamarioudaki, M.; Li, Z.; Donovan, R. J. *Chem. Rev.* **1996**, *96*, 635 and references therein. (b) Lautens, M.; Klute, W.; Tam, W. *Chem. Rev.* **1996**, *96*, 49 and references therein. (c) Trost, B. M. *Science* **1991**, *254*, 1471 and references therein. (d) Trost, B. M. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 259 and references therein. (e) Trost, B. M.; Krische, M. J. *Synlett* **1998**, 1 and references therein. (f) Noyori, R. *Asymmetric Catalysis in Organic Synthesis*; Wiley: New York, 1994. (g) *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; VCH: New York, 1993.

(2) For recent key examples, see: (a) Perch, N. S.; Widenhoefer, R. A. *J. Am. Chem. Soc.* **1999**, *121*, 6960. (b) Shibasaki, M.; Boden, C. D. J.; Kojima, A. *Tetrahedron* **1997**, *53*, 7371 and references therein. (c) Goeke, A.; Sawamura, M.; Kuwano, R.; Ito, Y. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 662. (d) Murakami, M.; Itami, K.; Ito, Y. *J. Am. Chem. Soc.* **1997**, *119*, 2950. (e) Fujii, N.; Kakiuchi, F.; Yamada, A.; Chatani, N.; Murai, S. *Chem. Lett.* **1997**, 425. (f) Hicks, F. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **1996**, *118*, 11688. (g) Yamaura, Y.; Hyakutake, M.; Mori, M. *J. Am. Chem. Soc.* **1997**, *119*, 7615. (h) La, D. S.; Alexander, J. B.; Cefalo, D. R.; Graf, D. D.; Hoveyda, A. H.; Schrock, R. R. *J. Am. Chem. Soc.* **1998**, *120*, 9720. (i) For asymmetric cyclopropanations, see: 1f and 1g.

(3) (a) Sato, Y.; Takimoto, M.; Hayashi, K.; Katsuhara, T.; Takagi, K.; Mori, M. *J. Am. Chem. Soc.* **1994**, *116*, 9771. (b) Sato, Y.; Takimoto, M.; Mori, M. *Tetrahedron Lett.* **1996**, *37*, 887. (c) Sato, Y.; Takimoto, M.; Mori, M. *Synlett* **1997**, 734. (d) Sato, Y.; Saito, N.; Mori, M. *Tetrahedron Lett.* **1997**, *38*, 3931. (e) Sato, Y.; Saito, N.; Mori, M. *Tetrahedron* **1998**, *54*, 1153. (f) Sato, Y.; Takanashi, T.; Hoshiba, M.; Mori, M. *Tetrahedron Lett.* **1998**, *39*, 5579.

(4) Details of the determination of stereochemistry, enantiomeric excess, and absolute configuration of all cyclized products are given in Supporting Information.

(5) (a) Miyashita, A.; Yasuda, A.; Takaya, H.; Toriumi, K.; Ito, T.; Souchi, T.; Noyori, R. *J. Am. Chem. Soc.* **1980**, *102*, 7932. (b) Uozumi, Y.; Suzuki, N.; Ogiwara, A.; Hayashi, T. *Tetrahedron* **1994**, *50*, 4293. (c) Hayashi, T.; Yamamoto, K.; Kumada, M. *Tetrahedron Lett.* **1974**, 4405. (d) von Matt, P.; Pfaltz, A. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 566. (e) Morrison, J. D.; Masler, W. F. *J. Org. Chem.* **1974**, *39*, 270. (f) Burk, M. J.; Feaster, J. E.; Harlow, R. L. *Organometallics* **1990**, *9*, 2653.

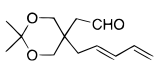
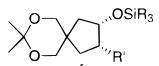
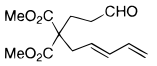
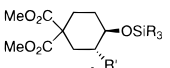
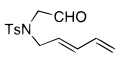
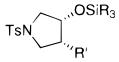
10.1021/ja994059l CCC: $19.00
Published on Web 02/25/2000

Table 2. Cyclization of **1** Using Using $Ni(cod)_2$ and Ligand **4** Under Various Conditions

run[a]	R_3SiH	solvent	temp (°C)	time (h)	yield (%) (**2**+**3**)	ratio[b] **2**/**3**	ee (%) **2**/**3**
1	$(EtO)_3SiH$ (**c**)	toluene	0	7	69	5.7/1	35/24
2	$(EtO)_3SiH$ (**c**)	DMF	0	3	74	12/1	58/41
3	$(EtO)_3SiH$ (**c**)	CH_3CN	0	2	79	>50/1	61/−
4	$(EtO)_3SiH$ (**c**)	DMF	−30	7	60	>50/1	73/−
5	$(EtO)_3SiH$ (**c**)	CH_3CN	−30	8	83	>50/1	73/−
6	Ph_2MeSiH (**e**)	toluene	0	3	88	1.7/1	17/77
7	Ph_2MeSiH (**e**)	DMF	0	3	87	1.1/1	39/81
8	Ph_2MeSiH (**e**)	DMF	−20	28	73	1/1.2	44/86
9	Ph_2MeSiH (**e**)	CH_3CN	−20	24	83	1/1	40/85

[a] All reactions were carried out using $Ni(cod)_2$ (10 mol %) and ligand **4** (20 mol %) in the presence of silane (5 equiv). [b] The ratio was determined by ^1H NMR.

Table 3. Cyclization of Various Substrates Using $Ni(cod)_2$ and Ligand **4**

run[a]	substrate / R_3SiH	solvent	temp (°C)	time (h)	yield (%) (**I**+**T**)[b]	product ratio[c] **I** / **T**	ee (%) **I** / **T**
	 **5**				 **6**: R'= (**I**) **7**: R'= (**T**)		
1	$(EtO)_3SiH$ (**c**)	CH_3CN	-30	10	80	> 50 / 1	64 / –
	 **8**				 **9**: R'= (**I**) **10**: R'= (**T**)		
2	$(EtO)_3SiH$ (**c**)	DMF	-30	24	51	1 / 2.6	42 / 66
3	Ph_2MeSiH (**e**)	DMF	0	9	61	7.3 / 1	61 / 66
	 **11**				 **12**: R'= (**I**) **13**: R'= (**T**)		
4	$(EtO)_3SiH$ (**c**)	CH_3CN	0	6	60	4.6 / 1	48 / 41
5	Ph_2MeSiH (**e**)	DMF	0	42	22	1 / 2.4	10 / 67

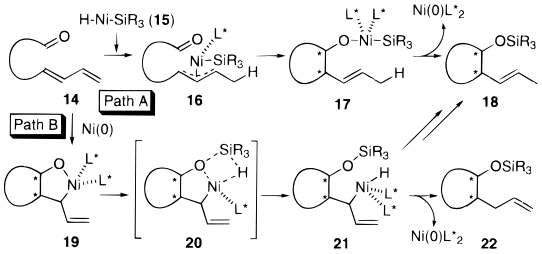
[a] All reactions were carried out using $Ni(cod)_2$ (10 mol %) and **4** (20 mol %) in the presence of silane (5 equiv). [b] Product **I** or **T** means that having an internal olefin or a terminal olefin in the side chain (R′), respectively. [c] The ratio was determined by ^1H NMR.

and **4** (20 mol %) in the presence of $(EtO)_3SiH$ (5 equiv) in DMF or CH_3CN at −30 °C afforded **2c** exclusively in 73% ee (60% yield) or 73% ee (83% yield), respectively.

It was very interesting that the use of a polar solvent (e.g., DMF, CH_3CN) in the presence of Ph_2MeSiH (5 equiv) increased the production and enantiomeric excess of **3e**. Thus, in the reaction in DMF or CH_3CN at −20 °C, the ratio of **2e** to **3e** was indicated to be 1/1.2 or 1/1, and the enantiomeric excess of **3e** reached up to 86 or 85%, respectively.

On the basis of these results, the asymmetric cyclizations of various substrates were investigated (Table 3). Cyclization of **5** with 10 mol % $Ni(cod)_2$ and ligand **4** in the presence of $(EtO)_3SiH$ in CH_3CN at −30 °C afforded **6c**[4] in 80% yield, 64% ee as a sole product (run 1). Cyclization of **8** using $(EtO)_3SiH$ in DMF at −30 °C afforded a mixture of six-membered ring compounds **9c** and **10c** in 51% yield, in which **10c** (66% ee) was produced in preference to **9c** (42% ee) in the ratio of 2.6 to 1 (run 2).[4] On the other hand, cyclization of **8** using Ph_2MeSiH in DMF afforded **9e** (61% ee) in preference to **10e** (66% ee) in the ratio of 7.3 to 1 in a total 61% yield (run 3).[4]

Scheme 2



It is noteworthy that this asymmetric cyclization is applicable to the construction of a pyrrolidine ring. Thus, cyclization of **11** with 10 mol % $Ni(cod)_2$ and ligand **4** in the presence of $(EtO)_3SiH$ in CH_3CN gave **12c** (48% ee) and **13c** (41% ee) (ratio of 4.6 to 1) in a total 60% yield (run 4).[4] On the other hand, the cyclization of **11** using Ph_2MeSiH produced **13e** (67% ee) in preference to **12e** (10% ee) in the ratio of 2.4 to 1 (run 5).[4]

The formation of **3**, **7**, **10**, or **13**, having a terminal olefin in the side chain, could not be accounted for by the above-mentioned mechanism,[3] in which π-allylnickel intermediate **16** was produced by the reaction of **14** and nickel hydride complex **15** (Scheme 2, Path A). Another pathway (path B), by which the formation of a cyclized product having a terminal olefin in the side chain would be accountable, is also shown in Scheme 2.

The mechanism of path B contains a sigma bond metathesis of silanes and the nickel/oxygen bond of oxanickelacycle **19**, which has been recently proposed by Montgomery in a Ni(0)-catalyzed cyclization of ynals in the presence of silanes.[6] Thus, oxanickelacycle **19** would be formed by oxidative cycloaddition of **14** to Ni(0) complex. Sigma bond metathesis of R_3SiH and the nickel/oxygen bond of **19** would produce nickel hydride intermediate **21**, which would afford **22**, having a terminal olefin in the side chain, directly by reductive elimination. The formation of **18**, having an internal olefin in the side chain, might be also accountable by the path B through reductive elimination from **21** via a π-allylnickel intermediate. Since both the ratio and enantiomeric excess of the cyclized product, having an internal olefin or a terminal olefin in the side chain, varied depending upon substrates and/or silanes, we speculated that both the mechanisms of path A and path B would operate in this asymmetric cyclization. Further mechanistic investigations are in progress.

In conclusion, we succeeded in realizing a nickel(0)-catalyzed asymmetric cyclization of 1,3-diene and tethered aldehyde for the first time. The present results should pave the way to a novel strategy for construction of cyclic compounds as an optically active form.

Supporting Information Available: Typical procedure for asymmetric cyclization; determination of stereochemistry, enantiomeric excess, and absolute configuration of the cyclized products; spectral data for substrates, products, and related compounds (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

JA994059L

(6) Tang, X.-Q.; Montgomery, J. *J. Am. Chem. Soc.* **1999**, *121*, 6098 and references therein.