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A New and General Synthetic Pathway to *Strychnos* Indole Alkaloids: Total Syntheses of (−)-Dehydrotubifoline and (−)-Tubifoline by Palladium-Catalyzed Asymmetric Allylic Substitution

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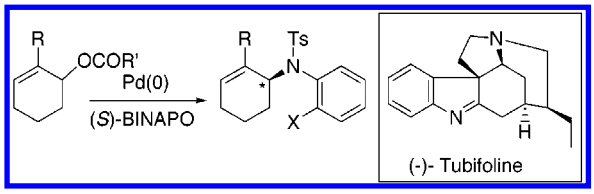
ABSTRACT



A novel procedure for the synthesis of an indole skeleton was developed. Treatment of a cyclohexenol derivative having a silyloxymethyl group at the 2-position with *N*-tosyl-*o*-bromoaniline in the presence of Pd_2dba_3·$CHCl_3$ and (*S*)-BINAPO gave compound 6a with 84% ee in 75% yield. Compound 6a was converted into 11, which was treated with $Pd(OAc)_2$ and Me_2PPh in the presence of Ag_2CO_3 to give indoline derivative 12. From 12, we succeeded in the total syntheses of (−)-dehydrotubifoline and (−)-tubifoline.

There are many alkaloids having an aromatic ring connected to a cyclohexane ring. Palladium-catalyzed asymmetric allylic substitution is a very attractive procedure for the synthesis of these alkaloids. We have already reported the syntheses of (−)-mesembrane,[1a] (−)-mesembrine,[1a] (+)-crinamine,[1b] (−)-haemanthidine,[1b] and (+)-pretazetine[1b] from 2-arylcyclohexenylamine derivatives **3** prepared by palladium-catalyzed asymmetric allylic substitution.[1] It is expected that intramolecular allylic substitution of **1a** using Pd(0) would afford indoline derivative **3a**. However, there is no functional group in **3a** except the double bond, and the synthesis of a natural product from **3a** would therefore be difficult. Thus, we made an alternative plan for the synthesis of indole alkaloids. If cyclohexenol derivative **4** having a functional group at the 2-position were reacted with *o*-bromoaniline derivative **5a** in the presence of a palladium catalyst with a chiral ligand,[2] compound **6** would be obtained as a chiral form. Treatment of **6** with Pd(0) would give indoline derivative **7**, which should be a useful precursor for the synthesis of indole alkaloids.

At first, we selected 2-carboethoxycyclohexenol derivative **4a**.[3] When methyl carbonate **4a** was reacted with allyl tosylamide **8** (1.1 equiv) in the presence of 2.6 mol % of $Pd_2(dba)_3$·$CHCl_3$ and 5.2 mol % of (*S*)-BINAPO[4] in DMF at room temperature for 3 h, allylamine derivative **9a** was obtained in 40% yield, but the ee of **9a** was only 5%[5] (Table

(1) (a) Mori, M.; Kuroda, S.; Zhang, C.-S.; Sato, Y. *J. Org. Chem.* **1997**, *62*, 5265. (b) Nishimata, T.; Mori, M. *J. Org. Chem.* **1998**, *63*, 7586. (c) Nishimata, T.; Yamaguchi, K.; Mori, M. *Tetrahedron Lett.* **1999**, *40*, 5713.

(2) After we reported the palladium-catalyzed asymmetric allylic substitution of a 2-arylcyclohexenol derivative, similar reactions were reported by two groups: (a) Trost, B. M.; Toste, F. D. *J. Am. Chem. Soc.* **2000**, *122*, 11262. (b) Hamada, Y.; Sakaguchi, K.; Hatano, K.; Hara, O. *Tetrahedron Lett.* **2001**, *42*, 1297.

(3) Graff, M.; Al Dilaimi, A.; Seguineau, P.; Rambaud, M.; Villeras, J. *Tetrahedron Lett.* **1986**, *27*, 1577.

(4) Grubbs, B. H.; DeVries, R. A. *Tetrahedron Lett.* **1977**, *18*, 1879.

(5) Conversion of **9a** into **9c** was carried out by treatment with $LiAlH_4$. The ee of **9c** was determined by HPLC analysis using DAICEL CHIRALPAK AD (hexane/^{i}PrOH 9:1).

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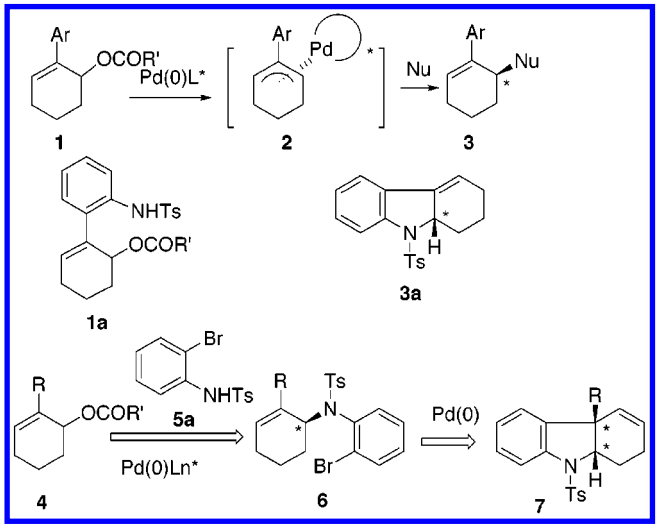
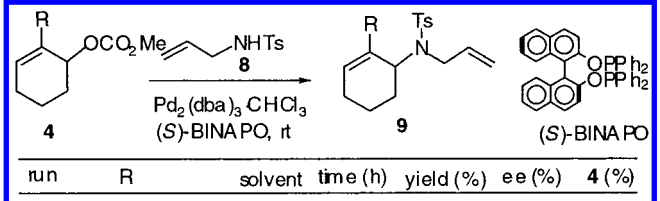
Scheme 1. Our Plan for the Synthesis of an Indole Skeleton



1, run 1). Treatment of **4b** and **4c** with **8** in the presence of a palladium catalyst did not afford the desired product (runs 2 and 3). In the case of **4c**, palladium black was precipitated during the reaction and none of the product was formed except the starting material. However, when cyclohexenol derivative **4d** having a benzyloxymethyl group at the 2-position was reacted with **8** in the presence of a palladium catalyst, the desired product **9d** was obtained in 49% yield and the ee showed 34%.[6] The result was very encouraging, and the silyl group was chosen as a protecting group. When compound **4e** (R = $CH_2OSi^tBuMe_2$) was treated with 2.6 mol % of $Pd_2(dba)_3{\cdot}CHCl_3$ and 5.2 mol % of (*S*)-BINAPO in THF at room temperature for 100 h, **9e** with 78% ee was obtained in 53% yield.[6] The use of DMF as a solvent enhanced the reaction rate, and **9e** was obtained in 70% yield after only 3.5 h (run 5). Various silyl groups were examined, and in each case, the ee was almost same (runs 6−8).

Table 1. Asymmetric Allylic Substitution[a]

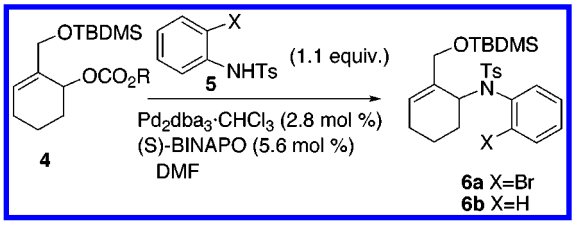


run	R		solvent	time (h)		yield (%)	ee (%)	4 (%)
1	CO_2Et	**4a**	DMF	3	**9a**	40	5	—
2		**4b**	THF	24		—	—	84
3	CH_2OH	**4c**	DMF	13		—	—	29
4	CH_2OBn	**4d**	THF	28	**9d**	49	34	36
5	$CH_2OTBDMS$	**4e**	THF	100	**9e**	53	78	23
6	$CH_2OTBDMS$	**4e**	DMF	3.5	**9e**	70	77	—
7	CH_2OTES	**4f**	DMF	2	**9f**	66	71	—
8	$CH_2OTBDPS$	**4g**	DMF	12	**9g**	57	75	—

[a] All reactions were carried out using $Pd_2(dba)_3{\cdot}CHCl_3$ (2.6 mol %) and (*S*)-BINAPO at room temperature.

Subsequently, *N*-tosylaniline **5b** (X = H) was used as a nucleophile, and **6b** was obtained in 85% yield (Table 2, run 1).

Table 2. Reaction with Aniline Derivatives



run	R		5, X	temp (°C)	time (h)		yield (%)	ee (%)
1	Me	**4e**	H	rt	3	**6b**	85	76
2	Me	**4e**	Br	rt	7	**6a**	78	80
3	$CH{=}CH_2$	**4h**	Br	0	21	**6a**	75	84
4	$CH{=}CH_2$	**4h**	Br	−20	168	**6a**	67	83

The use of *N*-tosyl-*o*-bromoaniline **5a** gave a desired compound **6a** in 78% yield, and the ee[7] was 80% (run 2). To enhance the reactivity of the leaving group, vinyl carbonate **4h** was used,[8] and the reaction was carried out at 0 °C to give **6a** with 84% ee in 75% yield (run 3). The lower reaction temperature did not affect the ee of **6a** (run 4).

Next, we tried to synthesize an indoline derivative from **6a** using a palladium catalyst. When a DMF solution of **6a** was warmed at 90 °C for 24 h in the presence of $Pd(OAc)_2$ (5 mol %), PPh_3 (10 mol %), and Ag_2CO_3[9] (1 equiv), we were pleased to find that indoline derivatives **10a** and **10b** were obtained in 50% yield in a ratio of 5.3 to 1. The result of an NOE experiment of **10a** showed that the stereochemistry of the fused five-six-membered ring was a *cis*-configuration. As a ligand, dimethylphenylphosphine gave **10** in high yield, although the ratio of **10a** to **10b** was 3 to 1 (run 3). Isomerization product **10b** was not found when DMSO was used as a solvent (run 5).

On the basis of these results, we focused on a total synthesis of *Strychnos* alkaloids, which include (−)-tubifoline, (−)-tubifolidine, and (−)-strychnine. Our target molecule was (−)-tubifoline,[10] which has been synthesized by several groups,[11] as a racemic[11a−d] or a chiral form.[11e] A retrosynthetic analysis of (−)-tubifoline is shown in Scheme 2. (−)-Tubifoline would be synthesized from **I**, which would be obtained from tetracyclic compound **II**. The synthesis of indoline derivative **III** from **IV** has already been demon-

(6) The ee's of **9d** and **9e** were determined after conversion into **9c**.[5]

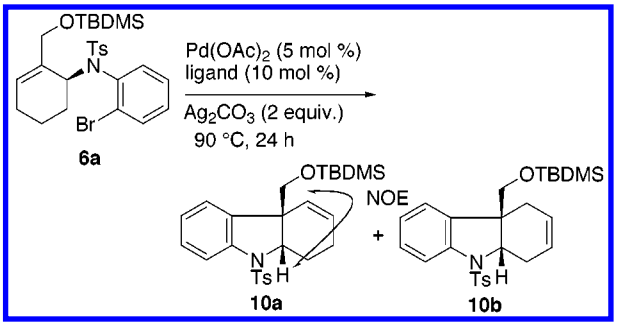
(7) The ees of **6a** and **6b** were determined by HPLC analyses using DAICEL CHIRALCEL OJ-R (CH_3CN/H_2O 9:1) and DAICEL CHIRALCEL OJ (hexane/^{i}PrOH 9:1) after desilylation by treatment with 4 N HCl, respectively.

(8) Mori, M.; Nishimata, T.; Nagasawa, Y.; Sato, Y. *Adv. Synth. Catal.* **2001**, *343*, 34.

(9) The use of silver salts suppressed alkene isomerization in the Heck reaction: Abelman, M. M.; Oh, T.; Overman, L. E. *J. Org. Chem.* **1987**, *52*, 4130.

(10) For the isolation and structural elucidation of this alkaloid, see: Kump, W. G.; Patel, M. B.; Rowson, J. M.; Schmid, H. *Helv. Chim. Acta* **1964**, *47*, 1497.

Table 3. Synthesis of an Indoline Derivative

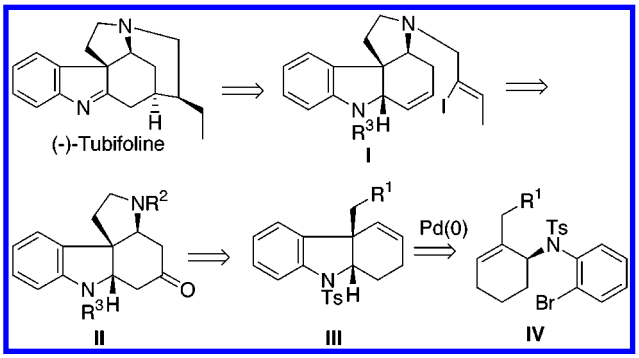


run	ligand	solvent	**10a** (%)	**10b** (%)	**6a** (%)
1	PPh_3	DMF	42	8	33
2	$PMePh_2$	DMF	52	13	29
3	PMe_2Ph	DMF	56	19	20
4	PMe_2Ph	C_3H_7CN	17	1	71
5	PMe_2Ph[a]	DMSO	47	0	38

[a] Reaction temperature: 105 °C.

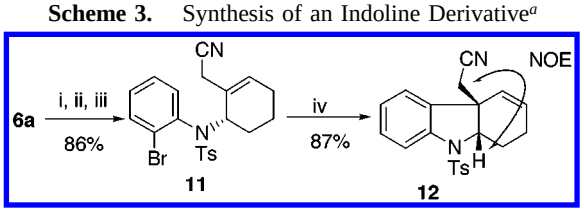
strated. Thus, for the synthesis of **II**, compound **IV** (R^1 = CN) would be suitable.

Scheme 2. Retrosynthetic Analysis of Tubifoline



Compound **6a** was converted into **11**, which was treated with 2 mol % of $Pd(OAc)_2$ and 4 mol % of PMe_2Ph in the presence of Ag_2CO_3 (1 equiv) in DMSO at 90 °C for 17 h to give indoline derivative **12** in 87% yield (Scheme 3). No olefin isomerization product was produced. The result of an

Scheme 3. Synthesis of an Indoline Derivative[a]

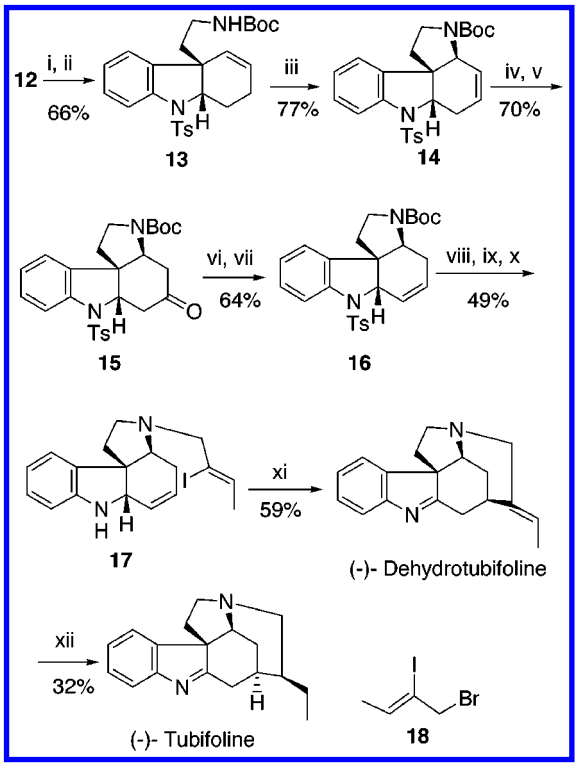


[a] (i) 4 N aqueous HCl; (ii) PBr_3; (iii) NaCN; (iv) 2 mol % $Pd(OAc)_2$, 4 mol % Me_2PPh, Ag_2CO_3 (1 equiv), DMSO, 90 °C, 17 h.

NOE experiment showed that the ring junction of the fused five-six-membered ring was also *cis*.

Treatment of **12** with $LiAlH_4$ followed by protection of nitrogen gave **13** in 66% yield. Allylic oxidation of **13** with $Pd(OAc)_2$ in the presence of benzoquinone and MnO_2[12] gave the expected tetracyclic compound **14** in 77% yield. The amide nitrogen attacked the double bond on the cyclohexene ring coordinated to Pd(II) to produce **14**. Regioselective hydroboration of **14** with 9-BBN proceeded smoothly at 50 °C followed by treatment with H_2O_2 and NaOH to give the alcohol, which was oxidized to give ketone **15** in 70% yield. Treatment of **15** with potassium hexamethyldisilazide and then $PhNTf_2$ afforded the enol triflate,[13] which was converted into olefin **16** by treatment with HCO_2H and $^iPr_2NEt$ in the presence of $Pd(OAc)_2$ and PPh_3[14] in 64% yield.

Scheme 4. Total Syntheses of (−)-Dehydrotubifoline and (−)-Tubifoline[a]



[a] (i) $LiAlH_4$; (ii) Boc_2O; (iii) 10 mol % $Pd(OAc)_2$, 40 mol % benzoquinone, MnO_2 (2 equiv) AcOH, 50 °C, 20 h; (iv) 9-BBN, 50 °C, then H_2O_2; (v) Swern oxidation; (vi) $PhNTf_2$, KHMDS; (vii) $Pd(OAc)_2$, PPh_3, HCO_2H, iPr$_2$NEt; (viii) Na-naphthalenide. (ix) CF_3CO_2H; (x) **18**, K_2CO_3; (xi) 10 mol % $Pd(OAc)_2$, Bu_4NCl (1 equiv) K_2CO_3 (5 equiv) DMF, 60 °C, 3 h. (xii) H_2, PtO_2, EtOH, rt.

Deprotection of the tosyl group of **16** with sodium naphthalenide followed by treatment with CF_3CO_2H gave

(11) (a) Danson, B. A.; Harley-Mason, J.; Foster, G. H. *Chem. Commun.* **1968**, 1233. (b) Takano, S.; Hirama, M.; Ogasawara, K. *Tetrahedron Lett.* **1982**, *23*, 881. (c) Ban, Y.; Yoshida, K.; Goto, I.; Oishi, T.; Takeda, E. *Tetrahedron* **1983**, *39*, 3657. (d) Amat, M.; Linares, A.; Bosch, J. *J. Org. Chem.* **1990**, *55*, 6299. (e) Amat, M.; Coll, M.-D.; Bosch, J.; Espinosa, E.; Molins, E. *Tetrahedron: Asymmetry* **1997**, *8*, 935.

(12) Hansson, S.; Heumann, A.; Rain, T.; Åkermark, B. *J. Org. Chem.* **1990**, *55*, 975.

diamine. Monoalkylation with **18**[15a] in the presence of K_2CO_3 proceeded smoothly to give **17** in 49% yield from **16**. Intramolecular Heck reaction using a palladium catalyst[15a,16] gave a pentacyclic compound in 59% yield, whose ^1H and ^{13}C NMR spectra agreed with those of (−)-dehydrotubifoline reported in the literature.[15] However, the $[\alpha]_D$ value of (−)-dehydrotubifoline is not known. Thus, hydrogenation of (−)-dehydrotubifoline with PtO_2 in EtOH was carried out to give (−)-tubifoline, whose $[\alpha]_D$ value[17] and ^1H and ^{13}C NMR spectra agreed with those reported in the literature.[10,18] The result indicated that the absolute configuration of the product **6a**, which was obtained by asymmetric allylic substitution, was *S*. Thus, we succeeded in the total synthesis of (−)-dehydrotubifoline and (−)-tubifolin from allylamine derivative **6a**, which was synthesized by palladium-catalyzed asymmetric allylic substitution, via 16 steps. All steps for the ring constructions were achieved using the palladium catalysts.

Further studies on the asymmetric synthesis of *Strychnos* alkaloids are now in progress.

Supporting Information Available: Experimental procedure and spectral data of **4h**, **9a**, **9d**−**f**, **6a**,**b**, **10a**, **11**−**17**, (−)-dehydrotubifoline, and (−)-tubifoline. This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) Cacchi, S.; Morera, E.; Orter, G. *Tetrahedron Lett.* **1984**, *25*, 4821.
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(16) Jeffery, T. *Tetrahedron Lett.* **1985**, *26*, 2667.
(17) 84% ee, $[\alpha]^{22}_D$ −311 (*c* 0.236, AcOEt).
(18) Schumann, D.; Schmid, H. *Helv. Chim. Acta* **1963**, *46*, 1996.