Catalytic Asymmetric Synthesis of Natural Products with Heterocyclic Rings

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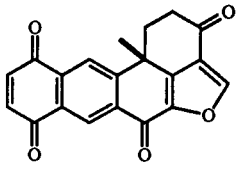
Introduction.

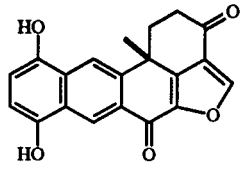
A catalytic asymmetric synthesis of useful compounds is one of the most challenging topics in modern synthetic organic chemistry. This review focuses on a catalytic asymmetric synthesis of natural products with heterocyclic rings such as halenaquinone, halenaquinol and tubifolidine. The catalytic asymmetric synthesis utilizes either an asymmetric Heck reaction [1] or a heterobimetallic asymmetric catalysis [2] as key steps.

I. Catalytic Asymmetric Synthesis of Halenaquinone and Halenaquinol.

Halenaquinone **1** and halenaquinol **2**, which have a benzylic quaternary carbon center as well as a unique pentacyclic skeleton, have been isolated from a variety of sea sponges (Chart I) [3]. These marine natural products have been shown to possess antibiotic, cardiotonic and protein tyrosine kinase inhibitory activity [4]. To date, only Harada and coworkers have succeeded in the total synthesis of **1** and **2** starting from optically pure Wieland-Miescher ketone [5]. We report here a full account of a catalytic asymmetric synthesis of **1** and **2** starting from commercially available 6,7-dimethoxy-1-tetralone **3** [6,7,8]. This synthesis features the use of an asymmetric Heck reaction or the first use of a cascade Suzuki cross-coupling and an asymmetric Heck reaction as well as the one-pot construction of a unique pentacyclic ring system from a tricyclic ring system using palladium chemistry. Moreover, a cascade Suzuki cross-coupling and a Heck Reaction using Ph_3As as an achiral ligand, leading to an efficient synthesis of (±)-**1** and (±)-**2**, are also described.



halenaquinone **1**

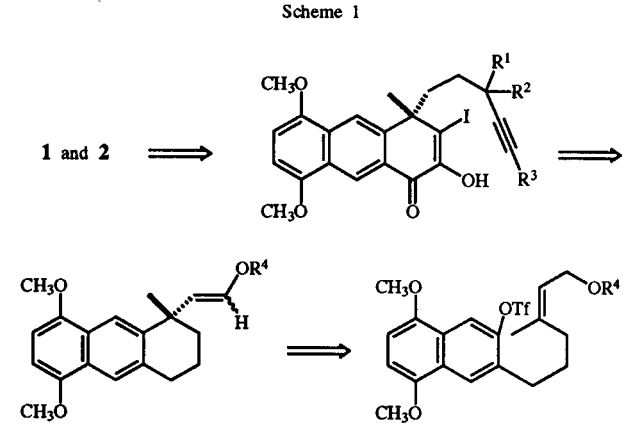


halenaquinol **2**

Chart 1

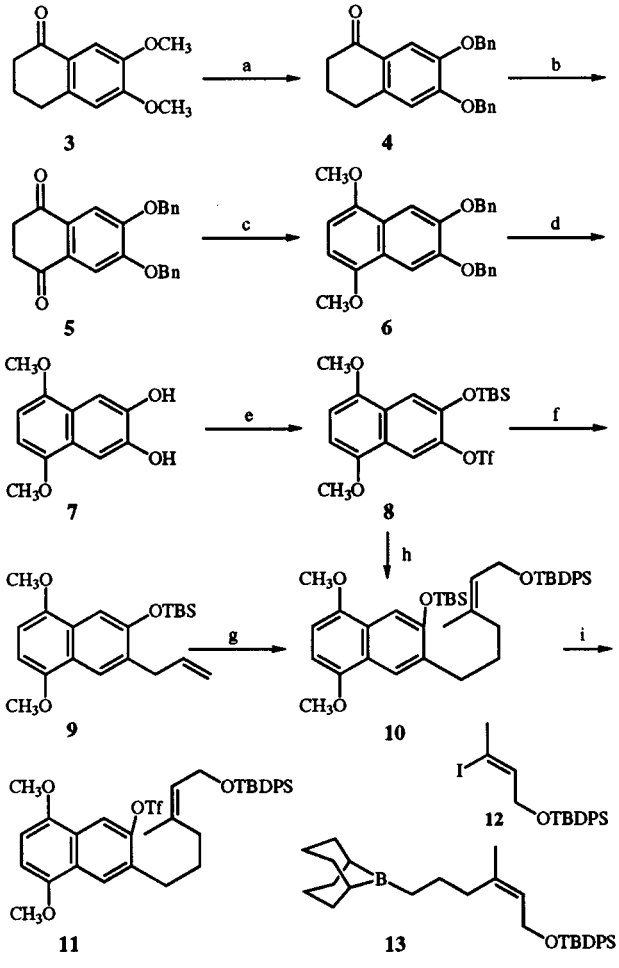
A retrosynthetic analysis for the catalytic asymmetric synthesis of **1** and **2** was made as shown in Scheme 1. The reason behind the adoption of the (*Z*)-configuration for the trisubstituted olefin substrate to the asymmetric Heck reaction stems from experience gained during a catalytic asymmetric synthesis of eptazocine, in which a benzylic quaternary carbon atom was introduced by similar means [9]. In that case we obtained a much higher enantiomeric excess when using the (*Z*)-trisubstituted olefin than when using the (*E*)-configuration.

Scheme 1



In order to determine the feasibility of the above-described analysis, the substrate **11** was first of all prepared by two different routes (Scheme 2). Commercially available 6,7-dimethoxy-1-tetralone **3** was efficiently converted to the catechol derivative **7** in a five-step sequence of reactions in 58% overall yield. This synthetic route to **7** is applicable to a large scale synthesis because of the easy purification of **4** and **6** by recrystallization. The catechol derivative **7** was transformed into **8** by monosilylation followed by trifluoromethanesulfonylation in 85% yield. Then, cross-coupling using allylmagnesium bromide [10] gave **9** in quantitative yield. Treatment of **9** with 9-borabicyclo[3.3.1]nonane (9-BBN) followed by Suzuki cross-coupling [11] using the alkenyl iodide **12** afforded **10** in 90% yield. Alternatively, **10** was prepared in a single step (69%) using the alkylborane **13** with a trisubstituted olefinic double bond. The resulting silyl ether **10** was converted to the triflate **11** by conventional means.

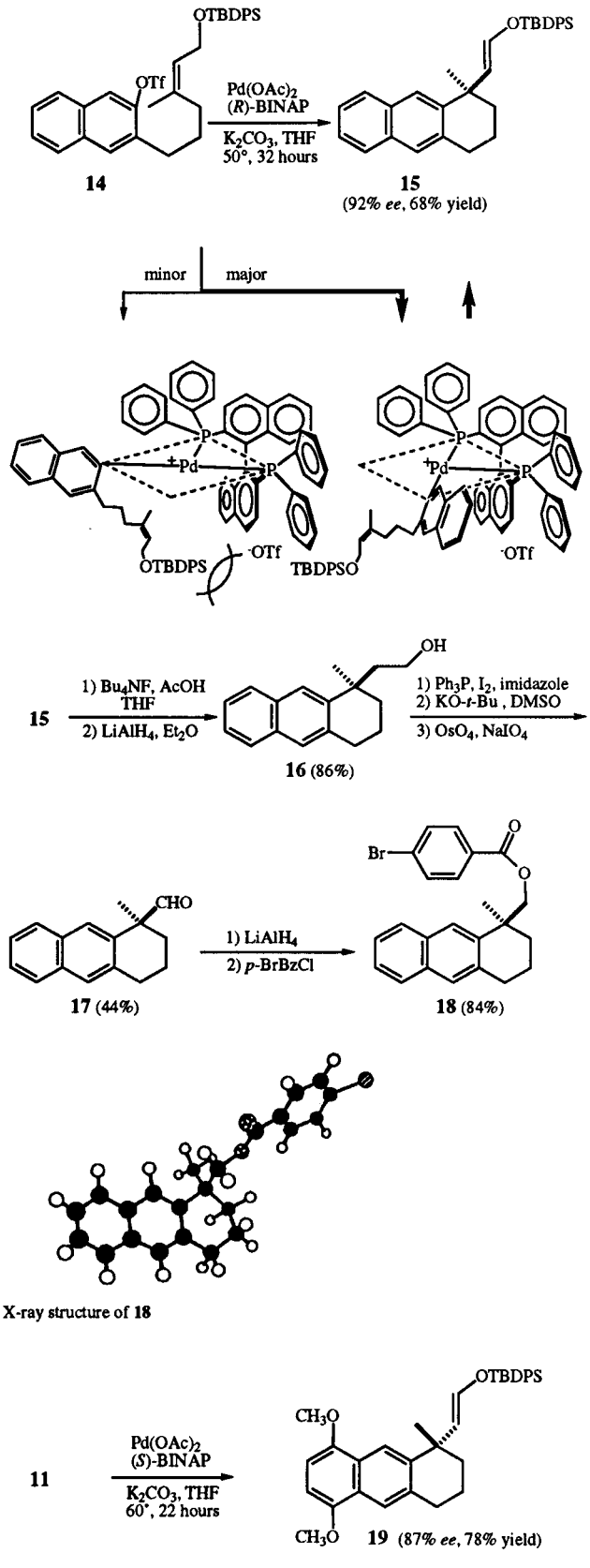
Scheme 2



Reaction conditions: (a) (1) BBr_3 (2.1 equivalents), CH_2Cl_2, -78° to rt, (2) BnBr (2.0 equivalents), K_2CO_3, Bu_4NI, DMF, 60° (two steps, 92%); (b) CrO_3 (5 equivalents), AcOH-H_2O, 0° to rt; (c) KHMDS (3 equivalents), THF, -78°, then MeI (6 equivalents), -78° to rt (63% from **4**); (d) H_2 (1 atmosphere), Pd-C, AcOEt, rt (quantitative); (e) (1) TBSCl (1.1 equivalents), Et_3N, CH_2Cl_2, 0°, (2) Tf_2O (1.3 equivalents), Et_3N, CH_2Cl_2, -78° to rt (two steps, 85%), (f) CH_2=$CHCH_2MgBr$ (5 equivalents), $PdCl_2$(dppf)•CH_2Cl_2 (9 mol %), Et_2O, -78° to rt (quantitative); (g) (1) 9-BBN (2.1 equivalents), THF, 0° to rt, (2) **12** (1.5 equivalents), $PdCl_2$(dppf)•CH_2Cl_2 (5 mol %), K_3PO_4•nH_2O, THF, 50° (90% from **9**); (h) **13** (1.3 equivalents), $PdCl_2$(dppf)•CH_2Cl_2 (10 mol %), K_2CO_3, THF, 50° (69%); (i) (1) Bu_4NF (1.0 equivalent), THF, 0°, (2) Tf_2O (1.3 equivalents), Et_3N, CH_2Cl_2, -78° to rt (two steps, 69%).

With the substrate **11** for an asymmetric Heck reaction available in large quantities, we then focused our attention on the crucial catalytic asymmetric cyclization. First of all, using the model compound **14**, the feasibility of an intramolecular Heck reaction was examined, and it turned out that treatment of **14** with palladium(II) acetate (10 mol %), 1,3-bis(diphenylphosphino)propane (dppp) (20 mol %) and potassium carbonate (3 equivalents) in tetrahydrofuran at 50° for 120 hours gave (±)-**15** in 42% yield. Moreover, based on the previous information obtained in

Scheme 3



X-ray structure of **18**

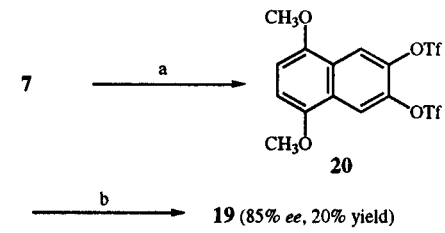
the catalytic asymmetric synthesis of eptazocine with a benzylic quaternary carbon center [9], **14** was treated with palladium(II) acetate (10 mol %), (*R*)-(+)-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl [(*R*)-BINAP] [12] (20 mol %), and potassium carbonate (3 equivalents) in tetrahydrofuran at 50° for 32 hours, giving rise to **15** in 92% *ee* and in 68% yield. The enantiomeric excess of **15** was determined by hplc analysis using DAICEL CHIRALCEL OD (hexane:2-propanol, 9:1) of 4-nitrobenzoate of **16**, and the absolute configuration of **15** was unequivocally determined by X-ray analysis of **18** derived from **15**. Having developed an effective catalytic asymmetric synthesis of the model compound **15**, we next attempted a catalytic asymmetric synthesis of **19**, and we were pleased to find that treatment of **11** with palladium(II) acetate (10 mol %), (*S*)-(-)-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl [(*S*)-BINAP] (20 mol %), and potassium carbonate (3 equivalents) in tetrahydrofuran at 60° for 22 hours gave **19** with 87% *ee* in 78% yield. The expected *S* configuration of **19** was confirmed by the fact that **19** was successfully converted to natural **1** and **2**.

Is it possible to develop another shorter synthetic route to optically active **19**? We noticed that the catechol derivative **7** could be converted to the ditriflate **20**, which was expected to be transformable into **19** by way of a cascade Suzuki cross-coupling and an asymmetric Heck reaction in a single step. Since the reaction rate of an asymmetric Heck reaction is generally lower than that of a Suzuki cross-coupling, a similar substrate **11** for an asymmetric Heck reaction would be generated in the reaction medium, leading to **19** with high enantiomeric excess. In order to examine the feasibility of the above-mentioned cascade reaction, first of all **7** was converted to **20** in 99% yield. Then, the cascade reaction was investigated in detail under a variety of reaction conditions, and it turned out that, against our expectations, the cascade reaction did not proceed effectively, instead giving rise to **21** and **22** as major products. The desired product **19**, however, was securely obtained in 20% yield under the conditions described in Scheme 4 and, as expected, the enantiomeric excess of resulting **19** was found to be 85%. Improvement of the cascade reaction to a synthetically useful extent is still under investigation.

We felt that the cascade Suzuki cross-coupling and Heck reaction process had an intrinsic interest even if lacking the asymmetric aspect, and so we decided to experiment with a range of achiral ligands for the conversion of **20** to **19**. We were pleased to find that the use of triphenylarsine as an achiral ligand gave racemic **19** in a much better yield (46%), and the results are summarized in Table 1 [13,14,15].

With large quantities of optically active **19** in 87% *ee* and (±)-**19** in hand, we then pursued a catalytic asymmetric synthesis of **1** and **2**. In accordance with the retrosynthetic analysis shown in Scheme 1, optically active **19** was first converted to the aldehyde, followed by reduction with sodium borohydride to give the alcohol **23** (93%). The alcohol **23** underwent trifluoromethanesulfonylation to afford the triflate **24**, which was then treated with the acyl anion equivalent derived from **31**. The resulting product was further converted to the ketone **25** in 82% overall yield from **23**. After protection of the carbonyl functionality as an acetal (98%), and of the ethynyl functionality with a triisopropylsilyl group (98%), **26** underwent benzylic oxidation to give **27** in 96% yield. Exposure of **27** to O_2 (1 atmosphere) in the presence of potassium *tert*-butoxide in *tert*-butyl alcohol gave the enol **28** in 79% yield. Treatment of **28** with sodium iodide and cupric sulfate pentahydrate in aqueous methanol afforded

Scheme 4



Reaction conditions: (a) Tf_2O (3 equivalents), pyridine, CH_2Cl_2, -78° to rt (99%); (b) **13** (1.1 equivalents), $Pd(OAc)_2$ (20 mol %), (*S*)-BINAP (40 mol %), K_2CO_3 (6 equivalents), THF, 60°.

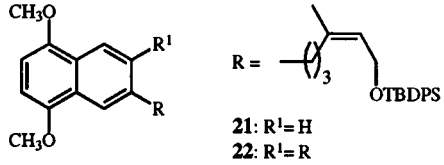
Table 1

Cascade Suzuki Cross-coupling and Heck Reaction Using Achiral Ligands

20 + **13** (1.3 equiv) $\xrightarrow[6\text{ equiv }K_2CO_3,\ THF,\ 60°]{\text{Pd(0)-ligand}}$ (±)-**19** + **21** + **22**

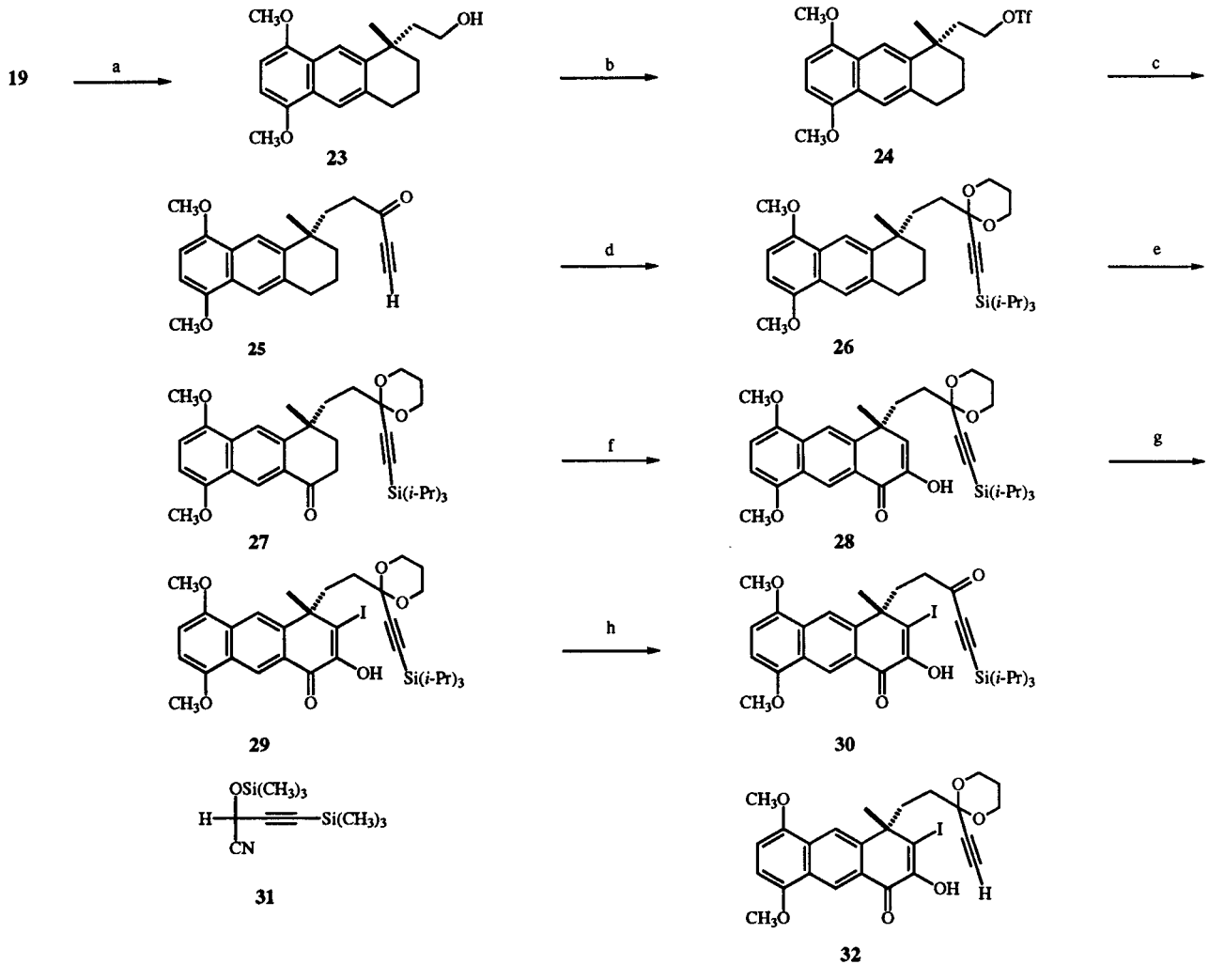
Entry	Ligand	Yield **19** (%)	**21** (%)	**22** (%)
1 [a]	Ph_3P	-	-	-
2 [a]	$(o\text{-tol})_3P$	trace	22	31
3 [a]	$(2\text{-furyl})_3P$	27	13	-
4 [a]	Ph_3As	41	25	-
5 [b]	DPPF	trace	30	20
6 [b]	$(Ph_2AsCH_2)_2$	trace	28	17
7 [c]	Ph_3As	46	16	-

[a] 20 mol % $Pd(OAc)_2$, 80 mol % ligand were used; [b] 20 mol % $Pd(OAc)_2$, 40 mol % ligand were used; [c] 10 mol % $Pd_2(dba)_3$, 80 mol % ligand were used.



21: R^1 = H
22: R^1 = R

Scheme 5

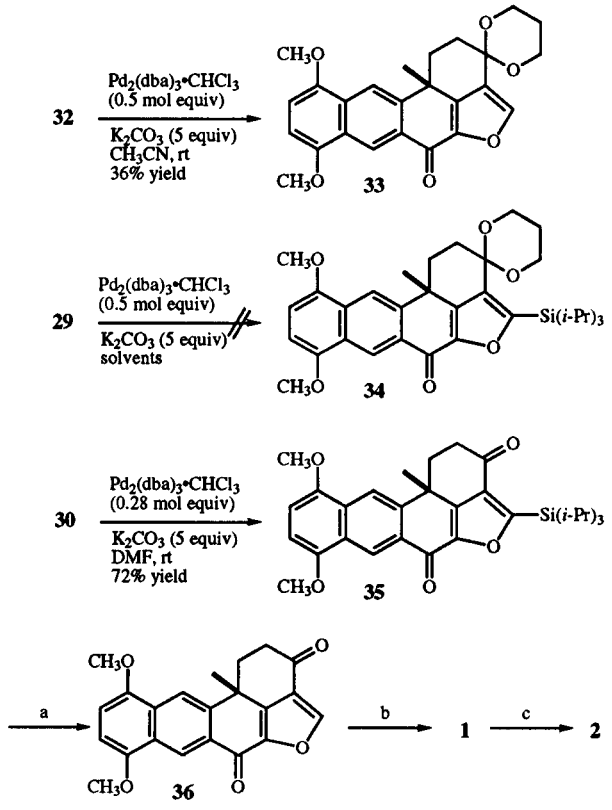


Reaction conditions: (a) (1) Bu_4NF (2 equivalents), AcOH (3 equivalents), THF, 0° to rt, (2) $NaBH_4$ (5 equivalents), MeOH, 0° to rt (two steps, 93%); (b) Tf_2O (1.2 equivalents), pyridine, CH_2Cl_2, -78° to rt; (c) LDA/**31** (1.5 equivalents), THF, -78°, then H^+, then OH^-, then Bu_4NF, AcOH (82% from **23**); (d) (1) $HO(CH_2)_3OH$ (10 equivalents), $TsOH•H_2O$, benzene, reflux (98%), (2) *n*-BuLi (2 equivalents), THF, -78° to -50°, then TIPSCl (2 equivalents), -78° to rt (98%); (e) DDQ (3 equivalents), CH_2Cl_2, H_2O, rt (96%); (f) O_2 (1 atmosphere), KO-*t*-Bu (5 equivalents), *t*-BuOH, 35° (79%); (g) NaI (10 equivalents), $CuSO_4•5H_2O$ (10 equivalents), MeOH, H_2O, rt (97%); (h) $TsOH•H_2O$, acetone, H_2O, 60° (98%).

the requisite alkenyl iodide **29** quite efficiently (97%) [16], and exposure of **29** to *p*-toluenesulfonic acid in aqueous acetone furnished **30** in 98% yield. Moreover, **32** was also synthesized from **24** in a five-step sequence of reactions (59% overall yield, i. LDA/**31**, -78°, then H^+, then ^-OH; ii. $HO(CH_2)_3OH$, $TsOH•H_2O$; iii. DDQ; iv. O_2, KO-*t*-Bu; v. NaI, $CuSO_4•5H_2O$).

Having synthesized **29**, **30**, and **32** as substrates for the crucial construction of the unique pentacyclic skeleton, we examined the cascade reaction in detail. First of all, compound **32** was treated with $Pd_2(dba)_3•CHCl_3$ (0.5 molar equivalents) and potassium carbonate (5 equivalents) in acetonitrile at room temperature for 24 hours, and we were pleased to find that the expected product **33** was obtained albeit in a modest 36% yield. In order to improve the yield, solvent and base effects as well as effects of additives such as silver carbonate and tetrabutylammonium chloride were investigated. Unfortunately, however, the chemical yield of **33** was not improved. Furthermore, in an attempt to improve the construction of the unique pentacyclic skeleton, the reaction of **29** was next examined under several reaction conditions, but no **34** was obtained, with **28** being obtained as the major product. Finally we were very pleased to find that treatment of **30** with $Pd_2(dba)_3•CHCl_3$ (0.28 molar equiva-

Scheme 6



Reaction conditions: (a) Bu_4NF (16 equivalents), AcOH (24 equivalents), CH_3CN, THF, 60° (83%); (b) CAN (6.7 equivalents), CH_3CN, H_2O, rt (99%); (c) $Na_2S_2O_4$, acetone, H_2O, 0° (quantitative).

lents) and potassium carbonate (5 equivalents) in dimethylformamide at room temperature for 8 hours gave the desired pentacycle **35** in a single step (72%). At the same time Larock and coworkers also reported a method for the synthesis of a variety of furan skeletons using a similar strategy [17]. The pentacyclic intermediate **35** was subjected to desilylation, which gave **36** in 83% yield, $[\alpha]_D^{23}$ +123.7° (*c* 0.335, dichloromethane, 87% *ee*). Compound **36** was then converted to halenaquinone **1** in 99% yield, and **1** was further converted to halenaquinol **2** using Harada's procedure (almost quantitative yield) [5].

In conclusion, we have achieved an efficient catalytic asymmetric synthesis of halenaquinone **1** and halenaquinol **2**, in which an asymmetric Heck reaction, and a cascade Suzuki cross-coupling and an asymmetric Heck reaction as well as a single step construction of a unique pentacyclic skeleton using palladium chemistry are involved. Moreover, a synthetically useful cascade Suzuki cross-coupling and a Heck reaction which use triphenylarsine as an achiral ligand have been developed, demonstrating the versatility of modern palladium chemistry. The new chemistry described herein should be quite useful for the synthesis of a variety of biologically significant compounds. Further studies along these lines are currently under investigation.

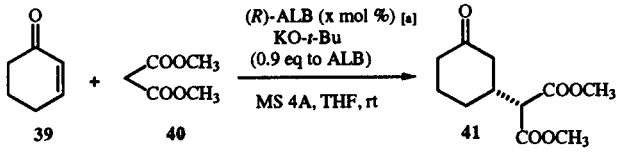
II. Catalytic Asymmetric Synthesis of 20-Deethyltubifolidine and Tubifolidine.

The *strychnos* alkaloids, which include tubifolidine (**37**), tubifoline, and strychnine, constitute an important group of architecturally complex and widely distributed monoterpenoid indole alkaloids [18]. Total syntheses of these natural products in the racemic or naturally occurring form have already been achieved by several groups [19]. To date, however, no catalytic asymmetric syntheses of the *strychnos* alkaloids have been accomplished. We therefore initiated a research program into the catalytic asymmetric synthesis of these indole alkaloids. 20-Deethyltubifolidine (**38**) and tubifolidine (**37**) were selected as the first target compounds. We report here the first catalytic asymmetric synthesis of **37** and **38** in which a highly practical catalytic asymmetric Michael addition of dimethyl malonate (**40**) to cyclohexenone (**39**), as well as a one-pot construction of the ABDE ring systems using 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ), were involved as key steps.

The related compounds of the racemic Michael adduct **41** have already been utilized for the synthetic studies of these alkaloids [20]. We thus concentrated first on the efficient synthesis of **41** in a catalytic asymmetric manner. We previously developed a variety of heterobimetallic asymmetric complexes, which we used to realize many efficient catalytic asymmetric reactions, including a Michael addition [2]. In fact, **41** was efficiently synthesized in up to 93% *ee* using either $LaNa_3$tris(binaphthoxide) complex, AlLibis(binaphthoxide) complex (ALB), or GaNabis(binaphthoxide) complex. Among these catalysts, we concluded that ALB was the most effective for the present Michael addition. Moreover, we have developed a strategy for the activation of ALB: the addition of nearly 1 equivalent of bases, such as butyllithium and potassium *tert*-butoxide, to ALB can accelerate a catalytic asymmetric Michael addition without lowering the high enantiomeric excess [2,21]. However, 3-5 mol % of the catalyst is still required to obtain the product in excellent yield and high enantiomeric excess. We intended to improve the catalytic asymmetric Michael addition to a practically useful level. After many attempts, we were pleased to find that addition of molecular sieves [MS 4A] [22] to the reaction medium greatly improved the catalytic asymmetric Michael addition. Actually, as shown in Table 1, the use of ALB (0.3 mol %), potassium *tert*-butoxide (0.27 mol %), and MS 4A gave **41** [23] in 99% *ee* and 94% yield even at room temperature. Furthermore we successfully carried out this reaction on a 20-30g scale. Addition of molecular sieves [MS 4A] appears to remove a trace amount of water that would otherwise gradually decompose the ALB-potassium *tert*-butoxide catalyst.

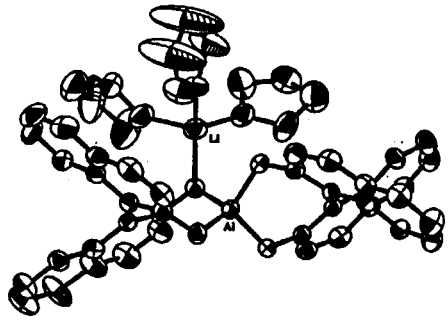
Table 2

A Greatly Improved Catalytic Asymmetric Michael Addition of **40** to **39**



Entry	ALB (x mol %)	KO-*t*-Bu	MS 4A	Time (hours)	Yield (%)	*ee* (%)
1 [b]	10	-	-	72	90	93
2 [c]	5	+	-	48	97	98
3 [c]	0.3	+	-	120	74	88
4 [c]	0.3	+	+ [e]	120	94	99
5 [d]	1.0	+	+ [f]	72	97	99

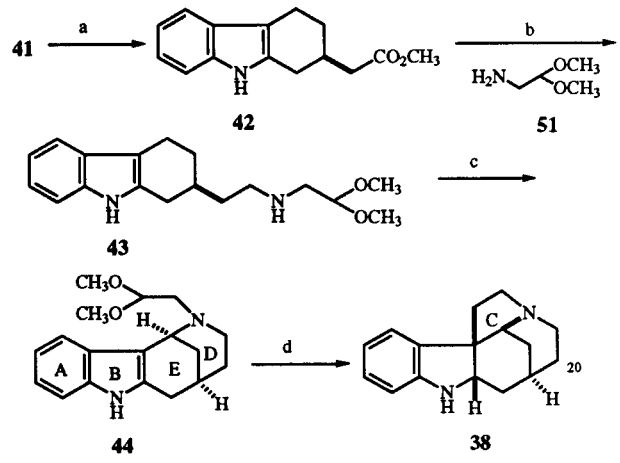
[a] (*R*)-AlLibis(binaphthoxide); [b] 200 mg scale reaction; [c] 400 mg scale reaction; [d] 10 g scale reaction; [e] MS 4A (8.3 g) was used for ALB (1 mmole); [f] MS 4A (2.0 g) was used for ALB (1 mmole).



X-ray structure of ALB ($C_{40}H_{24}AlLiO_4(thf)_3$)

Having obtained nearly optically pure **41** in large quantities, we next efficiently converted **41** to the indole derivative **42** in 92% overall yield, through a highly regioselective Fischer method [20,24] followed by decarbalkoxylation. Also at this stage, the enantiomeric excess of **42** was confirmed to be 99% [25]. The indole derivative **42** was further transformed into the amine **43** in a three-step reaction sequence (38% overall yield). It was expected that treatment of **43** with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone would produce the tetracyclic compound **44** in a one-pot reaction through the dehydrogenated intermediate [26]. Indeed, we could find, that exposure of **43** to 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (1.1 molar equivalents) and disodium hydrogen phosphate (10 molar equivalents) in degassed tetrahydrofuran at 0° for 1 hour gave **44** in 77% yield. To the best of our knowledge, this is the first example of a one-pot construction of the tetracyclic compound starting with **43**. The tetracyclic compound **44** was then transformed into 20-deethyltubifolidine (**38**), in a three-step reaction sequence (27% overall yield) [19a,27].

Scheme 7

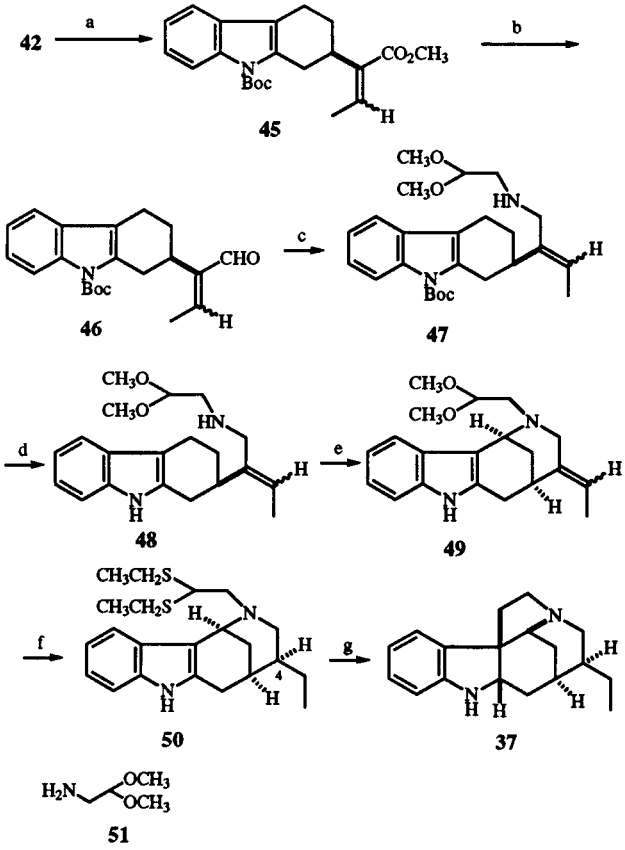


Reaction conditions: (a) (1) $PhNHNH_2$•HCl (1.05 equivalents), AcOH, 80°, (2) LiCl (2.0 equivalents), H_2O (1.0 equivalent), DMSO, 180° (two steps, 92% (99% *ee*)); (b) (1) LiOH (1.6 equivalents), THF-H_2O (3:1), rt, (2) **51** (2.4 equivalents), HOBt (1.2 equivalents), DCC (1.2 equivalents), DMAP (catalyst), THF, rt (two steps, 78%), (3) BH_3•THF (2.5 equivalents), THF, 60° (49%); (c) DDQ (1.1 equivalents), Na_2HPO_4 (10 equivalents), degassed THF, 0° (77%); (d) (1) EtSH (excess), BF_3•Et_2O (10 equivalents), MS 3A, CH_2Cl_2, 0° (77%), (2) DMTSF (2.1 equivalents), CH_2Cl_2, 0° (80%), (3) Raney Ni (W2) (excess), EtOH, reflux (44%).

Having achieved a practical catalytic asymmetric synthesis of **38**, we next pursued a catalytic asymmetric synthesis of tubifolidine (**37**). Toward this end, **42** was first protected as a *t*-butyl carbamate, and the resulting carbamate underwent aldol condensation followed by dehydration through the mesylate to give **45** in 86% overall yield (*E*:*Z* = 8:1). The ester **45** thus obtained was reduced with diisobutylaluminum hydride and then oxidized with manganese dioxide to furnish **46** in 91% overall yield. The next transformation of **46** to **47** constituted a relatively problematic step. After several attempts, it was found that treatment of **46** with **51** (2.0 molar equivalents) and Ti(O-*i*-Pr)$_4$ (2.5 molar equivalents) [28] followed by reduction with sodium borohydride in methanol gave **47** in 96% yield. The resulting **47** was deprotected by treatment with trifluoroacetic acid and anisole to afford **48** in 98% yield. Again, we were faced with the challenge of a crucial one-pot construction step using 2,3-dichloro-5,6-dicyano-1,4-benzoquinone [29]. We were pleased to find that treatment of **48** with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (1.1 molar equivalents) and disodium hydrogen phosphate (10 molar equivalents) in degassed tetrahydrofuran at -20° to 0° for 2 hours gave **49** in 52% yield (67% yield based on consumed **48**). The tetracyclic compound **49** was converted to **50** in 42% overall yield, through a stereoselective reduction followed by acetal exchange [30]. The dithioacetal **50** was finally trans-

formed into tubifolidine (**37**) in a three-step reaction sequence (24% overall yield). The optical rotation of **37** was $[\alpha]_D^{19}$ -61° (*c* 0.36, chloroform) [lit [31] $[\alpha]_D^{29}$ -67±3° (*c* 0.61, chloroform), lit [19c] $[\alpha]_D^{22}$ -41.6° (*c* 0.61, chloroform, 95.3% *ee*)]. Thus, a catalytic asymmetric synthesis of **37** was achieved in a highly stereocontrolled manner.

Scheme 8



Reaction conditions: (a) (1) $(Boc)_2O$ (1.2 equivalents), Et_3N (2.0 equivalents), DMAP (catalyst), CH_2Cl_2, rt (97%), (2) LDA (1.3 equivalents)/acetaldehyde (2.0 equivalents), THF, -78°, (3) MsCl (1.5 equivalents), *i*-Pr_2NEt (3.0 equivalents), toluene, rt, then DBU (4.0 equivalents), 50° (two steps, 89%); (b) (1) DIBAL (3.0 equivalents), toluene, -78° (conversion 97%), (2) MnO_2 (excess), pentane, rt (94%); (c) **51** (2.1 equivalents), Ti(O-*i*-Pr)$_4$ (2.5 equivalents), toluene, rt, then $NaBH_4$ (10 equivalents), CH_3OH (96%) 0°; (d) TFA (excess), anisole (10 equivalents), 0° (98%); (e) DDQ (1.1 equivalents), Na_2HPO_4 (10 equivalents), degassed THF, -20° to 0° (conversion 67%); (f) (1) H_2, 10% Pd/C (20 w/w%), AcOEt, rt, (2) EtSH (excess), BF_3•Et_2O (10 equivalents), MS 3A, CH_2Cl_2, 0° to rt (two steps, 42%); (g) (1) DMTSF (2.1 equivalents), CH_2Cl_2, 0° (68%), (2) $LiAlH_4$ (4.8 equivalents), THF, 0°, (3) Raney Ni (W2) (excess), EtOH, reflux (two steps, 35%).

In conclusion, we have developed a catalytic asymmetric synthesis of 20-deethyltubifolidine (**38**) and tubifolidine (**37**), in which only 0.3 mol % of the heterobimetallic asymmetric catalyst (ALB-potassium *tert*-butoxide-molecular sieves [MS 4A]) at room temperature is required for the efficient catalytic asymmetric Michael addition of **40** to **39**. In addition, the one-pot construction of the tetracyclic synthetic intermediates from the tricyclic intermediates with very elegant use of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone was noteworthy. We also believe that the indole derivative **42** readily obtainable in a nearly optically pure form would be an interesting building block for the preparation of a variety of optically active ligands. Further studies are currently under investigation.

Acknowledgements.

The chemistry in this review was created by my able coworkers whose names are described in many references.

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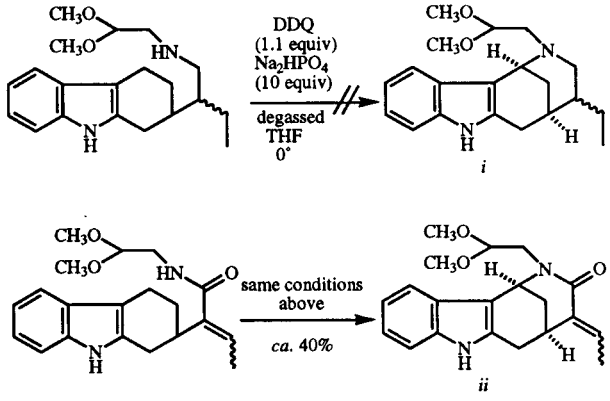

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