Asymmetric Synthesis of Isoindoline and Isoquinoline Derivatives Using Nickel(0)-Catalyzed [2 + 2 + 2] Cocyclization

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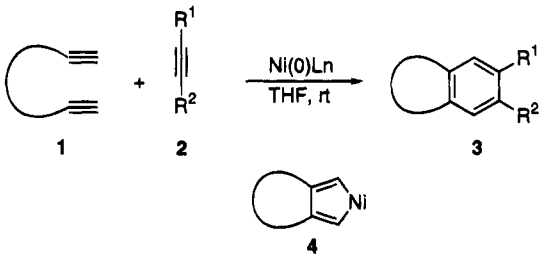
Summary: A nickel(0)-catalyzed asymmetric [2 + 2 + 2] cocyclization has been realized for the first time, giving the isoindoline **16a** in 73% ee (52% yield) and the isoquinoline **17b** in 54% ee (62% yield), respectively.

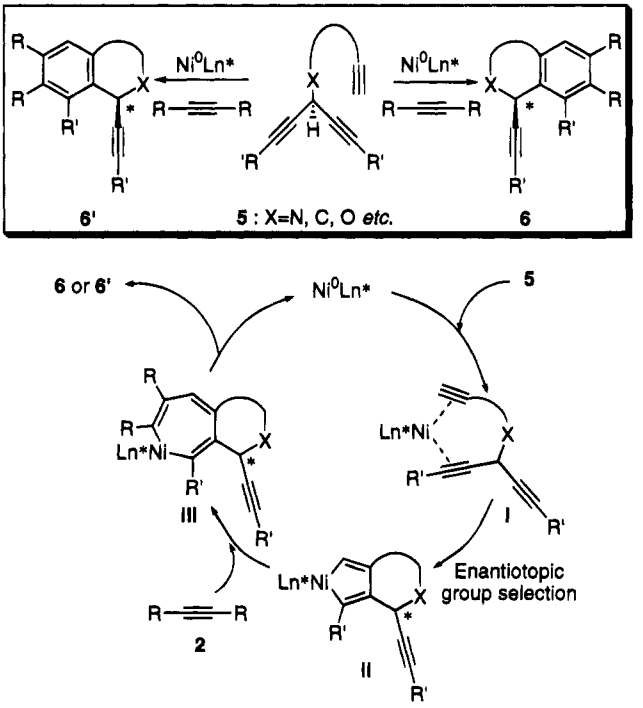
The [2 + 2 + 2] cocyclization of α,ω-diynes and alkynes in the presence of a transition metal complex is valuable in modern synthetic organic chemistry because regio- and stereospecific C—C bond formation occurs.[1,2] Recently, nickel(0)-promoted [2 + 2 + 2] cocyclization was reported.[3] The reaction mechanism was not clear, but it was speculated that formation of a nickelacyclopentadiene **4** as an intermediate by oxidative cyclization of the two alkynes was involved (Scheme 1).[3,4] If the nickelacyclopentadiene **4** is truly an intermediate and then the alkyne **2** is inserted into **4**, the reaction should proceed using a catalytic amount of a low valent nickel complex analogous to a rhodium-catalyzed cocyclization.[2]

Most analgesics such as morphine have chiral carbon centers at the benzylic position. For the construction of such centers,[5,6] we planned to use a nickel(0)-catalyzed [2 + 2 + 2] cocyclization of α,ω-diynes. Our basic strategy for the catalytic asymmetric synthesis of isoindoline and isoquinoline derivatives is shown in Scheme 2, which involves conceptually new enantiotopic group selective formation of nickelacyclopentadiene. According to the above-mentioned speculations, the two triple bonds of the triyne **5** (one of them is a straight-chain alkyne, and the other is one of two branched alkynes) react with zero valent nickel complex coordinated with a chiral ligand to give the nickelacyclopentadiene **II** in an optically active form *via* **I**. The insertion of alkyne **2** into **II** would afford the nickelacycloheptatriene **III**. Then reductive elimination would proceed, which provides the heterocycle **6** or **6'** having the benzylic chiral carbon center. Thus, a catalytic asymmetric synthesis of isoindoline and isoquinoline would be realized.

Scheme 1



Scheme 2



In order to realize the nickel-catalyzed asymmetric synthesis according to our strategy, use of acetylene or disubstituted alkynes **2** is necessary.[7,8] We examined the [2 + 2 + 2] cocyclization of diyne **7a** and gaseous acetylene. A balloon filled with gaseous acetylene was connected at the reaction vessel containing a THF solution of **7a** and 20 mol % nickel(0) complex, generated

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(1) (a) Vollhardt, K. P. C. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 539 and references cited therein. (b) Vollhardt, K. P. C. *Acc. Chem. Res.* **1977**, *10*, 1.

(2) (a) Grigg, R.; Scott, R.; Stevenson, P. *J. Chem. Soc., Perkin Trans. 1* **1988**, 1357. (b) Grigg, R.; Scott, R.; Stevenson, P. *Tetrahedron Lett.* **1982**, *23*, 2691. (c) Neeson, S. J.; Stevenson, P. J. *Tetrahedron* **1989**, *45*, 6239. (d) Neeson, S. J.; Stevenson, P. J. *Tetrahedron Lett.* **1988**, *29*, 813.

(3) (a) Bhatarah, P.; Smith, E. H. *J. Chem. Soc., Perkin Trans. 1* **1992**, 2163. (b) Bhatarah, P.; Smith, E. H. *J. Chem. Soc., Chem. Commun.* **1991**, 277. (c) Bhatarah, P.; Smith, E. H. *J. Chem. Soc., Perkin Trans. 1* **1990**, 2603.

(4) It was reported that the reaction of a hepta-1,6-diyne and a monosubstituted alkyne using a stoichiometric amount of nickel(0) complex afforded indan derivatives in good to moderate yields. However, it was also reported that the reaction using a catalytic amount of nickel(0) complex (20 mol %) went to 40–50% completion. See ref 3c.

(5) For some elegant examples of the catalytic asymmetric construction of chiral carbon centers at the benzylic position, see: (a) Noyori, R.; Ohta, M.; Hsiao, Y.; Kitamura, M.; Ohta, T.; Takaya, H. *J. Am. Chem. Soc.* **1986**, *108*, 7117. (b) Kitamura, M.; Hisao, Y.; Noyori, R.; Takaya, H. *Tetrahedron Lett.* **1987**, *28*, 4829. (c) Kitamura, M.; Hsiao, Y.; Ohta, M.; Tsukamoto, M.; Ohta, T.; Takaya, H.; Noyori, R. *J. Org. Chem.* **1994**, *59*, 297. (d) Takemoto, T.; Sodeoka, M.; Sasai, H.; Shibasaki, M. *J. Am. Chem. Soc.* **1993**, *115*, 8477.

(6) For an elegant example of the diastereoselective alkylation of tetrahydroisoquinolines, see: (a) Meyers, A. I.; Fuents, L. M. *J. Am. Chem. Soc.* **1983**, *105*, 117. (b) Meyers, A. I.; Dickman, D. A.; Bailey, T. R. *J. Am. Chem. Soc.* **1985**, *107*, 7974. (c) Meyers, A. I.; Bailey, T. R. *J. Org. Chem.* **1986**, *51*, 872. (d) Meyers, A. I.; Dickman, D. A.; Boes, M. *Tetrahedron* **1987**, *43*, 5095. (e) Meyers, A. I.; Boes, M.; Dickman, D. A. *Org. Synth.* **1989**, *67*, 60. (f) Meyers, A. I.; Guiles, J.; Warmus, J. S.; Gonzalez, M. A. *Tetrahedron Lett.* **1991**, *32*, 5505. For other examples of asymmetric synthesis of optically active alkaloids based on stoichiometric chirality transfer, see ref 5c.

(7) The nickel catalyzed [2 + 2 + 2] cocyclization of diyne **7b** and propargyl alcohol in the presence of 10 mol % nickel(0) complex, generated from $Ni(acac)_2$ (10 mol %) and DIBAH (2 equiv to Ni) in the presence of PPh_3 (40 mol %), smoothly proceeded to give an inseparable mixture of isoquinoline derivatives **23** (R_1 = H, R_2 = CH_2OH and R_1 = CH_2OH, R_2 = H) (1:2, the regioisomers of the hydroxymethyl group on the aromatic ring) in 72% yield.

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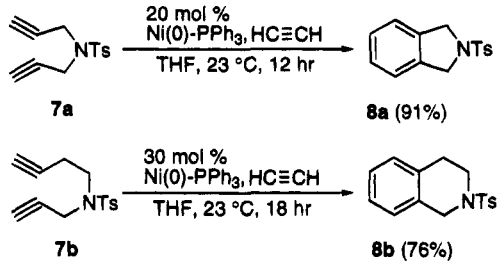
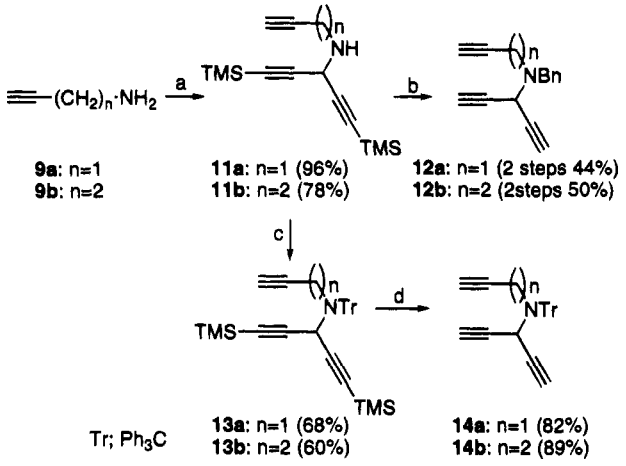
Scheme 3



Scheme 4[a]



[a] Reaction conditions: (a) TMS—≡—CHO **10**, $MgSO_4$, benzene, 23 °C; TMS—≡—H, BuLi, $BF_3{\cdot}Et_2O$, THF, -78 °C; (b) BnBr, K_2CO_3, CH_3CN, 23 °C; Bu_4NF, THF, -78 °C; (c) Ph_3CCl, K_2CO_3, CH_3CN, 23 °C; (d) Bu_4NF, THF, 0 °C

from $Ni(acac)_2$ (20 mol %) and DIBAH (2 equiv to Ni) in the presence of PPh_3 (80 mol %) at 0 °C, and the solution was stirred at room temperature for 12 h. The reaction smoothly proceeded to give the isoindoline derivative **8a** in 91% yield (Scheme 3). Treatment of **7b** with 30 mol % nickel(0) complex under the same conditions afforded the isoquinoline derivative **8b** in 76% yield.

The starting triynes for asymmetric [2 + 2 + 2] cocyclization were prepared as shown in Scheme 4. Condensation of the amine **9a** or **9b** with the aldehyde **10** followed by nucleophilic addition of lithium acetylide in the presence of $BF_3{\cdot}Et_2O$[9] afforded **11a** or **11b** in good yield. Reaction of **11a** or **11b** with benzyl bromide or trityl chloride afforded **12a**, **12b**, **13a**, or **13b**, respectively. Treatment of **13a** or **13b** with Bu_4NF provided **14a** or **14b**.

Scheme 5

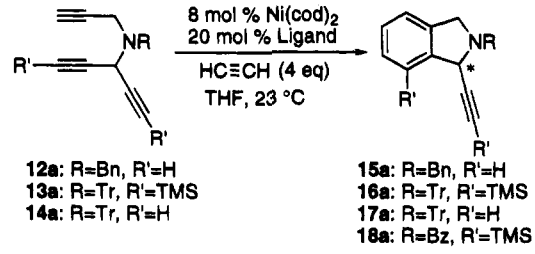
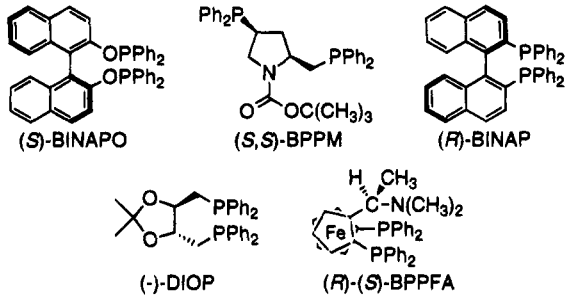


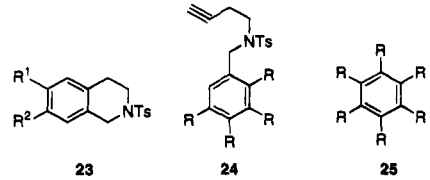
Table 1. Catalytic Asymmetric [2 + 2 + 2] Cocyclization of 13a and 14a

run	substrate	ligand	time (hr)	yield (%)	ee (%)	SM recover (%)
1	**14a**	dppb	1.5	74	—	—
2		(*S*)-BINAPO	16	66	12	—
3		(*S,S*)-BPPM	2	82	45	—
4	**13a**	dppb	5	83	—	—
5		(*R*)-BINAP	140	57	22	18
6		(*S*)-BINAPO	115	52	18	14
7		(-)-DIOP	18	87	0	—
8		(*S,S*)-BPPM	18	92	60	—
9		(*R*)-(*S*)-BPPFA	150	52	73	33



Initially, the [2 + 2 + 2] cocyclization of the triyne **12a** and gaseous acetylene in the presence of various chiral ligands was investigated. However, reproducible results for these reactions were not obtained because an excess amount of acetylene would act as an ligand to the nickel complex. Thus, a THF solution of acetylene (0.5 M solution) was prepared and the reaction of triyne **12a** and acetylene solution (4 equiv to substrate) in the presence of 8 mol % $Ni(cod)_2$ and various chiral ligands (20 mol %) was reinvestigated (Scheme 5). Unfortunately, only a low enantiomeric excess of **15a** was obtained [e.g., (*R*)-BINAP;[10a] 4% ee, 22% yield; (−)-DIOP;[10a] 1% ee, 65% yield; (*S,S*)-BPPM;[10a] 2% ee, 52% yield; (*S*)-BINAPO;[10b] 7% ee, 34% yield]. However, it was found that bulky substituents on the nitrogen atom affected the enantiomeric excess of the cyclized product (Table 1). Namely, the reaction of **14a** with acetylene in the presence of $Ni(cod)_2$ and (*S,S*)-BPPM as the chiral ligand afforded **17a** with 45% ee (82% yield, run 3). The ee of isoindoline was improved in the reaction of **13a** having TMS groups on the alkynes. The reaction of **13a** with acetylene utilizing (*S,S*)-BPPM afforded the isoindoline **16a** in 60% ee, 92%

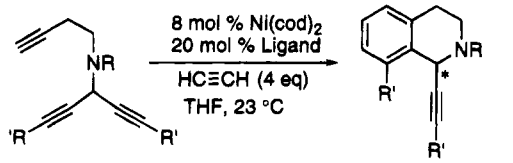
(8) The reaction of diyne **7b** with disubstituted alkynes **2a** ($R_1 = R_2$ = TMS), **2b** ($R_1 = R_2 = CH_2OH$), and **2c** ($R_1 = CH_2OH$, R_2 = TMS), in the presence of 10 mol % nickel(0) complex and PPh_3 (40 mol %) in THF, did not afford the cyclized products, presumably because of steric hindrance. When the reaction of **7b** with dimethyl acetylenedicarboxylate (DMAD) was carried out in the presence of 10 mol % nickel(0) complex and PPh_3 (40 mol %), only a small amount of the desired product **23** ($R_1 = R_2$ = COOMe) (7% yield) was obtained in addition to **24** (27% yield) and **25**. The yield of **23** ($R_1 = R_2$ = COOMe) was improved when PBu_3 (4 equiv to Ni) was used as the ligand because DMAD strongly coordinates to the low-valent nickel complex owing to back donation.



(9) Wada, M.; Sakurai, Y.; Akiba, K. *Tetrahedron Lett.* **1984**, *25*, 1083.

(10) (a) Kagan, H. B. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press, Inc.: New York, 1985; Vol. 5, p 1 and references cited therein. (b) Grubbs, R. H.; DeVries, R. A. *Tetrahedron Lett.* **1977**, 1879. Trost, B. M.; Murphy, D. J. *Organometallics* **1985**, *4*, 1143. (c) Hayashi, T.; Kumada, M. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press, Inc.: New York, 1985; Vol. 5, p 147.

Scheme 6



12b: R=Bn, R'=H
13b: R=Tr, R'=TMS
14b: R=Tr, R'=H

15b: R=Bn, R'=H
16b: R=Tr, R'=TMS
17b: R=Tr, R'=H
18b: R=Bz, R'=H

yield (run 8), and the use of (*R*)-(*S*)-BPPFA[10c] gives **16a** in 73% ee (52% yield, 76% conversion yield, run 9).[11]

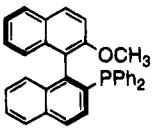
Subsequently, a [2 + 2 + 2] cocyclization of **12b**, **13b**, or **14b** to afford the isoquinoline derivative was examined. In this case, the reaction of the triyne **13b**, having a trityl group on the nitrogen atom and TMS groups on the alkynes, with acetylene in the presence of 8 mol % $Ni(cod)_2$ and PPh_3 or dppb did not proceed. In the reaction of the triyne **12b** or **14b**, having no substituents on the alkynes, with acetylene in the presence of 8 mol % $Ni(cod)_2$ and 20 mol % dppb, the isoquinolines **15b** and **17b** were obtained in 61% and 97% yield, respectively (Scheme 6). Next, a catalytic asymmetric [2 + 2 + 2] cocyclization of **12b** and **14b** was investigated, utilizing either (*S*,*S*)-BPPM or (*R*,*S*)-BPPFA as a chiral bidentate ligand, giving the isoquinolines **15b** [(*S*,*S*)-BPPM; 1% ee, 16% yield] and **17b** (Table 2, runs 3 and 4) with only low enantiomeric excess, respectively.[12] On the other hand, the enantiomeric excess of **17b** increased to 58% in the reaction of **14b** using a chiral monodentate ligand, (*S*)-MeO-MOP.[13] It was very surprising to observe that, in the reaction of **13a** using (*S*)-MeO-MOP under the same conditions, **16a** was obtained in 0% ee, 43% yield. Though the reason was not clear, it was quite interesting that the cyclization of **14b** using a chiral monodentate ligand provided a good result, although the isoindoline system (the cyclization of **13a**) was preferred for a chiral bidentate ligand. The isoquinoline derivative **17b** was converted to the known tricyclic amine **22** and the absolute configuration was determined by comparison of its $[\alpha]_D$ sign with the literature specific rotation for **22** (Scheme 7).[14]

In conclusion, a nickel(0)-catalyzed asymmetric [2 + 2 + 2] cocyclization has been realized for the first time. Although the enantioselectivity is still modest, it may be possible to develop a conceptually new methodology for the construction of benzylic chiral carbon centers, which are important for the synthesis of biologically active substances. Further studies along this line are in progress.

Table 2. Catalytic Asymmetric [2 + 2 + 2] Cocyclization of 14b

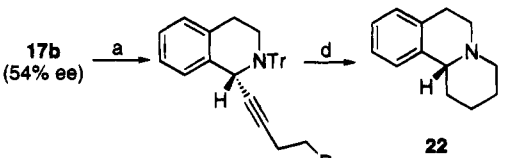
run	ligand	time (hr)	yield of **17b** (%)	ee (%)	SM recover (%)
1	dppb	45	97	—	—
2	(*R*)-BINAP	137	—	—	82
3	(*S*,*S*)-BPPM	40	42	6	53
4	(*R*)-(*S*)-BPPFA	42	22	1	78
5	(*S*)-MeO-MOP[a]	1.5	36	58	—
6[b]	(*S*)-MeO-MOP[a]	1.5	62	54	—

[a] The reaction was carried out using 40 mol % of (*S*)-MeO-MOP.
[b] Acetylene was used 10 eq to **14b**.



(*S*)-MeO-MOP

Scheme 7[a]



[a] Reaction conditions: (a) BuLi, HMPA, Et_2O, $BrCH_2CH_2OTBS$, -78 °C-reflux; TBAF, THF, 52%; (b) MsCl, Et_3N, CH_2Cl_2, 82%; (c) LiCl, DMF, 60 °C, 70%; (d) Pd/C, H_2, HCl-MeOH; K_2CO_3, MeOH, 47%

Supplementary Material Available: Characterization data for **11a,b**, **12a,b**, **13a,b**, **14a,b**, **15a,b**, **16a**, **17a,b**, and **19–21** and typical experimental procedures for catalytic asymmetric [2 + 2 + 2] cocyclization of **13a** and **14b** (3 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(11) The ees of **15a** and **17a** were determined by HPLC analysis with a chiral stationary phase column (**15a** → DAICEL CHIRALCEL OJ, hexane/2-propanol = 9/1; **17a** → DAICEL CHIRALCEL OD, hexane/2-propanol = 9/1). In the case of **16a**, after conversion to **18a** by deprotection of the trityl group and successive protection with a benzoyl group, the ee of **18a** was determined by HPLC analysis (DAICEL CHIRALPAK AS, hexane/2-propanol = 9/1). The absolute configurations of these isoindoline derivatives have not been determined yet.

(12) The ee of **15b** was determined by HPLC analysis with a chiral stationary phase column (DAICEL CHIRALCEL OJ, hexane/ethanol = 19/1). On the other hand, the ee of **17b** was determined by HPLC analysis after conversion to **18b** (DAICEL CHIRALPAK AD, hexane/ethanol = 19/1).

(13) Uozumi, Y.; Hayashi, T. *J. Am. Chem. Soc.* **1991**, *113*, 9887. Hayashi, T.; Iwamura, H.; Naito, M.; Matsumoto, Y.; Uozumi, Y. *J. Am. Chem. Soc.* **1994**, *116*, 775.

(14) (a) Horii, Z.; Ikeda, M.; Yamawaki, Y.; Tamaru, Y.; Saito, S.; Kodera, K. *Tetrahedron* **1963**, *19*, 2101. (b) Craig, J. C.; Chan, R. P. K.; Roy, S. K. *Tetrahedron* **1967**, *23*, 3573. Also see ref 6.