Table II. Catalytic Asymmetric Synthesis of the *cis*-Decalin Derivatives 5, 6, and 7 Using (*R*)-BINAP in 1-Methyl-2-pyrrolidinone[a]

run	substr	temp, °C	time, h	yield, %	$[\alpha]_D$ ($CHCl_3$), deg	ee, %
1[b]	1	60	12	54	+116	33
2[c]	1	60	37.5	74	+167	46
3[c]	2	40	44	70	+152	44
4[c]	3	40	88	66	+131	36

[a] 1-Methyl-2-pyrrolidinone (10 mL) was utilized for the substrate (1 mmol). [b] The alkenyl iodide was treated with $Pd(OAc)_2$ (5 mol %), (*R*)-BINAP (5.5 mol %), and Ag_2CO_3 (2 molar equiv) in 1-methyl-2-pyrrolidinone. [c] The $LnPd^0$ catalyst (3 mol %) was first generated in situ by reaction of $Pd(OAc)_2$ with 2 molar equiv of cyclohexene and 3 molar equiv of (*R*)-BINAP per Pd in the presence of Ag_2CO_3 (2 molar equiv) (1-methyl-2-pyrrolidinone solvent, 60 °C, 3 h), and then the alkenyl iodide was added.

5 h) (Table I). The structure of **5** was unequivocally determined from the ^{1}NMR spectrum (NOE) of the silyl ether **6** derived from **5** via a two-step sequence of reactions (i. $LiAlH_4$ in ether, ii. TBDMSCl and imidazole in DMF). Formation of the *cis*-decalin derivative **5** is well explained as follows. Oxidative addition of **1** to Pd(0) gives the alkenylpalladium iodide **4** and subsequent cyclization from the same face as an alkenyl side chain followed by syn-β-hydrogen elimination affords **5**.

Having established an intramolecular Heck-type reaction yielding the *cis*-decalin derivative **5** in a stereo- and regiocontrolled manner, we next turned our attention to application to a catalytic asymmetric synthesis utilizing the alkenyl iodide **1**, $Pd(OAc)_2$, and optically active bidentate ligands in the presence of Ag_2CO_3. In the first place, a catalytic asymmetric synthesis utilizing either (*S*,*R*)-BPPFA[8] or (*S*,*S*)-BPPM[8] as a chiral ligand was investigated under the various reaction conditions, giving only low enantiomeric excess, respectively (e.g. (*S*,*R*)-BPPFA in DMF → 3%, (*S*,*S*)-BPPM in DMF → 1%). However, we were pleased to find that the use of (*R*)-BINAP[8] in DMF resulted in the formation of (+)-**5** in 19% ee (69% yield). Encouraged by this interesting result, solvent effects were carefully examined to give 8% ee (CH_3CN), 1% ee (DMSO), 2% ee (THF), 20% ee (HMPA), 19% ee (1,1,3,3-tetramethylurea), and 23% ee (*N*,*N*'-(dimethylpropylene)urea), and finally we have found that the use of 1-methyl-2-pyrrolidinone gives 33% ee[9] (Table II). The various reaction conditions were further investigated in order to obtain higher ee, giving the highest ee as follows. The $LnPd^0$ catalyst (3 mol %) was generated in situ by reaction of $Pd(OAc)_2$ with 2 molar equiv of cyclohexene and 3 molar equiv of (*R*)-BINAP per Pd in the presence of Ag_2CO_3 (1-methyl-2-pyrrolidinone solvent, 60 °C, 3 h). Addition of the alkenyl iodide **1** in 1-methyl-2-pyrrolidinone and heating at 60 °C for 37.5 h afforded the cyclized product **5** in 46% ee (74%). Likewise, the alkenyl iodides **2** and **3** were also transformed into the optically active *cis*-decalin derivatives **6** and **7** in the range of 36–44% ee as shown in Table II. The enantiomeric excess (ee) was unequivocally determined by the HPLC analysis (DAICEL CHIRACEL OJ, hexane–2-propanol, 9:1) of **8** obtainable from either **5**, **6**, or **7**,[10] and assignment of the absolute configuration was achieved by application of the CD exiton chirality method to **9**.[11,12]

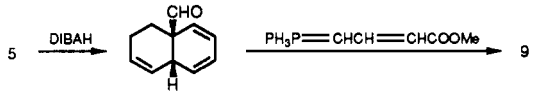
In conclusion, a catalytic asymmetric synthesis utilizing a Heck-type reaction has been realized for the first time. Although the enantioselectivity is still not excellent, the present result paves the way for further improvements. Further studies along this line are in progress.

(8) Kagan, H. B. *Asymmetric Synthesis*; Morrison, J. D., Ed; Academic Press, Inc.: 1985; Vol. 5, p 1.

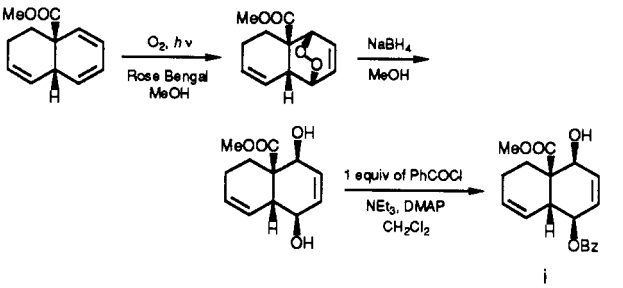
(9) Under the same reaction conditions, the use of 3 molar equiv of (*R*)-BINAP did not improve the enantiomeric excess.

(10) The cyclized products **5** and **7** were converted to **8** by treatment with $LiAlH_4$ in ether at 0 °C, while **6** was transformed into **8** on exposure to HF in aqueous CH_3CN at −30 °C.

(11) The conjugated ester **9** was synthesized as follows.



(12) The cyclized product **5** has been already converted to the highly functionalized compound i as shown below.



Preparation of Activated Imines and Their Condensation with Allylstannanes: Stereoselective Synthesis of 1,2-Amino Alcohols

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Received July 11, 1989

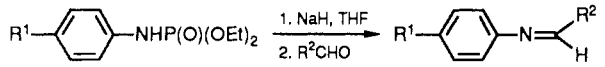
Summary: A modified Wadsworth–Emmons reaction affords hitherto inaccessible imines derived from aliphatic aldehydes and aromatic amines. Such highly activated imines condense rapidly and stereoselectively with oxygenated allylstannanes, at −78° C, under the influence of BF_3OEt_2. Analogous reactions may be induced with activated imines derived from aromatic aldehydes. A stereoselective preparation of *erythro* 1,2-amino alcohols has been developed based on the new chemistry.

Sir: We recently became interested in the synthesis of 1,2-amino alcohols[1] via Lewis acid promoted condensation

(1) For alternative methods see, e.g.: (a) Trost, B. M.; Sudhakar, A. R. *J. Am. Chem. Soc.* **1988**, *110*, 7933. (b) Barrett, A. G. M.; Spilling, C. D. *Tetrahedron Lett.* **1988**, *29*, 5733. (c) Sakaitani, M.; Ohfune, Y. *Tetrahedron Lett.* **1987**, *28*, 3987. (d) Kano, S.; Yuasa, Y.; Shibuya, S. *Heterocycles* **1987**, *26*, 373. (e) Fujita, M.; Hiyama, T. *J. Am. Chem. Soc.* **1984**, *106*, 4629. (f) Roskamp, E. J.; Pedersen, S. F. *J. Am. Chem. Soc.* **1987**, *109*, 6651.

0022-3263/89/1954-4739$01.50/0

Table I



1 2

entry	R^1	R^2	yield,[a] %
a	H	iBu	91
b	H	cyclohexyl	89
c	OMe	iBu	88
d	OMe	cyclohexyl	93
e	COOMe	(*E*)-2-styryl	95
f	COOMe	phenyl[7]	70
g	COOMe	iBu	90
h	COOMe	cyclohexyl	97

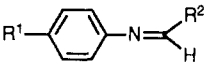
[a] Isolated yields, corrected (NMR) for the presence of some phosphoramide 1.[9]

of imines with oxygenated allylstannanes. The choice of those organometallics was suggested by their propensity to add to π-acceptors in a stereochemical manner which is virtually independent of the geometry of their olefinic linkage,[2] so that either geometrical isomer, or even mixtures of isomers, of such allylmetals may be conveniently utilized in a reaction. Similar condensations of imines with allyltributyltin or crotyltributyltin had been explored, briefly, by Keck[3] and by Yamamoto,[4] who identified the weak electrophilicity of ordinary imino linkages as a most serious obstacle undermining such processes.[5] Moreover, the unique effectiveness of $TiCl_4$ as a promoter of stannane–imine condensations,[3] stood in strident contrast to the great sensitivity of oxygenated allylstannanes to that Lewis acid,[3,6] and it raised serious questions about the possibility of achieving the desired transformations. As a result, imine/allystannane condensations remain yet to be developed to their full potential.

We sought to augment the proclivity of imines to participate in addition processes by introducing an N-activating group, which would effectively delocalize negative charge developing on the nitrogen atom during the reaction, without altering the propensity of the substrates to exist as the imino, rather than as the enamino, tautomers. The activating implement should permit reaction to occur with mild Lewis acid activators, and it should also be readily excised from the products, if necessary. We have determined that imines derived from aliphatic or aromatic aldehydes and methyl 4-aminobenzoate possess the desired reactivity profile. They appear to exist only in the imino form and they show no obvious tendency to tautomerize. More importantly, they condense rapidly with various allylstannanes under catalysis by BF_3OEt_2, affording products is 50–90% yield. A summary of our findings is presented herein.

Imines **2f**[7,22] and **2i–l** were easily generated by the direct condensation method (90+%).[8] Hitherto inaccessible[4] **2g–h** became readily available by a modified Wadsworth–Emmons procedure, which appeared to be rather general for the synthesis of imines derived from aromatic amines and aliphatic aldehydes,[9] as attested also by the facile preparation of compounds **2a–e**[10] (Tables I and II). Condensation of the very reactive carbomethoxyphenylimines with allyltributyltin,[11] crotyltributyltin,[12] or [(1*Z*)-1-alkoxypropen-3-yl]tributyltins[13] *occurred stereoselectively and virtually instantaneously* at −78 °C, in the presence of 2 equiv of BF_3OEt_2 (CH_2Cl_2) (Table III). This is in sharp contrast to the behavior of imines arising from

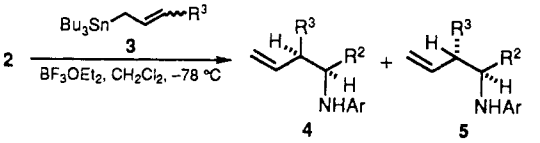
Table II



2

entry	R^1	R^2
i	H	phenyl[22]
j	COOMe	2-furyl
k	COOMe	2-NO_2-C_6H_4
l	COOMe	4-OMe-C_6H_4

Table III

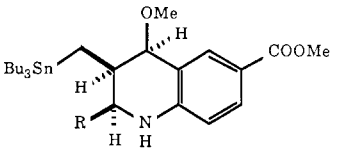


imine	R^3	entry 4/5	diastereomeric ratio[a]	yield,[b] %
2f	H	a	–	87
2f	(*E*,*Z*)-Me	b	4:1[c]	95
2f	(*Z*)-OMe	c	3:1	56[d]
2f	(*Z*)-OTHP	d	10:1	74
2g	H	e	–	96
2g	OMe	f	3:1	18[d]
2g	(*Z*)-OTHP	g	11:1	51
2h	H	h	–	82
2h	(*Z*)-OTHP	i	4:1	52
2i	(*Z*)-OTHP	j	5:1	12
2j	(*Z*)-OTHP	k	6:1	70[e]
2k	(*Z*)-OMe	l	4:1	66 + 15[f]
2l	(*Z*)-OMe	m	1:1	78[g]

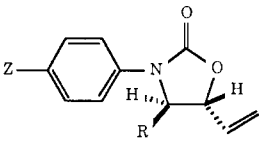
[a] Determined by 300-MHz proton NMR of crude reaction mixtures. [b] Yields of chromatographed products; mixture of syn and anti isomers. [c] Stereochemical assignment made on the basis of ref 3. [d] Compound **6** was formed as a significant side product. [e] Isolated yield of crude product. Substantial loss of this delicate material (up to 70%) occurs upon chromatography. [f] In this series, the stereoisomers were readily separable by chromatography. [g] Condensation occurred only at room temperature, resulting in erosion of the stereoselectivity.

(2) Yamamoto, Y.; Yatagai, H.; Naruta, Y.; Maruyama, K. *J. Am. Chem. Soc.* **1980**, *102*, 7107. See also ref 10.
(3) Keck, G. E.; Enholm, E. J. *J. Org. Chem.* **1985**, *50*, 147.
(4) Yamamoto, Y.; Komatsu, T.; Maruyama, K. *J. Org. Chem.* **1985**, *50*, 3115.
(5) Allylboranes appear to be uniquely successful in additions to imines, even to unactivated ones. For a discussion, see: Yamamoto, Y. *Aldrichimica Acta* **1987**, *20*, 45.
(6) Keck, G. E.; Boden, E. P. *Tetrahedron Lett.* **1984**, *25*, 265.
(7) The Wadsworth–Emmons preparation of **2f** was also carried out, in order to demonstrate the use of aromatic aldehydes in such reaction. The compound was normally made by direct condensation (ref 22).
(8) Cf. Castellano, J. A.; Goldmacher, J. E.; Barton, L. A.; Kane, J. S. *J. Org. Chem.* **1968**, *33*, 3501.
(9) Such imines, unavailable by direct condensation (ref 4), are considerably moisture-sensitive, yet they are isolable and even storable (desiccator, argon atmosphere) for a short time. Procedures for the preparation, isolation, and handling of the imines are furnished as supplementary material, together with hardcopy ^1H NMR spectra of a number of them.
(10) A single example of this variant of the Wadsworth–Emmons reaction has seemingly been recorded in the literature, in connection with the preparation of benzylideneaniline: Wadsworth, W. S., Jr.; Emmons, W. D. *J. Org. Chem.* **1964**, *29*, 2816. The requisite phosphoramides were best obtained by the reaction of the corresponding amines with diethyl phosphite/Et_3N/CCl_4: Atherton, F.; Openshaw. H.; Todd, A. *J. Chem. Soc.* **1945**, 660. Iminophosphoranes derived from aryl azides and PPh_3 or $P(OMe)_3$ were ineffective for the desired aza-Wittig couplings.
(11) Purchased from the Aldrich Chemical Co.
(12) Verdone, J. A.; Mangravite, J. A.; Scarpa, N. M.; Kuivila, H. G. *J. Am. Chem. Soc.* **1975**, *97*, 841.
(13) Obtained from allyl methyl ether or from allyl tetrahydropyranyl ether as described by: Koreeda, M.; Tanaka, Y. *Tetrahedron Lett.* **1987**, *28*, 143. 20–30-g batches are easily prepared by that excellent procedure. See also: Keck, G. E.; Abbott, D. E.; Wiley, M. R. *Tetrahedron Lett.* **1987**, *28*, 139.

aldehydes and simple aliphatic amines,[14] or even to the behavior of moderately activated benzalaniline[4] (Table III, entry 2i), which reacted slowly and in poor yield with oxygenated stannanes. Similarly, imine **21**, a compound in which activation by the *N*-carbomethoxyphenyl substituent is mesomerically reduced by a methoxy group, also underwent slow reaction only at room temperature, with consequent erosion of diastereoselectivity. Condensations with oxygenated stannanes were, of course, of particular interest to us. [(1*Z*)-1-[(Tetrahydropyranyl)oxy]propen-3-yl]tributyltin appeared to be the reagent of choice, affording products more stereoselectively and in better yield than [(1*Z*)-1-methoxypropen-3-yl]tributyltin. Furthermore, boron trifluoride promoted condensations of the latter reagent with imines **2f** and **2g** were marred by a competing Povarov reaction,[15] which gave dihydroquinolines **6**. Compound **6b** was in fact the major product



6a: R = Ph (17%)
6b: R = iBu (41%)

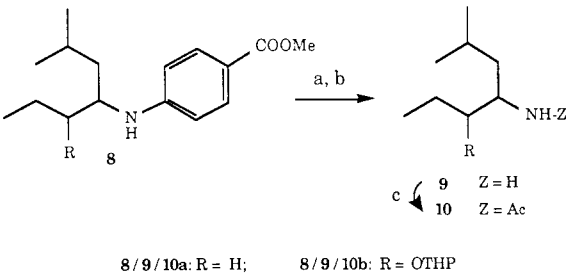


7

of the reaction between the stannane and **2g**. Interestingly, the dihydroquinolines were formed as single stereoisomers of all-cis stereochemistry (300-MHz ^{1}H NMR), suggesting an endo topological course for the Povarov cyclocondensation. This intriguing mode of reactivity was repressed by the use of the OTHP organometallic, presumably as a result of "anomeric" withdrawal of electron density from the vinyl ether oxygen, and consequent decrease in the nucleophilicity of the carbon atom β to oxygen in the enol ether system.

Diastereoselectivities varied from 3:1 to a substantial 10:1 in favor of the predicted syn product,[16] in agreement with the Seebach rule[17] and with other acyclic transition state models for similar additions to π-systems.[2,5] Stereochemical assignments were made by extensive NOE measurements[18] on oxazolones **7**;[19] results of these studies

Scheme I[a]



8/9/10a: R = H; 8/9/10b: R = OTHP

[a] (a) Aqueous NaOH, MeOH, reflux; (b) Li, NH_3(l), THF, tBuOH, add NH_4Cl; (c) Ac_2O, pyridine, 70–80% overall.

allowed subsequent stereochemical assignment in the methoxy series. It is noteworthy that diastereoselectivities, as well as yields, were not affected by the thermal history of the imine–Lewis acid mixture,[3] doubtless because of the rapidity with which condensations occurred.

Release of the nitrogen functionality from its aryl activating group added a useful new dimension to the new 1,2-amino alcohol synthesis. Thus, Birch-type reduction[20] (Li, NH_3/THF, tBuOH) of the acids[21] obtained by base hydrolysis of representative substrates **8** yielded the expected free amines, conveniently characterized as the acetamides (80% overall chromatographed yield) (Scheme I).

In conclusion, we have demonstrated the condensation of activated imines with allylstannanes under catalysis by the nonchelating BF_3OEt_2. The foundations are now established for a future study of issues of Cram–Felkin-type vs chelation-controlled reactivity with α-heterosubstituted imines and consequent development of an asymmetric variant of the new chemistry. We are actively investigating these matters and will report on additional developments in due course.

Acknowledgment. We thank the National Science Foundation (Grant CHE-8708130) and the Robert A. Welch Foundation (Grant C-1007) for their generous support of this work.

Supplementary Material Available: Experimental procedures for the preparation of activated imines and for their condensation with allylstannanes, spectral data for selected new compounds, hardcopy ^{1}H spectra of representative imines (16 pages). Ordering information is given on any current masthead page.

(14) We confirmed that these substances are unreactive towards allylstannanes: see discussion in ref 4.

(15) Cf. (a) Povarov, L. S. *Izv. Akad.Nauk. SSSR, Ser. Khim.* **1966**, 337 (*Chem. Abstr.* **1966**, *64*, 17539). (b) Elslager, E. F.; Worth, D, F. *J. Heterocyl. Chem.* **1969**, *6*, 597. For a review of similar reactions see: Jones, G. In *Comprehensive Heterocyclic Chemistry*; Katritzsky, A. R., Rees, C. W., Boulton, A. J., McKillop, A., Eds.; Pergamon Press: Oxford, U.K., 1984; Part 2A, pp 395–510, in particular pp 450–453. Interestingly, Povarov reactions did not interfere with condensation of the methoxystannane with imine **21**.

(16) Diastereoselectivities were determined by comparison of the integrated 300-MHz proton NMR spectra of crude **4/5** and of crude oxazolidinones **7**, thus removing ambiguities resulting from the presence of diastereomers at the level of the stereogenic carbon of undefined stereochemistry at the anomeric position of the THP moiety of **4/5**.

(17) Seebach, D.; Golinsky, J. *Helv. Chim. Acta* **1981**, *64*, 1413.

(18) We thank Dr. Alan M. Kook, of this department, for performing all the NOE measurements.

(19) The oxazolidinones were prepared from compounds **4/5** by treatment with dilute aqueous HCl (MeOH; 90–95%) followed by phosgenation (toluene/pyridine, 90%) and chromatographic purification.

(20) Recent review: Hook, J. M.; Mander, J. N. *Nat. Prod. Rep.* **1986**, *3*, 35.

(21) Direct reduction of the esters (Rabideau, P. W.; Huser, D. L.; Nyikos, S. J. *Tetrahedron Lett.* **1980**, *21*, 1401) was difficult.

(22) Bigelow, L. A.; Eatough, H. *Organic Syntheses*; Wiley: New York, 1941; Collect. Vol. I, p 80.

Regioselective Synthesis of (±)-11-Nor-9-carboxy-Δ^9-THC

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Received June 29, 1989

Summary: The regioselective synthesis of (±)-11-nor-9-carboxy-Δ^9-THC (**1**) has been carried out in eight steps and 14% yield from apoverbenone (**10**) and the bis-MOM ether of olivetol.

Sir: 11-Nor-Δ^9-tetrahydrocannabinol-9-carboxylic acid (11-nor-9-carboxy-THC, **1**), a principal human metabolite of Δ^9-tetrahydrocannabinol (THC, **2**), is the compound detected in the analytical procedures designed to ascertain

0022-3263/89/1954-4741$01.50/0